

Review article

The role of histamine in allergic disease: re-appraisal of its inflammatory potential

C. Bachert

Department of Oto-Rhino-Laryngology, Ghent
University Hospital, B-9000 Ghent, Belgium

Professor Claus Bachert, MD, PhD
Department of Oto-Rhino-Laryngology
Ghent University Hospital
B-9000 Ghent
Belgium

Accepted for publication 2 October 2001

Studies of allergic diseases, in particular asthma, rhinitis and urticaria, have suggested that histamine, a biogenic amine synthesized and stored mainly in mast cells and basophils, plays a prominent role in the pathophysiology of these diseases (1–3). Several immunologic and nonimmunologic stimuli, such as allergen, immunoglobulin (Ig)E, cytokines (interleukin (IL)-1, IL-3, IL-8, GM-CSF), substance P, complement C3a and C5a, platelet-activating factor (PAF), hyperosmolarity, physical stimuli (vibration, heat, cold), etc., induce the release of histamine from mast cells and basophils, following which it diffuses rapidly into the surrounding tissues and exerts its effects, before being metabolism and excreted in the urine (4).

In experimental asthma induced by allergen or exercise challenge, it has been demonstrated that the levels of histamine are increased in the circulation and implicated in bronchoconstriction (5–7). Studies of symptomatic asthmatics have also demonstrated that histamine levels are significantly increased in the bronchoalveolar lavage (BAL) of these individuals, compared with histamine levels in BAL of asymptomatic asthmatics (8,9). Similarly, allergen challenge in patients with allergic rhinitis significantly increases the levels of histamine in nasal secretions of these individuals (10–12), implicating a role for this mediator in the pathophysiology of allergic rhinitis. Indeed, nasal challenge with histamine has been shown to induce nasal blockage, sneezing and rhinorrhoea (13,14), likely as a result of sensory nerve stimulation in the nasal mucosa (15). In patients with cold urticaria, challenge with ice-water leads to a rapid rise in plasma histamine concentration within 2 min, which peaks at 5 min and returns to baseline values by 15–30 min (16).

Investigations of patients with chronic urticaria have also indicated that histamine is a central mediator in this allergic condition, with increased levels detected both in the lesions and normal skin of patients with urticaria, compared with skin of healthy individuals (17–19). Furthermore, the responsiveness of skin to histamine is also increased in patients with urticaria (19).

Apart from the classical activities of histamine, there is an increasing body of evidence that histamine also elicits pro-inflammatory and immune-modulatory effects, which might be of pathophysiological relevance. The findings of histamine receptors expressed on a variety of immune and nonimmune cells suggest a much wider and more critical role of this mediator in allergic disease, than is considered presently. Consequently, it is likely that antihistamines have a wider impact on allergic inflammation, and that effects on immune cells which have been linked to nonreceptor mediated pathways so far, may actually be receptor-dependent. This review aims to give an overview on a currently emerging new understanding of the role of histamine in allergic disease.

Histamine receptors

The effects of histamine arise from its interaction with one of at least three subclasses of specific histamine receptors, H₁, H₂ and H₃ (20,21). The histamine receptors are G protein-coupled receptors located on various histamine responsive target tissues and cells.

H₁ receptors are preferentially stimulated by 2-methylhistamine, which results in the activation of

phospholipase C and subsequently increased concentrations of the secondary messengers inositol-1,4,5-triphosphate (IP₃) and intracellular calcium (20–23), involved in signal transduction and potentiation of specific biologic effects. In contrast, studies of H₂ and H₃ receptors have suggested that these are stimulated preferentially by 4-methylhistamine and (R/N)- α -methylhistamine, respectively. Activation of these receptors is also associated with increases in IP₃ and intracellular calcium concentrations (20).

The use of more recently developed molecular cloning techniques, however, has demonstrated that other novel histamine receptors are also expressed in addition to the classical H₁, H₂ and H₃ receptors (24–26). Utilizing sequence analysis data from the human genomic database, Oda and colleagues (25) have cloned and characterized a novel orphan G-protein-coupled receptor, GPRv53. This receptor has the highest homology with the H₃ receptor, among all the known G-protein-coupled receptors, and possesses histamine binding and receptor activating/inhibiting features similar to the H₃ receptor. Analysis of tissues/cells expressing the GPRv53 receptor, however, suggests that this receptor is localized in peripheral blood leukocytes, spleen, thymus and colon, but not the brain, to which the expression of H₃ receptor is restricted. These findings suggest that there may be heterogeneity within the H₃ receptor. Similarly, Nakamura and colleagues have recently cloned the histamine H₄ receptor (HH4R) from human leukocyte cDNA (26). These studies demonstrated that the HH4R receptor had about 40% amino acid sequence homology, compared with the H₃ receptor, and like the GPRv53 receptor the HH4R receptor was also expressed in a variety of peripheral tissues, but not the brain. The specific function of these receptors is not clear and remains to be evaluated (Table 1).

Classical effects of histamine

In allergic disease, the interaction of histamine with the histamine H₁-receptor, mediates a variety of classical pathophysiological effects, including vascular permeability, smooth muscle contraction, vasodilatation and flushing, mucus secretion and pruritus, which either singly or in conjunction with one another lead to bronchial obstruction in asthma; nasal blockage, sneezing, itching and discharge in rhinitis; and itchy skin wheals/flare in urticaria (1,27). Histamine, acting via the H₁ receptor is also an important neurotransmitter in the central nervous system (28). Although the activation of H₂ receptors is primarily important in the augmentation of gastric acid secretion from parietal cells, it also contributes to increases in respiratory mucus secretion, nasal airways resistance and smooth muscle relaxation in the lower airways (20,27,29,30). In

contrast, the H₃ receptors have primarily been implicated in the autocrine regulation of histamine synthesis and release from nerve tissue (27). The demonstration that H₃ receptors are expressed in postganglionic cholinergic nerves in human bronchi (31) has prompted the hypothesis that stimulation of these receptors may act as a protective mechanism against excessive bronchoconstriction.

Pro-inflammatory effects of histamine

Although the classical effects of histamine, expressed at the organ level, are generally well documented and much emphasized in allergic disease, this is not the case for the increasing amount of evidence which suggests that histamine also directly or indirectly influences the activity of several inflammatory/effector/immunologic cell types involved in the pathogenesis of allergic disease. Consequently, it is likely that histamine plays a much wider and critical role as a pro-inflammatory mediator in allergic disease, than is considered presently. Indeed, several studies have demonstrated that histamine receptors are expressed on basophils, mast cells, neutrophils, eosinophils, lymphocytes, macrophages, epithelial cells and endothelial cells, and therefore is likely to modulate the function of these cells.

