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Histamine H1-receptor antagonists with immunomodulating activities: potential use for modulating T helper type 1 (Th1)/Th2 cytokine imbalance and inflammatory responses in allergic diseases

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Summary

Being a first-line treatment for hypersensitivity allergic disease, histamine H1-receptor antagonists possess anti-inflammatory activity in addition to being H1-receptor antagonists. While it is not purely a histamine-related condition, hypersensitivity allergic disease is associated with an increase in the number of T helper type 2 (Th2) cells and Th2 cytokines, and a decrease in the number of Th1 cells and Th1 cytokines. Suppression of Th2-type cytokine production in addition to H1-receptor blockade may therefore represent a successful therapeutic strategy for the treatment of hypersensitivity allergic diseases. H1-receptor antagonists have been reported to modulate immune cascade at various points by acting on T cell-related inflammatory molecules, including adhesion molecules, chemokines and inflammatory cytokines. These effects of H1-receptor antagonists may be optimized for the treatment of allergic diseases. Besides their ability to regulate inflammatory molecules, some H1-receptor antagonists have been reported to down-regulate Th2 cytokine production. In particular, it has been shown that several H1-receptor antagonists specifically inhibit the production of Th2, but not Th1, cytokines. Accumulating evidence indicates a crucial role for Th1/Th2 cytokine imbalance on the development of allergic diseases. Accordingly, the use of H1-receptor antagonist with Th2 cytokine inhibitory activity to modulate Th1/Th2 cytokine imbalance might be a favourable strategy for the treatment of hypersensitivity allergic diseases. Furthermore, the identification of H1-receptor antagonists which possess immunoregulatory activities in addition to their anti-histamine activity will provide an important insight into the development of novel immunoregulatory drugs.

Keywords: histamine H1-receptor antagonists, hypersensitivity allergic reaction, inflammatory cytokine, T cell migration, Th1/Th2 cytokine imbalance

Introduction

Histamine mediates allergic and inflammatory responses through histamine H1-receptors, and competitive inhibition of H1-receptors by H1-receptor antagonists provides a highly successful approach to controlling allergic reactions [1,2]. While H1-receptor antagonists remain the first-line treatment for hypersensitivity allergic disease, this is not purely a histamine-related condition, as a variety of immune-competent cells contribute to drive and maintain the reaction through cell–cell interactions or the production of soluble factors such as cytokines [3–5]. Among these cells, $CD4^+$ helper T (Th) cells play an important role in regulating hypersensitivity reactions. Based on cytokine production profiles, two distinct patterns of Th cells have been defined. Type 1 helper (Th1) cells produce interleukin (IL)-2 and interferon (IFN)-γ, whereas type 2 (Th2) cells secrete IL-4, IL-5 and IL-13 with other cytokines such as IL-6 and tumour necrosis factor (TNF)-α being produced by both Th1 and Th2 cells [6,7]. IL-4 is responsible for immunoglobulin (Ig)E production, while IL-13 induces IgG4 production by B cells [8]. Although IL-2 was identified originally as a potent T cell growth factor, this cytokine is essential for the peripheral homeostasis of $CD4^+CD25^+$ regulatory T cells (T_{reg}) [9]. In some allergic diseases, Th2 cells accumulate predominantly at the inflammatory sites and trigger the hypersensitivity

reaction [7,10–12]. The primary inflammatory lesion of asthma consists of accumulation of Th2 lymphocytes, and these cells orchestrate the asthmatic inflammation through the secretion of a series of cytokines such as IL-4 and IL-5 [13]. Despite the heterogeneity of allergic responses, involvement of Th2 cytokine-mediated inflammation is generally acknowledged [14].

