

The histamine-cytokine network in allergic inflammation

Gianni Marone, MD, Francescopaolo Granata, MD, Giuseppe Spadaro, MD, Arturo Genovese, MD, and Massimo Triggiani, MD, PhD *Naples, Italy*

Histamine is synthesized and released by human basophils, mast cells, and neurons. Its pleiotropic effects are mediated by the activation of 4 receptors: H₁, H₂, H₃, and H₄. With the advent of selective antagonists (the antihistamines widely used to treat allergic disorders), the H₁-receptor was the first member of the receptor family to be pharmacologically defined. Increasing evidence indicates that, in addition to exerting immediate vascular and bronchial responses, histamine might modulate the immune reaction by interacting with T cells, macrophages, basophils, eosinophils, and monocytes. We have shown that, *in vitro*, histamine induces a concentration-dependent release of IL-6 and β -glucuronidase from macrophages isolated from the human lung parenchyma. These effects are inhibited by fexofenadine, an H₁-receptor antagonist, but not by ranitidine, an H₂-receptor antagonist. This observation raises the possibility that long-term treatment with fexofenadine might have beneficial effects on immune dysregulation and tissue damage/remodeling associated with histamine-mediated macrophage activation. (*J Allergy Clin Immunol* 2003;112:S83-8.)

Key words: Antihistamines, basophils, fexofenadine, histamine, macrophages, mast cells

Histamine is a primary amine synthesized and stored within secretory granules of human mast cells (~3 pg/cell) and basophils (~1 pg/cell).^{1,2} The first biologic activity of histamine was reported in 1910 when it was detected as a uterine stimulant in ergot extracts.^{3,4} Human basophils and mast cells (Fc ϵ RI⁺ cells) can be both immunologically and nonimmunologically stimulated to release histamine,⁵⁻⁷ which is one of a heterogeneous group of mediators released during injury or inflammatory reactions (eg, prostaglandins, kinins, leukotrienes, lipoxins, and platelet-activating factors).^{5,6,8,9} Histamine was implicated as a relevant mediator of allergic reactions after Dale and Laidlaw^{3,10} found that its effects mimicked those occurring during anaphylaxis. These investigators demonstrated that intravenous injection of histamine caused bronchoconstriction in guinea pigs and a shock-like syndrome in rabbits.

Abbreviation used

BAL: Bronchoalveolar lavage

Bouvet and Staub^{11,12} provided definitive proof that histamine plays a pivotal role as a mediator of allergic reactions by demonstrating that a series of compounds with antihistamine activity protected guinea pigs from anaphylaxis. However, the toxicity of these compounds precluded their clinical use in humans. In 1942, Halpern¹³ described antergan, the first antihistamine used clinically in humans. Many new antihistamines followed in rapid succession, and this class of compounds became widely used in the mid- to late 1940s.¹⁴

ROLE OF HISTAMINE IN ALLERGIC DISORDERS

There is now compelling evidence that histamine plays a pivotal role in allergic inflammation. Challenging patients with allergy with specific antigens results in a local or systemic increase in histamine concentrations.¹⁵⁻¹⁷ Histamine-containing cells (eg, tissue mast cells) are present in human lung parenchyma and skin tissues and can be activated in response to many immunologic and nonimmunologic triggers.^{16,18,19} Peripheral blood basophils are also attracted by a number of chemokines from peripheral blood to sites of allergic inflammation.^{20,21} For instance, basophils can be found at the site of inflammation during late-phase reactions in human skin²² and in lung parenchyma in bronchial asthma.²⁰ This suggests that histamine released locally by tissue mast cells and infiltrating basophils is an endogenous mediator in allergic inflammation. These findings represent the rationale for using H₁-receptor antagonists to treat allergic rhinoconjunctivitis, urticaria, and atopic dermatitis.