Basophils and mast cells

Histamine receptor binding studies with specific receptor antagonists have demonstrated that basophils express predominantly H₂ receptors and that these are involved in the regulation of IgE-induced histamine release, as indicated by enhanced histamine release in the presence of anti-IgE and cimetidine (a H₂ receptor antagonist), but not in the presence of anti-IgE and thioperamide (a H₃ receptor antagonist) (32–34). Studies of partially purified human conjunctival mast cells, which are thought to be similar to human connective tissue mast cells in their response to a variety of secretagogues, have indicated the expression of H₁, H₂ and H₃ receptors, of which the H₁-receptors appear to be most active with respect to mediator release from these cells (35,36).

Neutrophils

Neutrophils have been shown to express H₁ and H₂ receptors (37,38). Functional studies have suggested that the effects of histamine on neutrophils are also mostly inhibitory and mediated via H₂ receptors. Autologous serum-induced chemotaxis of neutrophils in normal and atopic subjects is inhibited by histamine in a dose-dependent manner *in vitro*, and this inhibition is more marked in atopic individuals (39). Furthermore, incubation of neutrophils from these individuals with

Table 1 Characteristic features of histamine receptors

Histamine receptor type	G-protein type coupled	Preferential agonist	Location	Effect
H ₁	Gq-protein	2-methylhistamine	Blood vessels, smooth muscle, heart, CNS	↑ vascular permeability ↑ airway smooth muscle contraction ↑ vasodilatation and flushing ↑ mucus secretion ↑ pruritus, neurotransmission in CNS
H ₂	Gs-protein	4(5)-methylhistamine	Gastric mucosa, heart, uterus, CNS	↑ gastric acid secretion ↑ respiratory mucus secretion ↑ nasal airways resistance, smooth muscle relaxation in the lower airways
H ₃	Gi-protein	(R/N)- α -methyl-histamine	Airways, GI tract, CNS	↓ histamine synthesis and release from nerve tissue ↓ neurotransmitter release
H ₄ /GPRv53	Gi-protein	N- α -methylhistamine	Bone marrow, peripheral blood leukocytes, spleen, thymus, colon	?

cimetidine, but not promethazine, reverses the histamine-induced inhibition of neutrophil chemotaxis. Similarly, an *in vivo* study has demonstrated that administration of histamine by either infusion, subcutaneous injection or inhalation significantly decreased neutrophil chemotaxis in healthy volunteers (40). The effect of histamine inhalation was mimicked by inhalation of impromidine (H₂ agonist), but not by betahistidine (H₁ agonist), and blocked by prior treatment with oral cimetidine. Other studies have demonstrated that histamine, acting via H₂ receptor signalling, also inhibits the activation of neutrophils, as indicated by inhibition fMet-Leu-Phe induced superoxide (O₂⁻) formation, degranulation and membrane potential changes (41,42). The inhibitory effects of histamine and H₂ agonists could be reversed by treatment with cimetidine.

Eosinophils

Eosinophils also express H₁ and H₂ receptors, and in contrast to the inhibitory effect of histamine on basophils and neutrophils, the *in vitro* effect of histamine on eosinophils is generally stimulatory, at lower concentrations. Clark and colleagues (43) have demonstrated that while preincubation of eosinophils with 10⁻⁵M or higher concentrations of histamine inhibited the chemotactic response of eosinophils to endotoxin-activated serum (C5a), preincubation of eosinophils with a lower concentration of 10⁻⁶M histamine had the opposite effect, augmenting the C5a-stimulated eosinophil chemotaxis. Furthermore, H₂ and H₁ receptor antagonists, respectively, blocked these effects. The expression of a novel H₃ receptor, which may mediate the direct eosinophil chemotactic response towards histamine has also been reported (44). Although this receptor appears to have similar antagonist binding properties to those observed for the H₃ receptor found in the central nervous system (CNS), it does not bind (R/N)- α -methylhistamine with the same potency as histamine, suggesting differences between the characteristics and function of H₃ receptors

expressed in CNS and on the eosinophil. Other studies have demonstrated that histamine, acting via the H₁ receptor, also enhances eosinophil C3b receptor expression (45,46), a mechanism that may be of importance in the amplification of complement-dependent parasite killing. However, in a recent study, 0.1–50 μ M histamine was shown to inhibit eosinophil degranulation, as indicated by decreased release of C5a-mediated eosinophil peroxidase (EPO) (47). This study also demonstrated that selective H₂ receptor agonists produced an effect similar to that shown by histamine and that cimetidine, the H₂ receptor antagonist reversed this inhibitory effect of histamine. In contrast, treatment with neither mepyramine nor thioperamide (H₁ and H₃ receptor antagonists, respectively) significantly inhibited the C5a-induced release of EPO from eosinophils, suggesting the pivotal role of H₂ receptors in this respect. An association between histamine and eosinophil activity in allergic disease has also been demonstrated *in vivo* in patients with allergic rhinitis undergoing segmental allergen challenge, followed by airway sampling by BAL after 5 min and 48 h (48). Peripheral blood maximal histamine release in response to *in vitro* antigen challenge was also determined in each patient before segmental bronchoprovocation. The number of eosinophils in BAL samples collected after 48 h, in particular, were significantly increased and correlated with the maximal basophil histamine release noted for each individual, suggesting a direct causal relationship between basophilic mediator release and airway eosinophilia (Fig. 1).