There is a growing body of evidence that most of the second-generation H1-receptor antagonists exhibit additional pharmacological properties independent of their action on the H1-receptor [15–17]. A Th1/Th2 cytokine imbalance with a predominance of Th2 cytokines has been suggested to be crucial for the pathogenesis of hypersensitivity allergic diseases [18–20]. Accumulating data indicate that hypersensitivity allergic diseases are associated with an increase in the number of Th2 cells and Th2 cytokines and a decrease in the number of Th1 cells and Th1 cytokines. Therefore, drugs that solely antagonize histamine may not be completely effective in the treatment of allergic diseases. In particular, the modulation of Th1/Th2 cytokine imbalance, in addition to histamine blockade through the H1-receptor antagonist, might be beneficial for the successful treatment of hypersensitivity allergic diseases. However, little is known regarding H1-receptor antagonists that possess Th2 cytokine inhibitory activities.

In the present paper, we review data relating to the pharmacological effects of H1-receptor antagonists on T cell immunological function and discuss the potential use of these drugs for the treatment of allergic diseases and hypersensitivity.

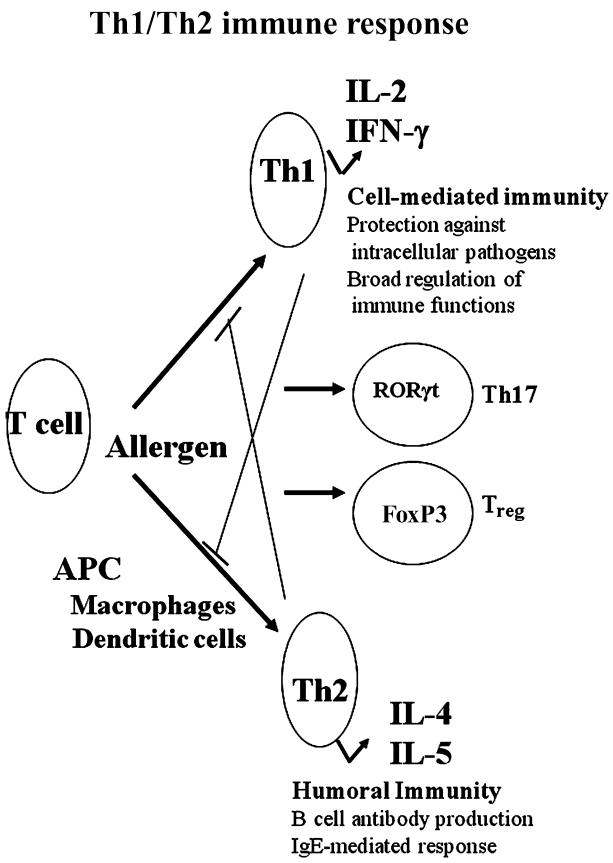

Fig. 1. T helper type 1 (Th1)/Th2 immune responses. Schematic representation of an overview of the Th1/Th2 immune response, its related immune-competent cells and cytokines.

The allergic cascade

Hypersensitivity allergic response is initiated by a series of complex inflammatory processes involving interactions between a number of diverse immune mediators and effector cells [3–5] (Fig. 1). In addition to classical Th1 and Th2 subtypes, Th17 cells have emerged recently as a third independent T cell subset [21], and T_{regs} are indispensable for the safe operation of the immune systems [22]. Interaction between numerous cell types and inflammatory mediators results in the initiation of an immune cascade. Th2 cells are crucial for the promotion of an IgE-based response. In contrast, Th1 cells promote cellular immune responses including the activation of cytolytic T cells, and the killing of intracellular pathogens by macrophages [23,24].

In the late-phase allergic response, inflammatory cytokines such as IL-6, TNF-α and endothelial adhesion molecules are critical for inflammatory responses [25]. The second-generation H1-receptor antagonists have multiple effects on allergic inflammatory response, and these drugs are capable of interfering with the immune cascade at various points through diverse mechanisms, including inhibition of the release of inflammatory mediators [15,16,26–29].