RELEVANCE OF HISTAMINE IN THE CYTOKINE NETWORK IN ALLERGIC INFLAMMATION

Since 1985, it has been shown that histamine can induce and/or modulate cytokine synthesis in allergic inflammation. Two types of effects have been described: (1) direct effects of histamine on cytokine production and (2) modulation of cytokine synthesis induced by immunologic stimuli. For example, histamine differentially modulates IL-4 and IFN- γ release from T cells²³;

From the Division of Clinical Immunology and Allergy, University of Naples Federico II, School of Medicine, Naples.

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Reprint requests: Prof. Gianni Marone, MD, Division of Clinical Immunology and Allergy, University of Naples Federico II, Via S Pansini 5, 80131 Napoli, Italy.

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inhibits TNF- α ²⁴ and IL-12 production by human monocytes²⁵; directly induces IL-10^{26,27} and IL-18 synthesis from human monocytes²⁸; inhibits IFN- γ , TNF- α , and IL-12 and enhances IL-10 production in LPS- or mitogen-activated, peripheral blood mononuclear cells^{24-26,29}; and enhances IL-1-induced production of IL-6 by monocytes.³⁰ These complex effects of histamine on immune cell cytokine production are mediated by the activation of H₁-,^{31,32} H₂-,^{24-26,29} and H₃-receptors.²⁷ A fourth type of histamine receptor (H₄) has been characterized both functionally and pharmacologically, and it has recently been cloned.³³⁻³⁵ Several characteristics of the H₄-receptor are similar to those of the histamine receptors previously identified on human eosinophils.³⁶

These fascinating findings suggest that histamine, traditionally considered a chemical mediator of acute inflammation, might play a more complex role than was previously thought in the modulation of the cytokine network. We have recently examined the possibility that low concentrations of histamine, such as those found in the bronchoalveolar lavage (BAL) fluid of patients with bronchial asthma^{15,37,38} or at other sites of allergic inflammation,¹⁸ might activate human lung macrophages. The rationale for studying this cell is the high prevalence of macrophages in the human lung parenchyma³⁹ and in the BAL fluid.^{40,41} In addition, macrophages are frequently found in close proximity to histamine-containing cells in human airways.⁴² Macrophages purified (>98%) from the lung parenchyma of thoracic surgery patients were incubated (1 to 18 hours) with low doses of histamine (10⁻⁹ to 10⁻⁷ mol/L), which comprise those released in vivo in various pathophysiologic conditions. As previously shown, histamine increased the basal release of β -glucuronidase, a marker of exocytosis in macrophages, in a concentration-dependent fashion.⁴³ Interestingly, histamine also induced the de novo synthesis of IL-6 from macrophages.⁴⁴ These effects were reproduced by the H₁-agonist 6-[2-(4-imidazolyl)ethylamino]-N-(4-trifluoromethylphenyl) heptane carboxamide but not by the H₂-agonist dimaprit, indicating that they were H₁-mediated events. Furthermore, histamine induced a concentration-dependent increase of intracellular Ca²⁺ concentrations in macrophages.⁴⁴

These results are in line with the general observation that H₁-receptor activation is associated with intracellular Ca²⁺ influx⁴⁵ and indicate that this signaling pathway is also active in human macrophages. The H₁-mediated activation of macrophages was confirmed by showing that histamine-induced IL-6 release was inhibited in a concentration-dependent fashion by increasing concentrations of the selective H₁-receptor antagonist fexofenadine⁴⁴ (Fig 1). Preincubation of human lung macrophages with fexofenadine (10⁻⁵ mol/L) inhibited intracellular Ca²⁺ concentration elevations induced by the subsequent addition of histamine (10⁻⁷ mol/L)⁴⁴ (Fig 2). The H₂-antagonist ranitidine had no influence on IL-6 release or Ca²⁺ signal induced by histamine (data not shown).

Our results provide the first evidence that low concentrations of histamine promote exocytosis and IL-6 production by activating H₁-receptors and inducing intracel-

lular Ca²⁺ signaling in macrophages. This observation raises the intriguing possibility that, by modulating macrophage functions, histamine might be implicated in the long-term control of inflammation and tissue remodeling. The observation that fexofenadine antagonizes the synthesis of IL-6 in macrophages is of potential clinical importance. In fact, it suggests that chronic administration of fexofenadine in patients with allergic disorders might prevent not only the acute symptoms, but also might interfere with some of the mechanisms involved in chronic inflammation and in the tissue damage and remodeling associated with the activation of macrophages.