Lymphocytes

Numerous studies on the expression of histamine receptors on lymphocytes and the effects mediated through these receptors have been published and more recently reviewed by Sachs and colleagues (49). These authors concluded that both H₁ and H₂ receptors are present on the lymphocytes, and although there are few data with respect to the functional significance of the H₁ receptors and the distribution of H₂ receptors on

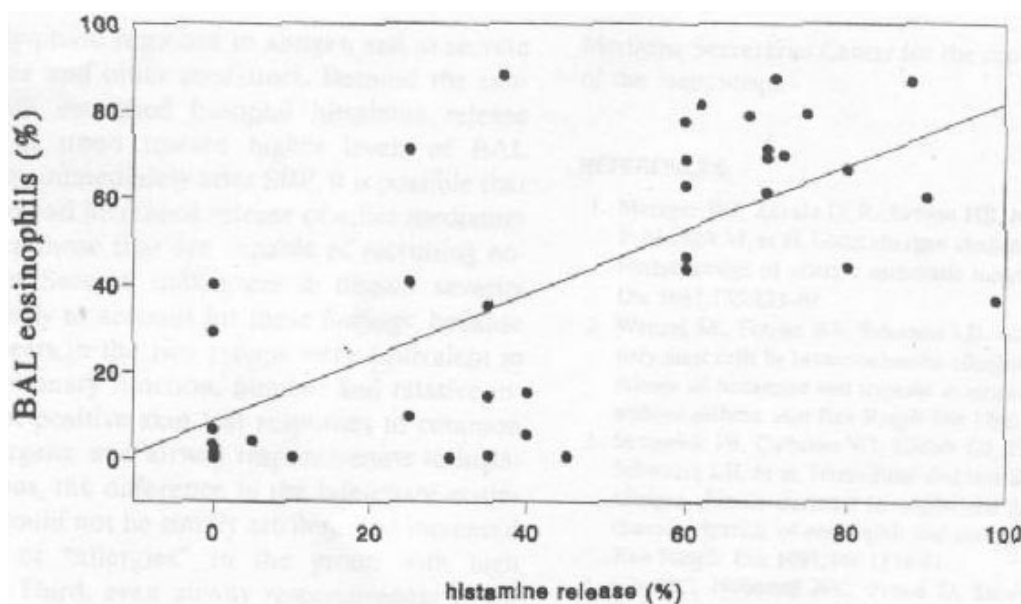


Figure 1. Correlation between histamine release and proportion of eosinophils in bronchoalveolar lavage (BAL) fluid obtained 48 h after antigen segmental bronchial provocation ($r = 0.67$, $P < 0.0001$, $n = 34$, Spearman's Rank test). (from Jarjour NN et al. 1997 – [47;] reprinted with permission).

different lymphocyte subsets, in general signalling via the H_1 receptor was associated with enhancement and signalling via the H_2 receptor with inhibition of lymphocyte responses. More recently, Jutel and colleagues (50) have demonstrated that Th1 and Th2 cells express distinct surface histamine receptor patterns (Th1 cells express predominantly H_1 receptors and Th2 cells express predominantly H_2 receptors), and that histamine enhances Th1-type responses and negatively regulates Th2-type responses, as indicated by increased release of tumour necrosis factor (TNF)- α and decreased release of IL-4 and IL-13, respectively. Furthermore, the differential response of these cells to histamine is a result of the type of intracellular signals generated by histamine stimulation. Whilst H_1 receptor signalling involves calcium-dependent phospholipase activation and generation of IP_3 , H_2 receptor signalling involves adenylate cyclase activation and cAMP formation. A receptor binding study of human peripheral blood lymphocytes has demonstrated that histamine trifluoromethyl-toluidine (HTMT) derivative lead to a two-phase increase in intracellular calcium and an increase in inositol phosphate production, of which the increase in calcium was competitively antagonized by high concentrations of histamine, but not by any of the classical H_1 , H_2 or H_3 receptor antagonists (51). These results suggest that there may be a specific binding site for HTMT on lymphocytes that is different to the three classic histamine receptors. Although, several functional studies suggest that histamine primarily modulates T-suppressor activity [e.g., delayed type hypersensitivity, cytotoxic T-lymphocyte-mediated target cell killing, cell-mediated lympholysis, and

natural killer activity] via H_2 receptor signalling (52), some studies suggest that stimulation of the H_2 receptors may also indirectly enhance the allergic cascade. It has been demonstrated that 10^{-6} - 10^{-4} M histamine inhibited Staphylococcal Enterotoxin A-induced synthesis of interferon (IFN)- γ and IL-2 and that these effects were reversed by treatment with cimetidine, but not by treatment with diphenhydramine (53). More recent studies have confirmed this finding by demonstrating that histamine inhibited lipopolysaccharide (LPS)-induced IFN- γ -gene expression from human peripheral blood mononuclear cells (PBMC) (54) and IFN- γ cytokine release human CD4+ T-cell clones, classified as either Th0, Th1 or Th2 on the basis of their IL-4 and IFN- γ secretion patterns (55). Histamine-induced inhibition of IFN- γ release was noted in Th1 clones, but not Th2 clones, and this effect was reversed by a H_2 , but not H_1 or H_3 , receptor antagonists. Furthermore, histamine has also been shown to directly increase the synthesis of the pro-inflammatory cytokines IL-1 β and IL-6 by lymphocytes, and anti-CD23- and anti-CD28-induced release of IL-4 and IL-5, but not IL-2 or IFN, from T cells can be inhibited by treatment with terfenadine (49).

Similarly, other studies have demonstrated that histamine leads to synthesis and release of a lymphocyte chemoattractant factor (LCF) from H_2 receptor bearing lymphocytes and to the release of two distinct types of lymphocyte migration inhibitory factors (LyMIFs) from a subset of only H_1 receptor bearing lymphocytes (56,57). It has been speculated that the production of LyMIFs resulting from lymphocyte H_1 receptor signalling may contribute to immobilization of effector

T lymphocytes chemokinetically attracted to certain inflammatory sites, with subsequent exacerbation of inflammation.

Monocytes and macrophages

Although there are comparatively few reports, some recent studies have demonstrated the presence of H₁ and H₂ histamine receptors on human monocytes and macrophages (58–61), suggesting that histamine may also modulate the activity of these cells in allergic disease. Indeed, differentiation of monocytes into macrophages leads to switching from H₂ to H₁ histamine receptors (58,60). Furthermore, histamine-induced H₁ receptor signalling induces the release of pro-inflammatory compounds such as TNF- α (58), prostaglandin D₂ (PGD₂ 59), and β -glucuronidase (61).