Th1/Th2 cytokine imbalance in allergic responses

The molecular and cellular mechanisms mediating the allergic inflammatory cascade are associated with various cell types. Nevertheless, a unifying mechanism of dysregulated Th2 cytokine-mediated allergic inflammatory response is acknowledged [14]. Direct evidence of the importance of Th2 cells in the pathogenesis of hypersensitivity allergic response was provided by transferring Th2 cells into naive mice [30]. In addition, depletion of Th2 cytokine-producing $CD4^+$ T cells prior to allergen sensitization of mice prevented airway inflammation and development of airway hyperresponsiveness [31].

Given the pathogenic role of Th2 cells, many allergic diseases, including atopic asthma, are associated with an increase in the number of Th2 cells and Th2 cytokines, and a decrease in the number of Th1 cells and Th1 cytokines [7,10–12,19]. These findings suggest that modulation of Th1/Th2 cytokine imbalance may be employed to treat hypersensitivity allergic diseases effectively. Hypersensitivity allergic inflammatory response is induced by interactions between a number of diverse immune mediators and effector cells, including histamine and Th2 cells. Accordingly, hista-

Table 1. Effect of H1-receptor antagonist on T cell immunological functions.

Study	H1-receptor antagonist	Subject	T helper type 1 (Th1)/Th2 concern
Albanesi *et al.* (1998) [33]	Cetirizine	ICAM-1 expression	Th1
Pesteill *et al.* (2003) [34]	Cetirizine	ICAM-1 expression, etc.	
Oddera *et al.* (2000) [35]	Mizolastine	ICAM-1 expression, etc.	Th1
Iida *et al.* (2008) [39]	Epinastine	ICAM-1 expression, etc.	Th1/Th2
Kanai *et al.* (2005) [40]	Epinastine	TARC production	Th2
Hung *et al.* (2007) [41]	Ketotifen	MDC production, etc.	Th1/Th2
Furukawa *et al.* (2004) [42]	Olopatadine	TARC production, etc.	Th2 recruit
Traidl-Hoffmann *et al.* (2006) [44]	Desloratadine, etc.	RANTES production, etc.	Th1
Kawano *et al.* (1996) [45]	Ketotifen	HLA-DQ expression	
Mahmoud *et al.* (2008) [46]	Levocetirizine	T cell population	
Maeda *et al.* (2003) [51]	Terfenadine	Cytokine production	Th2
Kanai *et al.* (2006) [52]	Epinastine	Cytokine production	Th2
Schroeder *et al.* (2001) [53]	Desloratadine	Cytokine production	Th2
Zhao *et al.* (2008) [57]	Carebastine	MIF production	

References which present data on the immunomodulatory effects of H1-receptor antagonists are summarized. ICAM-1, intercellular adhesion molecule-1; TARC, thymus and activation regulated chemokine; MDC, macrophage-derived chemokine; RANTES, regulated on activation, normal T expressed and secreted; HLA-DQ, human leucocyte antigen-DQ; MIF, migration inhibition factor.

mine blockade plus additional modulation of Th1/Th2 cytokine imbalance might lead to a successful therapeutic strategy for the treatment of hypersensitivity allergic diseases.

Immunomodulatory effects of H1-receptor antagonists

The cascade of immune responses involves a number of diverse immune mediators and effector cells. H1-receptor antagonists are capable of modulating T cell-related inflammatory molecules at various points in the immune cascade (summarized in Table 1).

Expression of adhesion molecules

In allergic contact dermatitis, atopic dermatitis and psoriasis, skin is a chronic site of inflammation. In these allergic diseases, intercellular adhesion molecule-1 (ICAM-1) plays an important role in the cell–cell interactions associated with T cell differentiation and function [32]. Cetirizine, a second-generation H1-antagonist, has the capacity to block the IFN-γ-induced expression of ICAM-1 in human keratinocytes [33]. This *in vitro* effect of cetirizine to inhibit ICAM-1 expression was confirmed in patients with active psoriasis vulgaris minima [34]. Mizolastine, a non-sedative H1-receptor antagonist, was able to down-regulate ICAM-1 expression *in vitro* [35], similar to the effect seen by cetirizine.