IN VITRO ANTI-INFLAMMATORY EFFECTS OF THE H₁-RECEPTOR ANTAGONISTS

Since 1975, it has been known that high concentrations of first-generation antihistamines inhibit in vitro histamine release from human basophils.⁴⁶ Moreover, certain H₁-antagonists prevent not only the release of histamine but also that of other pro-inflammatory mediators such as cysteinyl leukotrienes and platelet-activating factor.⁴⁷⁻⁴⁹ It is important to emphasize that not all H₁-receptor antagonists have such anti-inflammatory activities in vitro. Indirect evidence suggests that some H₁-receptor antagonists inhibit the release of pro-inflammatory mediators from human skin and nasal mucosa in vivo.^{50,51} These effects are probably not related to H₁-receptor antagonism but rather to interference with the cell membrane or to inhibition of the metabolic steps required for cell activation. Although these inhibitory effects are concentration dependent in vitro, they generally require higher doses than those recommended for symptom relief in allergic rhinoconjunctivitis or urticaria. Thus, their clinical relevance is still uncertain.

IN VIVO BRONCHOPROTECTIVE EFFECTS OF H₁-RECEPTOR ANTAGONISTS

It is well known that histamine inhalation causes bronchoconstriction in asthmatic patients.⁵² This effect of histamine inhalation is used as a tool to evaluate airway hyperreactivity in patients with allergic disorders. Histamine levels are higher in BAL fluid from asthmatic patients than from normal individuals,³⁸ and a correlation has been found between the concentration of BAL histamine and bronchial hyperreactivity.⁵³ Herxheimer⁵⁴ was the first to propose antihistamines be used to treat bronchial asthma. However, early antihistamines could not be given in high doses because of their sedative effects. Several studies have looked at the effects of antihistamines on histamine and methacholine challenge. For example, it has been shown that terfenadine causes a small but significant improvement in FEV₁ and a shift to the right of the dose-response curve of histamine challenge in asthmatic patients.⁵⁵ It should be noted, however, that high doses of antihistamines were used in these studies and that the continuous use of such doses to treat bronchial asthma might expose some patients to unwanted side effects.^{56,57}