Epithelial cells

Cultured human bronchial epithelial cells express functionally active H₁ and H₂ receptors, as indicated by histamine-induced generation of cGMP and cAMP, respectively, and blockage of cGMP and cAMP release by treatment with pyrilamine and tiotidine (62). The expression of H₁ receptors has also recently been demonstrated on cultured human nasal (63) and ocular (64) epithelial cells, suggesting that histamine may actively influence the activity of these cells as well. Indeed, the role of epithelial cells as modulators of inflammation, particularly in allergic airway disease, has been the subject of much discussion. Recent reviews have documented that bronchial and nasal epithelial cells can synthesize and release a large variety of biologically active mediators [including arachidonic acid metabolites, cell adhesion molecules, cytokines, endothelin, major histocompatibility complex class (MHC) II antigens, nitric oxide and neuropeptide-degrading enzymes] that influence the migration, activation and/or function of both inflammatory and structural cells involved in the pathophysiology of asthma and allergic rhinitis (65,66). An extensive study of the effects of histamine on mediator release from human bronchial epithelial cells showed that H₁ receptor activation with 2 mM histamine led to induction of cytoplasmic phospholipase A₂ mRNA, production of leukotriene B₄ (LTB₄), activation of the transcription factor IL-8 NF- κ B, and expression of IL-8 (67). Histamine-induced increase in LTB₄ was inhibited by incubation of the cells with specific 5-lipoxygenase-activating protein (FLAP) inhibitors and Zileuton, while expression of IL-8 was inhibited by diphenhydramine, and additionally FLAP inhibitors and Zileuton, suggesting a network of histamine-induced inflammatory mechanisms within the airways. Similarly, studies in human corneal/conjunctival epithelial cells have demonstrated that histamine stimulated the release of IL-6, IL-8 and GM-CSF from these cells

in a dose-dependent manner at physiologically and/or pathologically relevant concentrations (histamine EC₅₀s = 1.28–2.77 μ M), and that several H₁ receptor antagonists, but not ranitidine (H₂ antagonist) or thioperamide (H₃ antagonist), inhibited this cytokine release (68–70). In one study, increased expression of class II antigens (HLA-DR) and intercellular adhesion molecule-1 (ICAM-1) was noted on bronchial epithelial cells following treatment with histamine (71).

Endothelial cells

In view of the strategic positioning of endothelial cells at the blood–tissue interface, the contribution of these cells to the pathophysiology of allergic disease has been extensively investigated. The principal functions of endothelial cells that contribute to the pathophysiology associated with airway inflammation, in particular, can be broadly classified as: (i) adhesion molecule expression; (ii) chemokine production; (iii) alteration of endothelial permeability; and (iv) production of vasoactive mediators (72). Increased expression of adhesion molecules [such as P-selectin, E-selectin, VCAM-1, ICAM-1, ICAM-2 and PECAM-1] and leukocyte chemoattractants [such as IL-8, RANTES and eotaxin] trigger leukocyte recruitment and adhesion within the blood vessels, and together with vascular changes results in increased plasma leakage and transendothelial migration of the leukocytes to the site of inflammation in the underlying tissue.

The effect of histamine on vascular permeability has been well documented and is a consequence of H₁ receptor signalling, which results in the contraction of F-actin fibres of the endothelial cytoskeleton and subsequent formation of gaps in the postcapillary venules and extravasation of macromolecules (72).

In vitro studies have clearly demonstrated that functionally active H₁ and/or H₂ receptors are expressed on human endothelial cells present in a variety of tissues, including the airway mucosa, eye, skin, brain and umbilical vein (63,73–77), of which human umbilical vein endothelial cells (HUVEC) have been the most widely investigated in mechanistic studies, likely as a consequence of comparatively easier and greater access to these cells. A recent study has indicated that histamine itself regulates the expression of histamine receptor subtypes on endothelial cells and therefore influences the overall inflammatory response in allergic disease (78). The levels of mRNA for both the H₁ and H₂ receptors were downregulated by histamine, of which the effect on H₂ receptor mRNA was rapid and long lasting (24 h), compared with a less-pronounced, transient and shorter lasting (12 h) effect on the H₁ receptor mRNA. Moreover, the H₂ receptor mRNA was mainly downregulated as a result of H₁ receptor protein activation.

Histamine-induced receptor signalling on the

endothelial cells also directly modulates inflammatory changes in these cells. Treatment of HUVEC cultures with 10^{-4} M or 10^{-5} M histamine results in the release of lipophilic neutrophil chemoattractant activity from these cells, an effect blocked by cimetidine, but not diphenhydramine (79). Histamine (0.1–1 mM) also leads to a biphasic pattern of neutrophil adhesion to these cultures, which is mimicked by H_1 and H_2 receptors agonists, whereas H_3 agonists do not appear to have any effect (80). A detailed investigation of the underlying signal transduction mechanisms suggests that either histamine or H_1 or H_2 agonist-stimulated adhesion of neutrophils to endothelial cells involves activation of phospholipase C, nitric oxide synthase isozymes and guanylate cyclase, because inhibition of these enzymes with specific inhibitors can significantly decrease this adhesion. Activation of adenylate cyclase, however, decreases neutrophil adhesion. Histamine also stimulates eosinophil adhesion to HUVEC by directly upregulating and augmenting IL-4 and TNF- α -induced expression of VCAM-1 on the HUVEC (81). In contrast to neutrophil adhesion, eosinophil adhesion appears to be modulated by signalling via H_1 and H_3 receptors, because mepyramine and thioperamide, but not cimetidine, inhibited the histamine-induced VCAM-1 expression on HUVEC (Fig. 2).

Despite the obvious paucity of such data *in vivo*, several animal studies have demonstrated that super-

fusion of the mesentery with 10^{-7} – 10^{-3} M histamine induces leukocyte rolling and adhesion in postcapillary venules (82–85). The effect of histamine is mediated via both H_1 and H_2 receptor signalling and modulation of P-selectin on endothelial cells in the mesentery.

Conclusion

It is clear that during inflammation, histamine is released from basophils and mast cells and contributes to the course of inflammatory processes, either by enhancing or inhibiting inflammatory reactions, depending on its concentration and stimulation of either the H_1 or H_2 receptor subtype. Evidence suggests that low concentrations of histamine acting via H_1 receptors appear to have stimulatory effects on inflammatory cells, whereas high concentrations acting via the H_2 receptors have an inhibitory effect. Indeed, based on some experimental evidence, an early hypothesis proposed that airway hyper-reactivity to histamine in asthmatics was owing to an overall deficiency of histamine H_2 receptors on leukocytes and airway smooth muscles, or a physiological imbalance of histamine H_1 - and H_2 -receptors in the airways (86).

