Anti-inflammatory actions of new antihistamines

Histamine has been recognized as a major mediator producing allergic reactions and diseases [1]. Antihistamines are widely used for treatment of these conditions. First-generation antihistamines (traditional antihistamines) including hydroxyzine, chlorpheniramine and diphenhydramine display poor selectivity for H_1-receptors. They are effective in reducing histamine-related symptoms, but the use of them have been limited by sedation and troublesome gastro-intestinal symptoms due to their penetration of the blood–brain barrier and anticholinergic effects, respectively. Second-generation antihistamines (new antihistamines), including terfenadine, feofenadine, cetirizine, ketotifen, azelastine and ebastine, which display greater selectivity for H_1-receptors and lack of penetration of the blood–brain barrier, have been developed to reduce these side-effects [2–6]. Although second-generation antihistamines display antagonistic actions on H_1-receptors, several studies have demonstrated that the ability of new antihistamines to attenuate the production of inflammatory reactions, which appear to unrelated to their ability to antagonize the effects of histamine at H_1-receptor sites [2–6]. Thus, new antihistamines can modulate various inflammatory reactions besides their H_1-receptor antagonism.

The pathogenesis of allergic inflammation is complex and involves multiple inflammatory cells, cytokines and mediators. The clinical efficacy of oral and topical new antihistamines in allergic diseases and their anti-inflammatory actions have been investigated. A number of studies demonstrate that new antihistamines reduce clinical symptoms of allergic diseases. Several studies support the view that new antihistamines have anti-inflammatory effects *in vivo* [5–15]. For instance, new antihistamines such as cetirizine and azelastine attenuate eosinophil recruitment into the site of allergic inflammation [8,14], and intracellular adhesion molecule-1 (ICAM-1) expression on epithelial cells from the site of allergic inflammation [11,12,14]. Extensive studies have been conducted to clarify the mechanism in anti-inflammatory actions of new antihistamines; these actions are outlined as follows:

- Downregulation:
    Mediator release
    ICAM-1 expression
    Superoxide generation
    Chemotaxis
    Cytokine expression
- Upregulation:
    Number and function of β_2-adrenoceptor

New antihistamines can attenuate mediator release. For instance, new antihistamines inhibit histamine release from IgE-sensitized basophils [16,17]. In addition, it has also been reported that new antihistamines inhibit the synthesis and release of arachinoid acid metabolites including leukotriene C4 from mast cells and basophils [16,18]. Interestingly, new antihistamines inhibit chemical mediator release from cells stimulated with not only IgE but also nonimmunogenic agents including calcium ionophore, indicating that antihistamines can block IgE receptor-mediated signal pathway as well as other intracellular signal transduction pathway(s) [2]. New antihistamines attenuate the recruitment of eosinophils into the sites of allergic inflammation via the inhibition of ICAM-1 expression. For instance, cetirizine inhibits eosinophil recruitment into the airway of allergic bronchial asthmatics challenged with corresponding allergen [19]. Similarly, cetirizine inhibits eosinophil recruitment into the skin induced by platelet-activating factor (PAF) [20]. Analysis of the mechanism in cetirizine-dependent attenuation of eosinophil recruitment into the sites of allergic inflammation has revealed that cetirizine selectively inhibits eosinophil adhesion to human umbilical vein endothelial cells (HUVEC) but not neutrophils [21]. Subsequent studies have demonstrated that new antihistamines such as ketotifen and azelastine inhibit ICAM-1 expression on tumour necrosis factor-α (TNFα) -stimulated HUVEC [22] and nasal epithelial cells from the patients with allergic rhinitis challenged with corresponding allergen [14,23], resulting in the attenuation of eosinophil recruitment into the sites of allergic inflammation. New antihistamines can modulate eosinophil functions. Several studies have demonstrated that new antihistamines inhibit survival, chemotaxis, generation of superoxide and degradation of eosinophils [24–28]. Neutrophils are well known to generate superoxide anions which cause the tissue damage. Although cetirizine dose not inhibit neutrophil recruitment, this drug reduces the generation of superoxide anions from neutrophils [29].