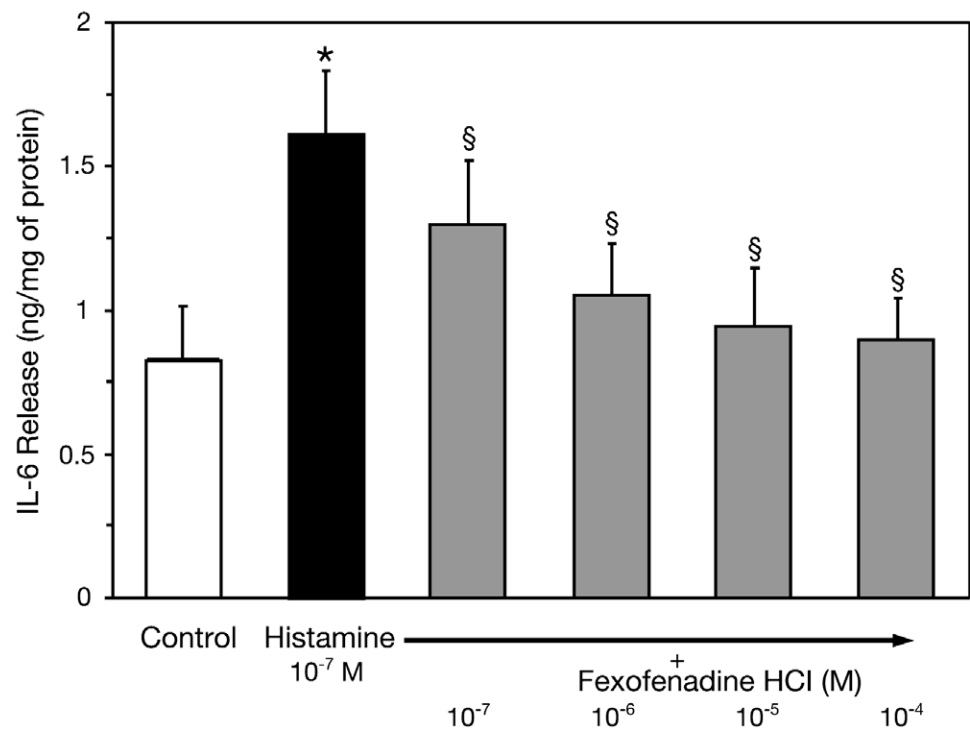


FIG 1. Effect of increasing concentrations of the H_1 -receptor antagonist fexofenadine on histamine-induced release of IL-6 from human lung macrophages. The cells were preincubated (37°C , 15 min) with RPMI or with increasing concentrations of fexofenadine (gray bars) and were then incubated (37°C , 6 hours) with histamine (10^{-7} mol/L) (black bar). At the end of incubation, the supernatant was collected and centrifuged ($100g$, 4°C , 5 min). IL-6 was determined by an ELISA technique. The data are the mean $\pm$ SE of 4 experiments. * $P < .05$, compared with control. § $P < .05$, compared with histamine alone. Reproduced with permission from Triggiani M et al. J Immunol 2001;166:4083-91.⁴⁴ Copyright 2001. The American Association of Immunologists.

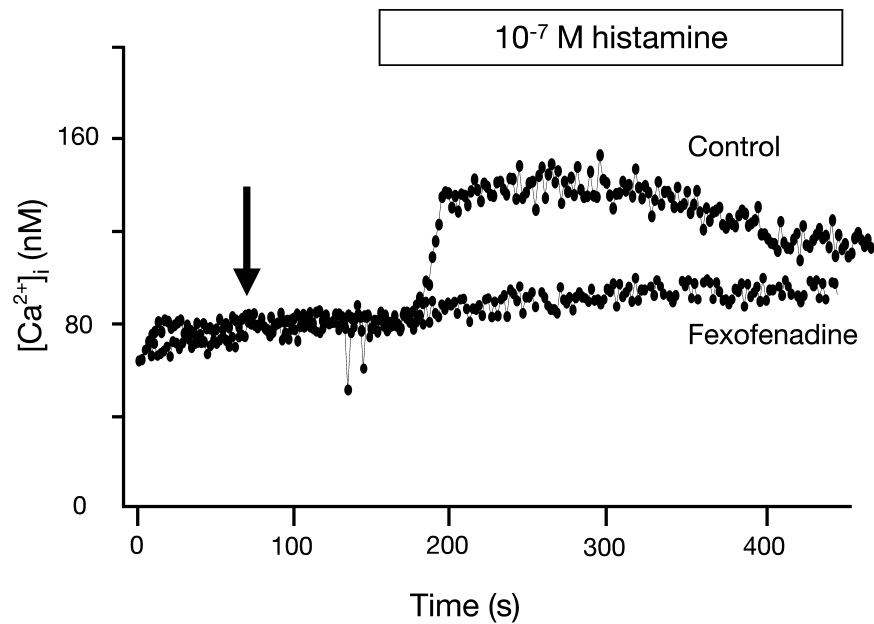


FIG 2. Single cell trace representative of the effect of 10^{-7} mol/L histamine on intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in the absence (Control) or in the presence of 10^{-5} mol/L fexofenadine. The experiments were performed with an acquisition interval of 2 seconds. The period of incubation with histamine is indicated by the bar. The arrow indicates the time of addition of fexofenadine. Reproduced with permission from Triggiani M et al. J Immunol 2001;166:4083-91.⁴⁴ Copyright 2001. The American Association of Immunologists.