However, with regard to the pathophysiology of allergic disease, it is noteworthy that histamine directly enhances the activity of eosinophils, Th2 lymphocytes,

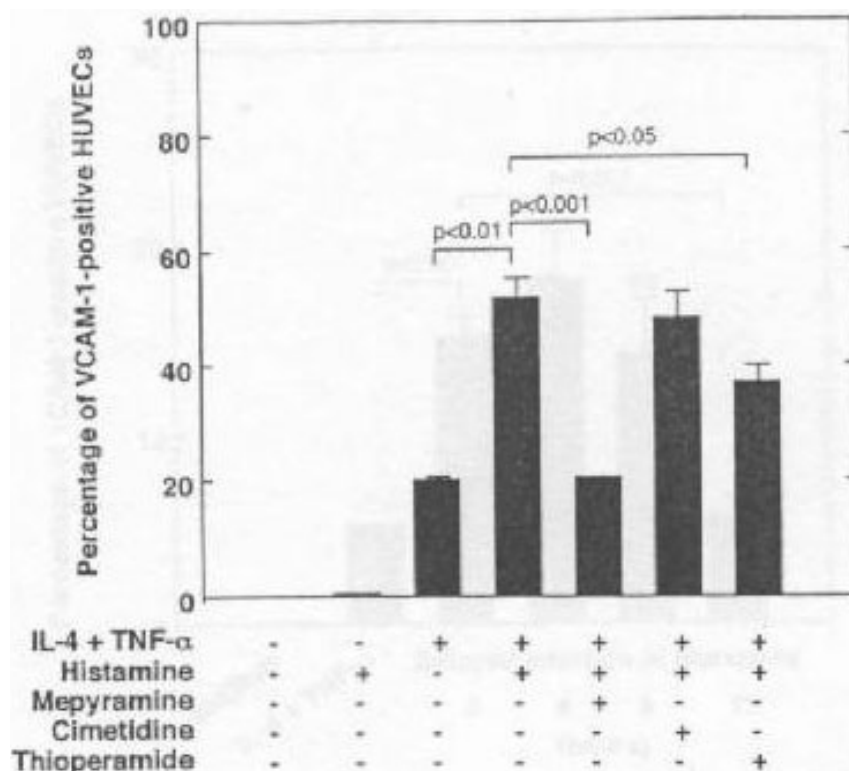


Figure 2. Selective histamine receptor antagonists inhibit VCAM-1 expression in interleukin (IL)-4 plus tumour necrosis factor (TNF)- α -stimulated HUVECs. (from Saito H *et al.* 1996 – [80]; reprinted with permission).

macrophages, epithelial and endothelial cells, all of which are known to play a role in allergic inflammation. In contrast, histamine inhibits the activity of basophils and neutrophils, and decreases the release of IFN- γ and IL-2 from Th1 clones, but not Th2 clones. Thus, in view of the effector cell function of eosinophils and Th2 lymphocytes in allergic diseases, it is likely that histamine plays a more prominent pro-inflammatory role than is appreciated hitherto.

In view of the growing evidence of both direct and indirect effects of histamine on inflammatory/immunologic/effector cells, it is likely that many of the reported anti-inflammatory/allergic effects of the newer second generation antihistamines actually do result as a consequence of their effects at the H₁ receptor, rather than at some nonhistamine receptors, as has been speculated by some investigators (87,88). It has been suggested that in consequence of the basic structure and generally cationic amphiphilic nature of antihistamines, many of the anti-inflammatory/allergic effects observed with these compounds are nonspecific and result from an ionic association with cell membranes, decreased Ca²⁺ binding, and inhibition of membrane associated enzymes, rather than from blockade and antagonism of H₁ receptor signalling. Furthermore, despite extensive documentation of the anti-inflammatory/allergic effects of antihistamines, the clinical relevance of these effects has been questioned mostly because many of these effects have been demonstrated *in vitro* at high concentrations of the compounds investigated, and also there are comparatively few studies showing a correlation between clinical efficacy and specific anti-inflammatory/allergic effects (87).

However, a recent editorial by Church (24) has re-evaluated the putative underlying mechanisms and clinical relevance of the anti-inflammatory effects of antihistamines in view of more recent data. Studies in SV40-immortalized cells have shown that transient expression of the human histamine H₁-receptor results in an agonist-independent activation of the biochemical cascade involving the secondary messenger IP₃ and that this constitutive histamine receptor activity can be decreased by treatment with several H₁-antihistamines. It has been suggested that this indicates existence of the

histamine H₁-receptor as an equilibrium between its inactive and active forms. Because the H₁-antihistamines can downregulate constitutive histamine H₁-receptor activity, then it is likely that these compounds act as inverse agonists which combine with and stabilize the inactive form of the receptor shifting the equilibrium towards the active form, rather than H₁-antagonists. Furthermore, because agonist-independent activation has been shown to result in NF κ B activation in SV40 cells, and low concentrations of some H₁-antihistamines can downregulate the expression of this transcription factor in parallel with inhibiting the generation of a variety of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8, TNF- α and GM-CSF), then it is likely that the antihistamines exert their anti-inflammatory effects by both receptor-dependent and receptor-independent mechanisms. Compared with receptor-dependent mechanisms, the receptor-independent mechanisms are likely to require higher concentrations of the antihistamines in order to observe anti-inflammatory effects.

Whilst the receptor-independent anti-inflammatory effects of antihistamines are unlikely to be clinically relevant, as a consequence of the requirement for high drug concentrations, it has been suggested that the receptor-dependent effects of the antihistamines may actually be clinically relevant, although not as marked as the effects for corticosteroids. Indeed, there is now some evidence of an association between clinical efficacy and anti-inflammatory/allergic effects of an antihistamine in patients with seasonal allergic rhinitis whose treatment dosing regimen was modified from the recommended one of on-demand treatment to that of continuous treatment (89). In a study of infants sensitized to grass pollen or house dust mite, treatment with an antihistamine for 18 months was also shown to significantly reduce the incidence of asthma, compared with placebo (90). Further studies are clearly needed to determine precisely the receptor/s involved in expressing the anti-inflammatory/allergic effects of antihistamines in order to gain a better understanding of the true therapeutic index for this class of compounds and their use in the management of allergic disease.

References

1. WHITE MV. The role of histamine in allergic diseases. *J Allergy Clin Immunol* 1990;**86**:599–605.
2. GREAVES MW, SABROE RU. Allergy and the skin. I – Urticaria *Br Med J* 1998;**316**:1147–1150.
3. FRIEDMANN PS. Assessment of urticaria and angio-oedema. *Clin Exp Allergy* 1999;**29**:109–112.
4. WHITE MV, SLATER J, KALINER M. Histamine and asthma. *Am Rev Respir Dis* 1987;**135**:1165–1176.
5. BARNES PJ, BROWN MJ. Venous plasma histamine in exercise- and hyperventilation-induced asthma in man. *Clin Sci* 1981;**61**:159–162.
6. HOWARTH P, DURHAM S, LEE T, KAY B, CHURCH M, HOLGATE S. Influence of albuterol, cromolyn sodium and ipratropium bromide on the airway and circulating mediator responses to allergen provocation in asthma. *Am Rev Respir Dis* 1985;**132**:986–992.
7. BUSSE WW, SWENSON CA. The relationship between plasma histamine concentrations and bronchial obstruction to antigen challenge in allergic rhinitis. *J Allergy Clin Immunol* 1989;**84**:658–666.