A variety of cells, including lymphocytes, participate in the production of allergic inflammation by expressing various cytokines. The inhibition of cytokine production which promotes allergic inflammation is an important strategy controlling allergic inflammation. New antihistamines such as azelastine, terfenadine and ketotifen inhibit interleukin (IL) -2, IL-3, IL-4 and IL-5 production by mitogen-stimulated peripheral blood lymphocytes [30], indicating that these drugs could attenuate the production of allergic inflammation by inhibiting the production of TH2-type T-lymphocyte-derived cytokines. In addition, cetirizine

inhibits monocyte chemotactic protein-1 (MCP-1) and RANTES production by interferon-stimulated keratinocytes [31]. Interestingly, glucocorticosteroids inhibit the production of IL-8 but not monocyte chemotactic protein-1 (MCP-1) and RANTES, indicating that distinct mechanism is involved in the regulation of MCP-1 and RANTES production [31].

Airway epithelial cells are well known to express various cytokines which are possibly involved in the production of allergic inflammation of the asthmatic airway. In this issue of *Clinical and Experimental Allergy*, Arnold *et al.* have examined the role of cetirizine on IL-8 release from human alveolar type U epithelial cell lines, A549 [32]. This study demonstrated that cetirizine attenuated IL-8 release by TNFα and PMA-stimulated A549, but not by IL-1-β and respiratory syncytial virus (RSV)-stimulated A549, indicating that an inhibition of cetirizine on IL-8 release is stimulus-dependent. The promoter of the gene contains sequences for binding several nuclear transcription factors. Transcriptional factors participate to various extents in the inducible expression of the genes. Arnold *et al.* analysed the mechanism in the inhibitory effect of cetirizine on IL-8 release by airway epithelial cells. The results indicated that the attenuation of IL-8 release by cetirizine resulted from downregulation of accessible DNA-binding sites of the nuclear factor kappa B (NF-κB). H$_1$-receptor antagonist, azelastine, has been shown to inhibit IL-1, IL-6, TNFα and granulocyte macrophage-colony stimulating factor mRNA expression and DNA-binding activity of NF-κB [33]. NF-κB participates to various extent in the inducible expression of the genes encoding these cytokines. Thus, the inhibition by cetirizine and azelastine of cytokine expression might be mediated by the inhibition of DNA-binding activity of NF-κB. These studies indicate that NF-κB is a molecular target of anti-inflammatory actions of new antihistamines. However, a precise mechanism remains to be determined.

β_2-adrenergic bronchodilator is widely used to treat bronchial asthma. β_2-adrenoceptor desensitization may occur during long-term treatment of bronchial asthmatics with β_2-adrenergic agonists and may limit the efficacy of β_2-adrenergic agonists. New antihistamines have favourite activities which are increasing the density of β_2-adrenoceptors and preventing downregulation of the number of β_2-adrenoceptors. The density of β_2-adrenoceptor on circulating lymphocytes has been regarded as a model frequently used to study β_2-adrenoceptor function in man. Ketotifen increases β_2-adrenoceptor density on lymphocytes from bronchial asthmatics who have been treated with β_2-adrenergic bronchodilator. The increases in density and the improvement of functions of β_2-adrenoceptors were accompanied by a significant increase in peak expiratory flow rate in response to inhaled β_2-adrenergic bronchodilator, salbutamol [34]. In addition, the number of β_2-adrenoceptors was higher in azelastine and terbutaline-treated guinea pig lung than that in terbutaline only, showing that azelastine may prevent β-adrenergic agonist-induced downregulation of the number of β-adrenoceptors [35].