Chemokines

Thymus and activation-regulated chemokines (CCL17) and macrophage-derived chemokines (CCL22) are designated as Th2 type chemokines and play a role in the recruitment of Th2 cells. CCL17 has been reported to be involved in cutaneous disease such as atopic dermatitis [36,37], and CCL22 has also been reported to associate with atopic dermatitis [38]. In human peripheral blood $CD4^+$ T cells, the non-sedative H1-antagonist epinastine suppresses CCL17 expression [39,40]. This inhibitory effect of epinastine may be partially responsible for its attenuating effect on allergic diseases. Expression of CCL22 in human peripheral blood $CD4^+$ T cells is also inhibited by the H1-receptor antagonists ketotifen and olopatadine [41,42]. The monokines induced by IFN-γ (CXCL9) and IFN-inducible protein 10 (CXCL10) are Th1 cell-attracting chemokines [43]. In human peripheral mononuclear cells, the H1-receptor antagonist ketotifen causes the down-regulation of lipopolysaccharide (LPS)-induced expression of CXCL9 and CXCL10 [41]. The H1-receptor antagonist desloratadine also suppresses CXCL10 expression in keratinocytes [44].

Expression of human leucocyte antigen (HLA) molecule

T cells recognize antigenic peptides associated with class I HLA molecules or class II HLA molecules. HLA-DQ is a HLA class II molecule and presents primarily exogenous peptides that penetrate within cells by endocytosis [45]. HLA-DQ antigen is the crucial restriction element in *Dermatophagoides farinae* antigen-related response on macrophages. The H1-receptor antagonist ketotifen was reported to prevent macrophages from inducing allergen-activated T lymphocytes' responsiveness to IL-2 at least in part by decreasing expression of the HLA-DQ antigen [45].

Modulation of lymphocyte population

In patients with seasonal allergic rhinitis, the H1-receptor antagonist levocetirizine reduced the percentage of