H₁-RECEPTOR ANTAGONISTS IN PATIENTS WITH ALLERGIC DISORDERS OF UPPER AND LOWER AIRWAYS

The efficacy of H₁-receptor antagonists in allergic rhinitis has been clearly demonstrated.⁵⁸ Several early studies evaluated the effects of H₁-receptor antagonists in bronchial asthma.⁵⁹ In persistent asthma, these early studies generally failed to demonstrate a beneficial effect by using even high doses of H₁-receptor antagonists,⁶⁰ and these agents might or might not have a glucocorticoid-sparing effect in asthma.^{61,62} However, allergic rhinitis and bronchial asthma often coexist, and these 2 diseases are closely related anatomically and immunopathologically. Recent studies have shown that conventional doses of H₁-receptor antagonists might be associated with a reduction of concurrent asthma symptoms and improvement of pulmonary function in patients with coexisting mild to moderate bronchial asthma and allergic rhinitis.⁶³ The results of these studies suggest that there might be a potential role for some antihistamines in the treatment of patients with mild to moderate asthma associated with allergic rhinitis.

DO H₁-RECEPTOR ANTAGONISTS INFLUENCE THE NATURAL HISTORY OF ALLERGIC DISORDERS?

Most of the clinical trials examining the efficacy of drugs in the treatment of allergic diseases had end point evaluation after months or a few years. However, an increasing amount of evidence indicates that significant structural and functional airway remodeling occurs even in early phases of bronchial asthma.⁶⁴ This process occurs over years, even in patients in apparent clinical remission, and leads to irreversible changes in the bronchial wall that might result in uncontrolled asthma.⁶⁵ As a consequence, new drugs for the treatment of bronchial asthma should be evaluated for their impact on the long-term evolution of the disease. Novel end points should be assessed, including the drug's ability to prevent or reverse bronchial damage as well as tissue and vascular remodeling.

The observation that histamine induces a concentration-dependent release of pro-inflammatory cytokines (IL-6) and lysosomal enzymes from human lung macrophages, and that these effects are inhibited by fexofenadine,⁴⁴ raises the intriguing possibility that long-term administration of H₁-receptor antagonists might be beneficial in the long-term evolution of allergic disorders. In support of this hypothesis, evidence suggests that H₁-receptor antagonists can prevent or delay asthma development in infants with atopic dermatitis.^{66,67}

Perhaps we could learn a lesson from hypertension treatment, in which lowering blood pressure is no longer the primary end point. Other effects, such as the reduction of cardiovascular tissue remodeling or long-term morbidity and mortality, are evaluated to assess the efficacy of pharmacologic treatments. By analogy, new treatments of bronchial asthma should examine not only

improvement of FEV₁, but also the reduction of lung tissue remodeling, and the long-term evolution of lung function, morbidity, and mortality.

SUMMARY

The central role played by histamine in the pathophysiology of inflammatory and allergic disorders has been clearly established. Histamine is released in vivo during allergic reactions, and administering exogenous histamine reproduces signs and symptoms typical of allergic diseases. Histamine exerts immediate pro-inflammatory effects mediated mostly by the activation of H₁-receptors. However, the possibility is emerging that this mediator can also influence local immune responses and tissue damage by modulating the release of cytokines as well as the activity of cells such as macrophages, basophils, eosinophils, and fibroblasts. Thus, we might envisage that histamine has a fundamental and possibly dual role in bronchial asthma, ie, as an acute pro-inflammatory molecule and as a long-term immune modulator regulating the complex network of cytokines operating in this disease.

The observation that fexofenadine inhibits the activation of macrophages induced by histamine suggests a new perspective in the long-term treatment of allergic inflammation. Indeed, it is conceivable that long-term treatment with fexofenadine might positively influence the tissue damage and remodeling occurring in chronic asthma. A better knowledge of the regulatory role of histamine on the functions of immunocompetent cells, and the effects of activating histamine receptors on these cells, might lead to new therapeutic approaches to control the long-term evolution of bronchial asthma.

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