There are several possible mechanisms by which new antihistamines regulate inflammatory reactions: (1) prevention of an increase in intracellular calcium and interference with calcium utilization, (2) modulation of intracellular cAMP levels, (3) inhibition of protein kinase C (PKC) activity, (4) inhibition of G-protein function, and (5) inhibition of NF-κB binding (Fig. 1). An elevation of intracellular calcium levels plays an important step in the activation of various intracellular signals such as calcium–calmodulin cascades and PKC. Catalytic activation of calcium-dependent enzymes which can act as intracellular signals elicit a variety of cell functions. New antihistamines can modulate intracellular calcium-dependent signal transduction pathways at several different mechanisms. Ketotifen decreases intracellular calcium levels by preventing calcium influx [36]. The inhibition of the binding of calcium to calcium channels may account for the prevention of calcium influx. Azelastine inhibits superoxide generation by neutrophils in response to phorbol myristyl acetate and formyl-methionyl-leucyl-phenylalanine and decreases inositol triphosphate, intracellular free calcium, and PKC activity [37]. Azelastine can affect calcium–calmodulin pathways. Azelastine interacts with calmodulin resulting in the inhibition of calcium-calmodulin-dependent enzyme, phosphodiesterase [38]. Cetirizine which has ionization and lipophilicity behaviour can directly dissolve into the cell membrane and stabilize the cell membrane [39], whose pharmacological properties may relate to the inhibition of release of calcium from intracellular stores. Intracellular cAMP can modulate various cell functions. Terfenadine, inhibits antigen-induced histamine release from sensitized guinea pig lung and rat peritoneal mast cells [40], and ketotifen also inhibits antigen-induced histamine release from human sensitized basophils [17], correlating with an increase in intracellular cAMP levels which prevents intracellular calcium mobilization. Azelastine inhibits histamine and TNFα release,
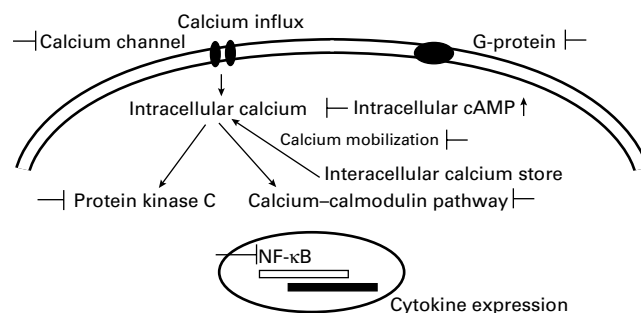

Fig. 1. Intracellular mechanism in anti-inflammatory effects of new antihistamines

possibly mediating through the inhibition of PKC activity [41,42]. Finally, Köller and colleagues, and Rihoux and colleagues have reported that the inhibition by cetirizine of mediator release may result from downregulation of G-protein activity [43,44]. Consequently, they have proposed that G-protein might be a molecular target for anti-inflammatory actions of cetirizine. They indicate new insight into the mechanism in anti-inflammatory actions of new antihistamines. There are a variety type of G-proteins which individually regulate intracellular signals and cell functions; therefore, the identification of G-protein whose functions are modulated by cetirizine and the downstream signals of G-protein which regulate mediator release remain to be determined.

Quite recently, Tamaoki *et al.* have shown that azelastine inhibits PAF-induced microvascular leakage in airways, possibly involving inhibition of the release of neutrophil elastase from activated neutrophils [45]. Their results may indicate new pharmacological actions of azelastine.

In summary, histamines play an important role in the production of allergic reactions. New antihistamines represent the first line of treatment of these conditions, especially in nose, conjunctiva and skin. These drugs can modulate various inflammatory reactions besides their H_1-receptor antagonism. The mechanisms in anti-inflammatory actions of new antihistamines have been extensively investigated; however, further studies focusing on analysis of intracellular mechanism in anti-inflammatory effects are needed to clarify the anti-inflammatory actions.

References

1 Bachert C. Histamine — a major role in allergy? Clin Exp Allergy, 1998; 28 (Suppl. 6):15–9.

2 Rimmer SJ, Church MK. The pharmacology and mechanisms of action of histamine H1-antagonists. Clin Exp Allergy 1990; 20 (Suppl. 2):3–17.

3 Simons FER. The antiallergic effects of antihistamines (H_1-receptor antagonists). J Allergy Clin Immmunol 1992; 90: 705–15.

4 Busse WW. Role of antihistamines in allergic disease. Ann Allergy 1994; 72:371–5.

5 Simons FER, Simons KJ. The pharmacology and use of H_1-receptor- antagonist drugs. New Engl J Med 1994; 330:1663–70.

6 Du Buske LM. Clinical comparison of histamine H_1-receptor antagonist drugs. J Allergy Clin Immunol 1996; 98:S307–18.

7 Sheffer AL. Cetirizine: antiallergic therapy beyond traditional H_1 antihistamines. J Allergy Clin Immunol 1990; 86:1040–6.