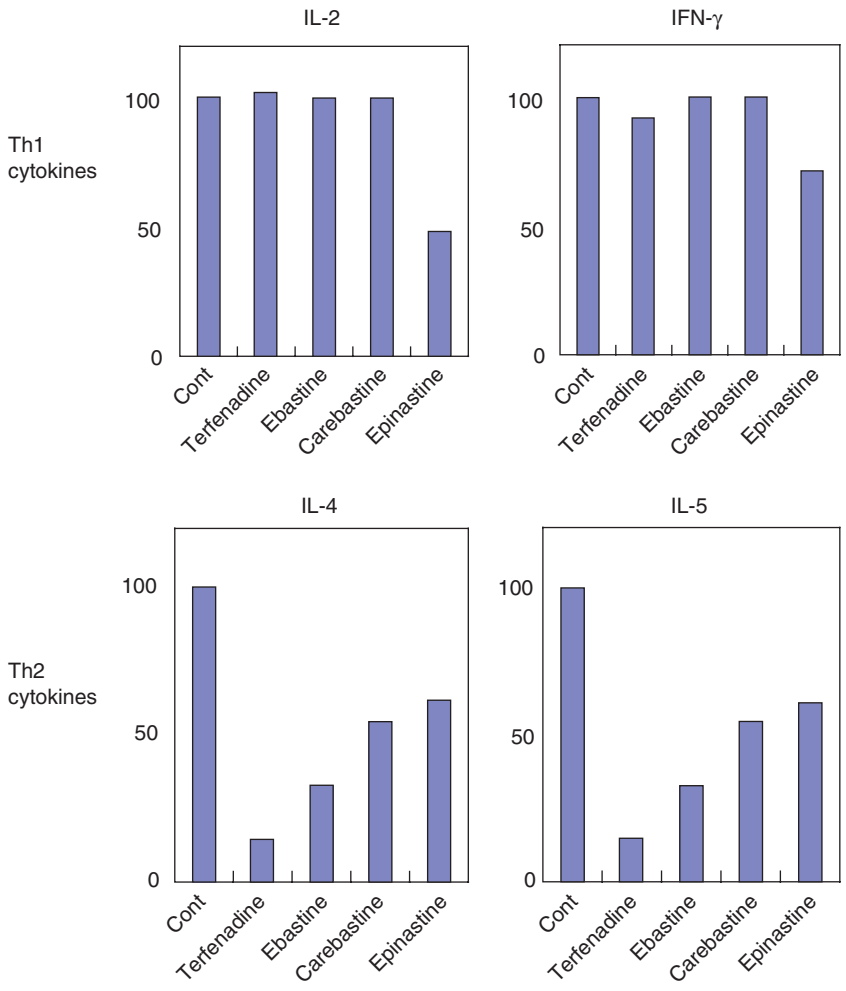

Fig. 2. Effect of H1-receptor antagonists on T helper type 1 (Th1)/Th2 cytokine production. Effects of terfenadine (64 μM), ebastine (5 μM), carebastine (100 μM) and epinastine (100 μM) on Th1/Th2 cytokine production in co-stimulatory conditions by anti-CD3 with anti-CD28 [54–56].

$CD4^+CD29^+$, $CD4^+CD212^+$ and $CD4^+CD54^+$ inflammatory T lymphocytes, while increasing that of $CD4^+CD25^+$ regulatory T cells [46]. T_{regs} are known to suppress several features of allergic inflammation, and Th2 responses to allergens are normally suppressed by $CD4^+CD25^+$ T_{regs} [47]. Therefore, these levocetirizine-induced changes in the T cell subpopulation are expected to contribute to the improved clinical prognosis in seasonal allergic rhinitis patients.

Modulation of Th1/Th2 cytokines and inflammatory cytokines

H1-receptor antagonists have been shown to interfere with T cell-related inflammatory molecules at various points of the immune cascade. Importantly, accumulating data indicate that Th2 type cytokines play a crucial role in the pathogenesis of hypersensitivity allergic diseases. Targeting disease-inducing Th2 cells [48] and use of the Th2 cytokine modulator [49,50] are regarded as promising strategies for the treatment of allergic diseases, including asthma. Therefore, modulation of the Th1/Th2 cytokine imbalance may lead to effective therapies for hypersensitivity allergic diseases.

It has been shown that some H1-receptor antagonists inhibit Th2 cytokine production in several experimental conditions [51–53]. Accordingly, application of these drugs may modulate Th1/Th2 cytokine imbalance. In addition to these reports regarding H1-receptor antagonists, several H1-receptor antagonists have shown specific inhibitory activity on Th2, but not Th1, cytokine production [54–56]. Under co-stimulatory conditions, the second-generation H1-receptor antagonists terfenadine, ebastine and carebastine clearly inhibited the production of Th2-type cytokines IL-4 and IL-5 as well as the proliferative response. However, production of the Th1-type cytokines IL-2 and IFN-γ was unaffected. In addition, ebastine and carebastine inhibited transendothelial migration of activated T cells and production of the proinflammatory cytokines IL-6 and TNF-α by T cells and macrophages. In contrast, the H1-receptor antagonist epinastine inhibited Th1-type cytokine production in addition to suppressing Th2-type cytokines (Figs 2 and 3, and Table 2).