8. 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**:83–87.
9. BROIDE DH, GLEICH GJ, CUOMO AJ et al. Evidence of ongoing mast cell and eosinophil degranulation in symptomatic asthma airway. *J Allergy Clin Immunol* 1991;**88**:637–648.
10. TOGIAS A, NACLERIO R, PROUD D et al. Mediator release during nasal provocation: a model to investigate pathophysiology of rhinitis. *Am J Med* 1985;**79**:26–33.
11. NACLERIO R, PROUD D, TOGIAS A et al. Inflammatory mediators in late antigen-induced rhinitis. *N Eng J Med* 1985;**313**:65–70.
12. ANDERSON M, NOLTE H, OLSSON M, STAHL SKOV P, PIKORIN U. Measurement of histamine in nasal lavage fluid: comparison of a glass fibre based fluorimetric method with two radioimmunoassays. *J Allergy Clin Immunol* 1990;**86**:815–820.
13. MCLEAN J, MATHEWS K, SOLOMON W, BRAYTON P, CIARKOWSKI A. Effect of histamine and methacholine on nasal airway resistance in atopic and non-atopic subjects. *J Allergy Clin Immunol* 1977;**59**:165–170.
14. DOYLE W, BOEHM S, SKONER D. Physiologic responses to intranasal dose–response challenges with histamine, methacholine, bradykinin and prostaglandin in adult volunteers with and without nasal allergy. *J Allergy Clin Immunol* 1990;**86**:924–935.
15. TOGIAS A. Unique mechanistic features of allergic rhinitis. *J Allergy Clin Immunol* 2000;**105**:S599–S604.
16. KAPLAN AP, BEAVAN MA. *In vivo* studies of the pathogenesis of cold urticaria, cholinergic urticaria and vibration-induced swelling. *J Invest Dermatol* 1976;**67**:327–332.
17. ORMEROD AD. Urticaria – Pathophysiology. In: HOLGATE, ST, CHURCH, MK, eds. *Allergy*. London: Mosby Wolfe, 1995;21.1–21., 12.
18. ATKINS PC, SCHWARTZ LB, ADKINSON NF, VON ALLMEN C, VALENZANO M, ZWEIMAN B. *In vivo* antigen-induced cutaneous mediator release. simultaneous comparisons of histamine, tryptase and prostaglandin D₂ release and the effect of oral corticosteroid administration. *J Allergy Clin Immunol* 1990;**86**:360–370.
19. ATKINS PC, VON ALLMEN C, VALENZANO M, OLSON R, SHALIT M, ZWEIMAN B. Determinants of *in vivo* histamine release in cutaneous allergic reactions in humans. *J Allergy Clin Immunol* 1990;**86**:371–379.
20. HILL SJ. Distribution, properties, and functional characteristics of three classes of histamine receptors. *Pharmacol Rev* 1990;**42**:45–83.
21. HAAKSMA EEJ, LEURS R, TIMMERMAN H. Histamine receptors: subclasses and specific ligands. *Pharmacol Ther* 1990;**47**:73–104.
22. LI H, CHOE N, WRIGHT A, ADLER K. Histamine provokes turnover of inositol phospholipids in guinea pig and human airway epithelial cells via an H₁-receptor/G protein-dependent mechanism. *Am J Respir Cell Mol Biol* 1995;**12**:416–424.
23. MARMY N, MOTTAS J, DURAND J. Signal transduction in smooth muscle cells from human airways. *Respir Physiol* 1993;**91**:295–306.
24. CHURCH MK. H₁-antihistamines and inflammation. *Clin Exp Allergy* 2001;**31**:1341–1343.
25. 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**:36781–36786.
26. NAKAMURA T, ITADANI H, HIDAKA Y, OHTA M, TANAKA K. Molecular cloning and characterisation of a new human histamine receptor, HH4R. *Biochem Biophys Res Commun* 2000;**279**:615–620.
27. HOWARTH PH. Histamine and asthma: an appraisal based on specific H₁-receptor antagonism. *Clin Exp Allergy* 1990;**20S**:31–41.
28. PANULA P, AIRAKSINEN MS, PIROVOLA U, KOTILAINEN E. A histamine-containing neuronal system in human brain. *Neuroscience* 1990;**34**:127–132.
29. KNIGHT DA, STEWART GA, THOMPSON PJ. Histamine tachyphylaxis in human airway smooth muscle. The role of H₂ receptors and the bronchial epithelium. *Am Rev Respir Dis* 1992;**146**:137–140.
30. TAMAOKI J, NAKATA J, TAKEYAMA K, CHIYOTANI A, KONNO K. Histamine H₂ receptor-mediated airway goblet secretion and its modulation by histamine-degrading enzymes. *J Allergy Clin Immunol* 1997;**99**:233–238.
31. ICHINOSE M, BELVISI MG, BARNES PJ. Histamine H₃ receptors inhibit neurogenic microvascular leakage in airways. *J Appl Physiol* 1990;**68**:21–25.
32. TEDESCHI A, LORINI M, ARQUATI M, MIADONNA A. Regulation of histamine release from human basophil leukocytes. role of H₁, H₂ and H₃ receptors. *Allergy* 1991;**46**:626–631.
33. BULL HA, COURTNEY PF, BUNKER CB, RUSTIN MH, PEARCE FL, DOWD PM. Basophil mediator release in atopic dermatitis. *J Invest Dermatol* 1993;**100**:305–309.
34. KLEINE-TEBBE J, SCHRAMM J, BOLZ M, LIPP R, SCHUNACK W, KUNKEL G. Influence of histamine H₃-antagonists on human leukocytes. *Agents Actions* 1990;**30**:137–139.
35. YANNI JM, MILLER ST, GAMACHE DA, SPELLMAN JM, XU S, SHARIF NA. Comparative effects of topical ocular anti-allergic drugs on human conjunctival mast cells. *Ann Allergy Asth Immunol* 1997;**79**:541–545.
36. SHARIF NA, XU S, MILLER ST, GAMACHE DA, YANNI JM. Characterization of the ocular antiallergic and antihistaminic effects of olopatadine (AL-4943A), a novel drug for treating ocular allergic diseases. *J Pharmacol Exp Therap* 1996;**278**:1252–1261.
37. WESTCOTT S, KALINER M. Histamine H-1 binding site on human polymorphonuclear leukocytes. *Inflammation* 1983;**7**:291–300.
38. GESPACH C, ABITA JP. Human polymorphonuclear neutrophils. Pharmacological characterisation of histamine receptors mediating the elevation of cyclic AMP. *Mol Pharmacol* 1982;**21**:78–85.
39. RADERMECKER M, MALDAGUE MP. Depression of neutrophil chemotaxis in atopic individuals. An H₂ histamine receptor response. *Int Arch allergy Appl Immunol* 1981;**65**:144–152.
40. BURY TB, CORHAY JL, RADERMECKER MP. Histamine-induced inhibition of neutrophil chemotaxis and T-lymphocyte proliferation in man. *Allergy* 1992;**47**:624–629.
41. SELIGMANN BE, FLETCHER MP, GALLIN JI. Histamine modulation of human neutrophil oxidative metabolism, locomotion, degranulation, and membrane potential changes. *J Immunol* 1983;**130**:1902–1909.
42. BURDE R, SEIFERT R, BUSCHAUER A, SCHULTZ G. Histamine inhibits activation of human neutrophils and HL-60 leukemic cells via H₂-receptors. *Naunyn-Schmiedeberg Arch Pharmacol* 1989;**340**:671–678.
43. CLARK RA, SANDLER JA, GALLIN JI, KAPLAN AP. Histamine modulation of eosinophil migration. *J Immunol* 1977;**118**:137–145.
44. RAIBLE DG, LENAHEAN T, FAYVILEVICH Y, KOSINSKI R, SCHULMAN ES. Pharmacological characterization of a novel histamine receptor on human eosinophils. *Am J Respir Crit Care Med* 1994;**149**:1506–1511.
45. ANWAR AR, KAY AB. The ECF-A tetrapeptides and histamine selectively enhance human eosinophil complement receptors. *Nature* 1977;**269**:522–524.