8 Rédier H, Chanez P, De Vos C et al. Inhibitory effect of cetirizine on the bronchial eosinophil recruitment induced by allergen inhalation challenge in allergic patients with asthma. J Allergy Clin Immunol 1992; 37:215–24.

9 Walsh GM. News and commentary. Clin Exp Allergy 1994; 24:81–5.

10 Jinquan T, Reimert CM, Deleuran B, Zacharise C, Simons C, Thestrup-Pederson K. Cetirizine inhibits the in vivo and ex vivo chemotactic response of T lymphocytes and monocytes. J Allergy Clin Immunol 1995; 95:99–86.

11 Bagnasco B, Canocia CW. Influence of H1-receptor antagonists on adhesion molecules and cellular traffic. Allergy 1995; 50:17–23.

12 Fance L, Ciprandi G, Pronzato C et al. Cetirizine reduces ICAM-1 on epithelial cells during nasal minimal persistent inflammation in asymptomatic children with mite-allergic asthma. Int Arch Allergy Immunol 1996; 109:272–6.

13 Gupta SK. Effect of cetirizine and prednisolone on cellular infiltration and cytokine mRNA expression during allergen-induced late cutaneous responses. Clin Exp Allergy 1996; 26:68–78.

14 Ciprandi G, Ricca V, Passalacqua G et al. Seasonal rhinitis and azelastine: long- or short-term treatment. J Allergy Clin Immunol 1997; 99:301–7.

15 Bousquet J. Antihistamines in severe/chronic rhinitis. Clin Exp Allergy 1998; 28 (Suppl. 6):49–53.

16 Nabe M, Agrawal DK, Sarmiento EU, Townley RG. Inhibitory effect of terfenadine on mediator release from human blood basophils and eosinophils. Clin Exp Allergy 1989; 19:515–20.

17 Castillo JG, Sanz ML, Oehling A. Action of ketotifen on histamine release and intracellular cAMP levels in basophil cultures from pollinic subjects. Allergol Immunopathol (Madr) 1986; 14:107–13.

18 Nabe M, Miyagawa H, Agrawal DK, Sugiyama H, Townley RG. The effect of ketotifen on eosinophils as measured at LTC4 release and by chemotaxis. Allergy Proc 1991; 12:267–71.

19 Rédier H, Chanez P, De Vos C et al. Inhibitory effect of cetirizine on the bronchial eosinophil recruitment induced by allergen inhalation challenge in allergic patients with asthma. J Allergy Clin Immunol 1992; 90:215–24.

20 Fadel R, David B, Herpin-Richard N, Borgnon A, Rassemont R, Rihoux JP. In vivo effects of cetirizine on cutaneous reactivity and eosinophil migration induced by platelet-activating factor (PAF-acether) in man. J Allergy Clin Immunol 1990; 86:314–20.

21 Kyan-Aung U, Hallsworth M, Haskard D, De Vos C, Lee TH. The effects of cetirizine on the adhesion of human eosinophils and neutrophils to cultured human umbilical vein endothelial cells. J Allergy Clin Immunol 1992; 90:270–2.

22 Miki I, Kusano A, Ohta S et al. Histamine enhanced the TNF-alpha-induced expression of E-selectin and ICAM-1 on vascular endothelial cells. Cell Immunol 1996; 171:285–8.

23 Ciprandi G, Pronzato C, Passalacqua G et al. Topical azelastine reduces eosinophil activation and intercellular adhesion molecule-1 expression on nasal epithelial cells: an antiallergic activity. J Allergy Clin Immunol 1996; 98:1088–96.

24 Sedgwick JB, Busse WW. Inhibitory effect of cetirizine on cytokine-enhanced in vitro eosinophil survival. Ann Allergy Asthma Immunol 1997; 78:581–5.

25 Okada C, Eda R, Miyagawa H et al. Effect of cetirizine on

human eosinophil superoxide generation, eosinophil chemo-taxis and eosinophil peroxidase in vitro. Int Arch Allergy Immunol 1994; 103:384–90.