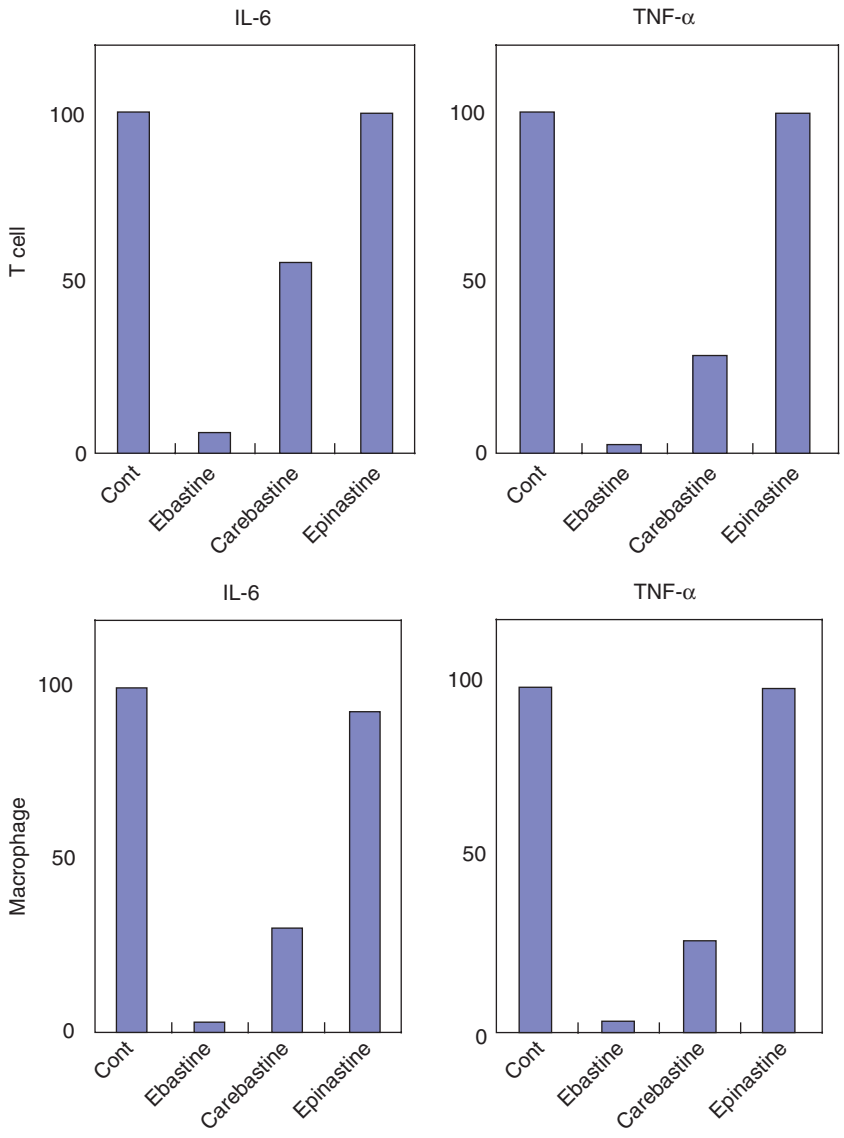

Fig. 3. Effect of H1-receptor antagonists on proinflammatory cytokine production. Effects of ebastine (5 μM), carebastine (100 μM) and epinastine (100 μM) on proinflammatory cytokine production in co-stimulatory conditions by anti-CD3 with anti-CD28 [54–56].

Table 2. Summary of immunomodulatory effects of H1 receptor antagonists.

		T cells					Macrophage
Group	Drug	Proliferation	IL-2 IFN-γ	IL-4 IL-5	IL-6 TNF-α	Migration	IL-6 TNF-α
I	Terfenadine	↓	→	↓			
	Ebastine	↓	→	↓	↓	↓	↓
	Carebastine	↓	→	↓	↓	↓	↓
II	Epinastine	↓	↓	↓	→	→	→
III	Cetirizine	→	→	→	→	→	→
	Ketotifen	→	→	→	→	→	→

The effects of ebastine, carebastine, epinastine, cetirizine, and ketotifen on the proliferation, cytokine production [T helper type 1 (Th1)-type cytokines, Th2-type cytokine and proinflammatory cytokines], and transendothelial migration of T cells, and proinflammatory cytokine production of macrophages are summarized. →, unaltered; ↓, reduced; ↑, enhanced. Grouping was performed based on the experimental results obtained from our studies [54–56]. IL, interleukin; IFN, interferon; TNF, tumour necrosis factor.