46. ANWAR AR, KAY AB. H₁-receptor dependence of histamine-induced enhancement of human eosinophil C3b rosettes. *Clin Exp Immunol* 1980;**42**:196–199.
47. EZEAMUZIE CI, PHILIPS E. Histamine H₂ receptors mediate the inhibitory effect of histamine on human eosinophil degranulation. *Br J Pharmacol* 2000;**131**:482–488.
48. JARJOUR NN, SEDGWICK JB, SWENSEN CA, BUSSE WW. Late allergic airway response to segmental bronchopulmonary provocation in allergic subjects is related to blood basophil histamine release. *J Allergy Clin Immunol* 1997;**99**:87–93.
49. SACHS B, HERTL M, MERK HF. Histamine receptors on lymphocytes: distribution and functional significance. *Skin Pharmacol Appl Skin Physiol* 2000;**13**:313–323.
50. JUTEL M, KLUNKER S, AKDIS M et al. Histamine upregulates Th1 and downregulates Th2 responses due to different patterns of surface histamine 1 and 2 receptor expression. *Int Arch Allergy Immunol* 2001;**124**:190–192.
51. QUI R, MELMON KL, KHAN MM. Effects of histamine trifluoromethyl-toluidine (HTMT) on intracellular calcium in human lymphocytes. *J Pharmacol Exp Therap* 1990;**253**:1245–1252.
52. ROCKLIN RE. Histamine and H₂ Antagonists in Inflammation and Immunodeficiency. New York: Marcel Dekker, 1990.
53. CARLSSON R, DHOLSTEN M, SJOGREN HO. Histamine modulates the production of interferon-gamma and interleukin-2 by mitogen-activated human mononuclear blood cells. *Cellular Immunol* 1985;**96**:104–112.
54. HORVATH BV, SZALAI C, MANDI Y, et al. Histamine and histamine-receptor antagonists modify gene expression and biosynthesis of interferon gamma in peripheral human blood mononuclear cells and in CD19-depleted cell subsets. *Immunol Lett* 1999;**70**:95–99.
55. LAGIER B, LEBEL B, BOUSQUET J, PENE J. Different modulation by histamine of IL-4 and interferon-gamma (IFN-gamma) release according to the phenotype of human Th0, Th1 and Th2 clones. *Clin Exp Immunol* 1997;**108**:545–551.
56. CENTER DM, CRUIKSHANK WW, BERMAN JS, BEER DJ. Functional characteristics of histamine receptor-bearing mononuclear cells. I. Selective production of lymphocyte chemoattractant lymphokines with histamine as a ligand. *J Immunol* 1983;**131**:1854–1859.
57. BERMAN JS, MCFADDEN RG, CRUIKSHANK WW, CENTER DM, BEER DJ. Functional characteristics of histamine receptor-bearing mononuclear cells. II. Identification and characterization of two histamine-induced lymphokines that inhibit lymphocyte migration. *J Immunol* 1984;**133**:1495–1504.
58. WANG KY, ARIMA N, HIGUCHI S, et al. Switch of histamine receptor expression from H₂ to H₁ during differentiation of monocytes into macrophages. *FEBS Lett* 2000;**473**:345–348.
59. PYNART G, GROOTEN J, VAN DEVENTER SJ, PEPPIENBOSCH MP. Cysteinyl leukotrienes mediate histamine hypersensitivity ex-vivo by increasing histamine receptor numbers. *Mol Med* 1999;**5**:685–692.
60. MIROSSAY L, CHASTRE E, CALLEBERT J, et al. Histamine H₂ receptors and histidine decarboxylase in normal and leukemic human monocytes and macrophages. *Am J Physiol* 1994;**267**:R602–R611.
61. CLUZEL M, LIU MC, GOLDMAN DW, UNDEM BJ, LICHTENSTEIN LM. Histamine acting on histamine type : receptor increases beta-glucuronidase from human lung macrophages. *Am J Respir Cell Mol Biol* 1990;**3**:603–609.
62. DEVALIA JL, DAVIES RJ. Human nasal and bronchial epithelial cells in culture. An overview of their characteristics and function. *Allergy Proc* 1991;**12**:71–79.
63. HAMANO N, TERADA N, MAESAKO K, et al. Expression of histamine receptors in nasal epithelial cells and endothelial cells – the effects of sex hormones. *Int Arch Allergy Immunol* 1998;**115**:220–227.
64. SHARIF NA, XU SX, MAGNINO PE, PANG IH. Human conjunctival epithelial cells express Histamine-1 receptors coupled to phosphoinositide turnover and intracellular calcium mobilisation. Role in ocular allergic and inflammatory diseases. *Exp Eye Res* 1996;**63**:169–178.
65. DEVALIA JL, WANG JH, DAVIES RJ. Airway epithelial cells. In: *Cellular Mechanisms in Airway Inflammation*. PAGE, CP, BANNER, KH, SPINA, D, , eds. Basel: Birkhäuser-Verlag, 2000;245–262.
66. DEVALIA JL, RUSZNAK C, DAVIES RJ. Epithelial cell dysfunction in rhinitis. In: *Asthma and Rhinitis*, 2nd edn. BUSSE, WW, HOLGATE, ST, , eds. London: Blackwell Science Ltd., 2000;841–854.
67. AOKI Y, QIU D, ZHAO GH, KAO PN. Leukotriene B₄ mediates histamine induction of NF-κB and IL-8 in human bronchial epithelial cells. *Am J Physiol-Lung Cell Mol Physiol* 1998;**274** 6 (18–16): , L1030–, L1039.
68. SHARIF NA, WIERNAS TK, GRIFFIN BW, DAVIS TL. Pharmacology of [3H]-pyrilamine binding and of the histamine-induced inositol phosphates generation, intracellular Ca²⁺ mobilisation and cytokine release from human corneal epithelial cells. *Br J Pharmacol* 1998;**125**:1336–1344.
69. WEIMER LK, GAMACHE DA, YANNI JM. Histamine-induced cytokine secretion from human conjunctival epithelial cells: inhibition by the histamine H₁ antagonist emedastine. *Int Arch Allergy Immunol* 1998;**115**:288–293.
70. YANNI JM, WEIMER LK, SHARIF NA, XU SX, Gamache DA, Spellman JM. Inhibition of histamine-induced human conjunctival epithelial cell responses by ocular allergy drugs. *Arch Ophthalmol* 1999;**117**:643–647.
71. VIGNOLA AM, CAMPBELL AM, CHANEZ P, et al. Activation by histamine of bronchial epithelial cells from non-asthmatic subjects. *Am J Respir Cell Mol Biol* 1993;**9**:411–417.
72. BURKE-GAFFNEY A, HELLEWELL PG. Contribution of endothelial cells to airway inflammation. In: *Cellular Mechanisms in Airway Inflammation*. PAGE, CP, BANNER, KH, SPINA, B, , eds. Basel: Birkhäuser-Verlag, 2000;223–244.
73. OKAYAMA M, BARANIUK JN, HAUSFELD JN, MERIDA M, KALINER MA. Characterization and autoradiographic localization of histamine H₁ receptors in human nasal turbinates. *J Allergy Clin Immunol* 1992;**89**:1144–1150.
74. CRAWFORD KM, MACCALLUM DK, ERNST SA. Agonist-induced Ca²⁺ mobilization in cultured bovine and human corneal endothelial cells. *Current Eye Res* 1993;**12**:303–311.
75. KOIZUMI H, OHKAWARA A. H₂ histamine receptor-mediated increase in cultured human keratinocytes. *J Dermatol Sci* 1999;**21**:127–132.
76. JANSEN-OLESEN I, OTTOSON A, CANTERA L, et al. Role of endothelium and nitric oxide in human cranial arteries and detection of mRNA encoding H₁- and H₂-receptors by RT-PCR. *Br J Pharmacol* 1997;**121**:41–48.
77. 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.
78. SCHAEFER U, SCHMITZ V, SCHNEIDER A, NEUGEBAUER E. Histamine-induced homologous and heterologous regulation of histamine receptor subtype mRNA in cultured endothelial cells. *Shock* 1999;**12**:309–315.