26 Eda R, Townley RG, Hopp RJ. Effect of terfenadine on human eosinophil and neutrophil chemotactic response and generation of superoxide. Ann Allergy 1994; 73:154–60.

27 Busse W, Randlev B, Sedgwick J. The effect of azelastine on neutrophil and eosinophil generation of superoxide. J Allergy Clin Immunol 1989; 83:400–5.

28 Ezeamuzie CI, Al-Hage M. Effect of anti-asthma drugs on human eosinophil superoxide anions release and degranulation. Int Arch Allergy Immunol 1998; 115:162–8.

29 Van Neste D, Ghys L, Antoine JL, Rihoux JP. In vitro effects of cetirizine and histamine on human neutrophil function. Ann Allergy 1987; 59:13–9.

30 Konno S, Asano K, Okamoto K, Adachi M. Inhibition of cytokine production from human peripheral blood leukocytes by anti-allergic agents in vitro. Eur J Pharmacol 1994; 264: 265–8.

31 Albanesi C, Pastore S, Fanales Belasio E, Girolomoni G. Cetirizine and hydrocortisone differentially regulate ICAM-1 expression and chemokine release in cultured human keratino-cytes. Clin Exp Allergy 1998; 28:101–9.

32 Arnold R, Rihoux J-P, König W. Cetirizine counter-regulates interleukin-8 release from human epithelial cells (A549). Clin Exp Allergy 1999; 29:1681–91.

33 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.

34 Brodde OE, Howe U, Egerszegi S, Konietzko N, Michel MC. Effect of prednisolone and ketotifen on β_2-adrenoceptors in asthmatic patients receiving β_2-bronchodilators. Eur J Clin Pharmacol 1988; 34:145–50.

35 Yin KS, Hayashi K, Taki F, Watanabe T, Takagi K, Satake T. Effect of azelastine on the down regulation of β-adrenoceptors in guinea pig lung. Arzneimittelforschung 1991; 41:525–7.

36 Martin U, Roemn E. Ketotifen, a histamine release inhibitor. Mon Allergy 1997; 12:145–9.

37 Ueta E, Osaki T, Kawasaki N, Nomura Y. Suppression of respiratory burst of polymorphonuclear leukocytes by azelas-tine hydrochloride (Azeptin). Eur J Clin Pharmacol 1994; 47:139–45.

38 Middleton E Jr, Ferriola P, Drzewiecki G, Sofia RD. The effect of azelastine and some other antiasthmatic and antiallergic drugs on calmodulin and protein kinase C. Agents Actions 1989; 28:9–15.

39 Pagliara A, Testa B, Carrupt PA et al. Molecular properties and pharmacokinetic behavior of cetirizine, a zwitterionic H1-receptor antagonist. J Med Chem 1998; 41:853–63.

40 Akagi M, Mio M, Miyoshi K, Tasaka K. Antiallergic effects of terfenadine on immediate type hypersensitivity reactions. Immunopharmacol Immunotoxicol 1987; 9:257–79.

41 Chand N, Nolan K, Sofia RD, Diamantis W. Inhibitory effect of azelastine on protein kinase C and diphosphoinoositide kinase in rat mast cells. Arzneimittelforschung 1990; 40:162–5.

42 Nakata Y, Hide I. Calcium signaling and protein kinase C for TNF-α secretion in a rat mast cell line. Life Sci 1998; 62:1653–7.

43 Köller M, Hilger RA, Rihoux JP, König W. Cetirizine exerts anti-inflammatory effects on human neutrophils. Int Arch Allergy Immunol 1996; 110:52–6.

44 Rihoux JP, Masliah J, Bereziat G, König W. G proteins as biological targets for anti-allergic drugs? Int Arch Allergy Immunol 1997; 113:339–41.

45 Tamaoki J, Yamawaki I, Tagaya E et al. Effect of azelastine on platelet-activating factor-induced microvascular leakage in rat airways. Am J Physiol 1999; 276:L351–7.

S. HAYASHI
S. HASHIMOTO*
First Department of Internal Medicine
Nihon University School of Medicine
30-1 Oyaguchikamimachi
Itabashi-ku
Tokyo 173–8610
Japan

*Correspondence