Ebastine inhibited Th2 cytokine production at low concentration, while carebastine and epinastine required high concentrations to suppress Th2 cytokine production. However, other investigators demonstrated that carebastine and epinastine antagonists suppress T cell-mediated cytokine production at low concentrations [51–53,57]. Meanwhile, clinically effective dosage of cetirizine resulted in the inhibition of ICAM-1 expression in patients with active psoriasis vulgaris minima [34], but cetirizine requires higher (supraclinical) concentration to inhibit ICAM-1 expression *in vitro* [33]. Therefore, several aspects need to be considered when evaluating *in vitro* results and extrapolating them to clinically relevant situation.

Ebastine specifically inhibited Th2 cytokine production, and this drug is used to treat patients with allergic rhinitis effectively [58], which is characterized pathologically by Th2-type allergic inflammation [59]. The H1-receptor antagonist desloratadine also inhibited *in vitro* production of the Th2 cytokine IL-4 from anti-IgE-stimulated human basophils [53], and this drug relieves significantly the signs and symptoms of seasonal allergic rhinitis, which is a Th2 type allergic disease [60]. These results raise the possibility that these H1-receptor antagonists exhibit favourable clinical efficacy not only by histamine blockade, but also by blocking the generation of Th2 type cytokines. In this regard it is noteworthy that epinastine, which inhibits Th1-type cytokine production in addition to Th2 cytokine suppression, is reportedly effective against the Th1-type inflammatory skin disease psoriasis vulgaris [56,61,62]. Furthermore, atopic dermatitis [63], in which both Th1 and Th2 attracting factors are elevated [38], is also treated effectively by epinastine.

Carebastine, which is an active metabolite of ebastine, possesses histamine blockade activity approximately 10–100 times greater than that of ebastine [64]. However, ebastine displayed 10 times greater *in vitro* inhibition of Th2 cytokine production than carebastine [56], suggesting that a mechanism other than H1-receptor antagonism is involved in the inhibition of Th2 cytokine production by ebastine. Furthermore, terfenadine, ebastine and carebastine are similar in their chemical structure, and these three compounds inhibited specifically the production of Th2 and inflammatory cytokines, but not Th1 cytokine. Therefore, their chemical structure might be unique, with specific inhibition of Th2 cytokine production independent of histamine blockade.

Concluding remarks

The various compounds aimed at modulating Th2 cell functions that are being developed indicate that modulation of the Th1/Th2 cytokine imbalance is a promising strategy for the treatment of hypersensitivity allergic diseases. Some H1-receptor antagonists are able to down-regulate Th2 cytokine production in several experimental conditions. These Th2 cytokine inhibitory activities may partially reflect a therapeutic mode of action of these drugs in hypersensitivity allergic diseases. In particular, specific inhibitory profiles of Th2 cytokine but not Th1 cytokine production have been shown for terfenadine, ebastine and carebastine. Because these three compounds possess a similar chemical structure, further evaluation of these drugs may provide a clue to understanding their pharmacological activity on Th2 cytokine inhibitory activity.

It has been suggested that TNF-α, which is produced in considerable quantities in asthmatic airways, may potentially be involved in the development of bronchial hyperresponsiveness by directly altering the contractile properties of the airway smooth muscle [65]. Increased levels of IL-6 have also been detected in the blood and bronchoalveolar lavage of patients with asthma, and bronchial biopsies of these patients reveal an increased expression of IL-6 [66]. Furthermore, anti-TNF-α therapy is reportedly effective for the treatment of patients with rheumatoid arthritis and Crohn's disease [67,68]. As T cells and macrophages migrate and accumulate at the inflammatory sites and produce proinflammatory cytokines such as TNF-α and IL-6, which trigger and maintain the inflammatory disorders, drug development based on the chemical structure of ebastine and carebastine might be beneficial for the treatment of inflammatory disorders in which TNF-α and IL-6 may play a role in their pathophysiology, as well as allergic diseases including bronchial asthma.

Disclosure

The authors have nothing to disclose.

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