79. FARBER HW, WELLER PF, ROUNDS S, BEER DJ, CENTER DM. Generation of lipid neutrophil chemoattractant activity by histamine-stimulated cultured endothelial cells. *J Immunol* 1986;**137**:2918–2924.
80. SCHAEFER U, SCHNEIDER A, RIXEN D, NEUGEBAUER E. Neutrophil adhesion to histamine stimulated cultured endothelial cells is primarily mediated via activation of phospholipase C and nitric oxide synthase isozymes. *Inflammation Res* 1998;**47**:256–264.
81. SAITO H, SHIMIZU H, MITA H, MAEDA Y, AKIYAMA K. Histamine augments VCAM-1 expression in IL-4 and TNF α -stimulated human umbilical vein endothelial cells. *Int Arch Allergy Immunol* 1996;**111**:126–132.
82. KUBES P, KANWAR S. Histamine induces leukocyte rolling in post-capillary venules – a P-selectin-mediated event. *J Immunol* 1994;**152**:3570–3577.
83. LEY K. Histamine can induce leukocyte rolling in rat mesenteric venules. *Am J Physiol* 1994;**267** (Heart Circ Physiol 36) H1017–H1023.
84. ASAKO H, KUROSE I, WOLF R, et al. Role of H1 receptors and P-selectin in histamine-induced leukocyte rolling and adhesion in post-capillary venules. *J Clin Invest* 1994;**93**:1508–1515.
85. 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**:390–399.
86. CHAND N. Is airway hyperactivity in asthma due to histamine H2-receptor deficiency? *Med Hypotheses* 1980;**6**:1105–1112.
87. CHURCH MK. Non H₁-receptor effects of antihistamines. *Clin Exp Allergy* 1999;**29**:39–48.
88. SIMONS FER. Antihistamines in rhinitis and asthma. In: *Asthma and Rhinitis*, 2nd edn. BUSSE, WW, HOLGATE, ST, , eds. London: Blackwell Science Ltd., 2000;1643–1659.
89. CIPRANDI G, PASSALACQUA G, MINCARINI M, RICCA V, CANONICA GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;**79**:507–511.
90. ALLERGIC FACTORS ASSOCIATED WITH THE DEVELOPMENT OF ASTHMA and THE INFLUENCE OF CETIRIZINE IN A DOUBLE-BLIND, RANDOMISED PLACEBO-CONTROLLED TRIAL: first results of ETAC. Early treatment of the atopic child. *Pediatr Allergy Immunol* 1998;**9**:116–124.