

REVIEW

Anti-inflammatory properties of desloratadine

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Summary

Background Allergic rhinitis (AR) is associated with robust infiltration of immune cells and mediators that may contribute to clinical manifestations of the disease.

Objective To review the complex immune effector mechanisms involved in the allergic response and discuss their effects on the pathophysiological and clinical manifestations of AR. Desloratadine, a novel antihistamine, was used as a probe with the goal of attaining a better understanding of the inflammatory processes underlying the allergic response.

Methods Data were obtained from abstracts and peer-reviewed journals. The pathophysiology of the allergic response has been extensively studied. This paper presents only data from studies that used desloratadine at physiologically relevant concentrations.

Results Key mediators involved in the allergic response and in pathophysiological and clinical manifestations of the immune response were reviewed. Desloratadine was used as a probe to further elucidate the mechanisms involved during an allergic response.

Conclusions Some have proposed a link between the pathophysiology of AR and the clinical manifestation of symptoms. Desloratadine, a new-generation antihistamine, has demonstrated anti-inflammatory effects *in vitro*; indeed, desloratadine is capable of intervening at various points in the immune cascade. Although *in vitro* results do not necessarily correlate with clinical efficacy, the anti-inflammatory properties of desloratadine may contribute to its efficacy in patients with AR, allergy-induced asthma, and other related allergic conditions. Antihistamines that modulate in the immune system at various stages may optimize treatment of allergic disease.

Keywords allergic diseases, anti-inflammatory properties, desloratadine, pathophysiology

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Introduction

Allergic rhinitis (AR) is a global health condition affecting 10–30% of the US population [1] and an estimated 20% of the population worldwide [2]. Extrapolation from 1993 US census data suggests that each year, approximately 80 million people experience at least one symptom associated with AR [3]. AR can substantially impair cognitive functioning, disrupt quality of life (e.g. diminished ability to concentrate, disrupted sleep pattern), and negatively impact work and school performance [1]. It is now appreciated that morbidity associated with AR is, in part, linked to the fact that AR is closely associated with, or predisposes patients to, a variety of other conditions, including asthma, sinusitis, otitis media, nasal polyposis, and lower respiratory tract infection [4]. Extensive research has established the link between AR and allergic asthma; results suggest that the manifestations of these two conditions arise from a common underlying systemic inflammatory process [5].

Antihistamines have demonstrated clinical efficacy against symptoms of AR and consequently remain a first-line therapy for many allergic conditions [6]. Recognition that H₁-receptor antagonism is not the sole mechanism by which these drugs provide relief for patients with AR has prompted efforts to further delineate the mechanisms of action of newer antihistamines. Recognition of the pleiotropic effects of newer-generation antihistamines further supports their use in the treatment of AR and other allergic conditions. Specifically, several second-generation antihistamines (e.g. loratadine, fexofenadine, cetirizine) have proven anti-inflammatory properties, including down-regulation of cell adhesion molecule expression [7] and inhibition of cytokine production [8–10]. The clinical significance of the anti-allergic and anti-inflammatory properties of antihistamines is a critical area of research [11].

This paper reviews the immune effector mechanisms involved in the allergic response and discusses their effects on the pathophysiological and clinical manifestations of AR. We conclude by using desloratadine, a novel antihistamine, as a probe in attaining a better understanding of the inflammatory processes that underlie the allergic response. Extensive characterization of its anti-inflammatory properties supports the use of desloratadine as an ideal tool to enhance our knowledge of the allergic cascade.

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Pathophysiology of the allergic response

AR is initiated through a series of complex inflammatory processes involving a number of diverse immune mediators and effector mechanisms [12, 13]. Interactions between numerous cell types and inflammatory mediators result in an immune cascade. The allergic response comprises three distinct phases: sensitization, early-phase responses, and late-phase responses. The sensitization process begins when the patient is first exposed to an allergen. The allergen is subsequently opsonized by resident antigen-presenting cells (e.g. dendritic cells, macrophages), which then prime naïve allergen-reactive T cells. Once activated, these T cells produce and secrete several cytokines, primarily IL-4, the principal cytokine involved in B cell priming and differentiation [11]. This sensitization phase culminates with the production of allergen-specific IgE antibodies [13] that bind to the surfaces of mast cells and basophils, causing degranulation and subsequent mediator release [12]. The presence of IgE on respiratory mast cells sets the stage for the early-phase inflammatory response, which begins following re-exposure to allergen. Although the immune response has been initiated, patients generally remain asymptomatic throughout the sensitization phase. The allergic response can be divided into early- and late-phase responses, with each phase being associated with specific immune mediators and pathophysiological consequences [11].

Early-phase inflammatory response

The early-phase response commences when a previously sensitized patient is re-exposed to a specific allergen, stimulating the cross-linking of adjacent basophil- or mast cell-bound IgE antibodies (Fig. 1) [12]. This event initiates degranulation of mast cells and basophils, thereby releasing preformed inflammatory mediators (e.g. histamine, tryptase, bradykinin) and *de novo* synthesized pro-inflammatory substances (e.g. leukotriene C₄ (LTC₄), prostaglandin D₂ (PGD₂), cytokines).

Histamine, the most abundant mediator involved in an allergic reaction, predominates during the early-phase response. Because nasal histamine challenge mimics many of the symptoms associated with AR (e.g. nasal itching, sneezing, rhinorrhea, and nasal congestion), histamine has been implicated as a principal mediator involved in the allergic cascade. The direct allergic effects of histamine are mediated through activation of H₁ receptors found primarily on vascular endothelium and bronchial and vascular smooth muscle cells, cardiac myocytes, and cells of the central nervous system. This process induces expression of endothelial cell adhesion molecules (e.g. P-selectin, intercellular adhesion molecule (ICAM-1)) and triggers the production of numerous cytokines (e.g. IL-8) and chemokines (e.g. eotaxin) [2, 14].

During the early-phase reaction, preformed inflammatory mediators (e.g. tryptase, eosinophil chemotactic factor), in

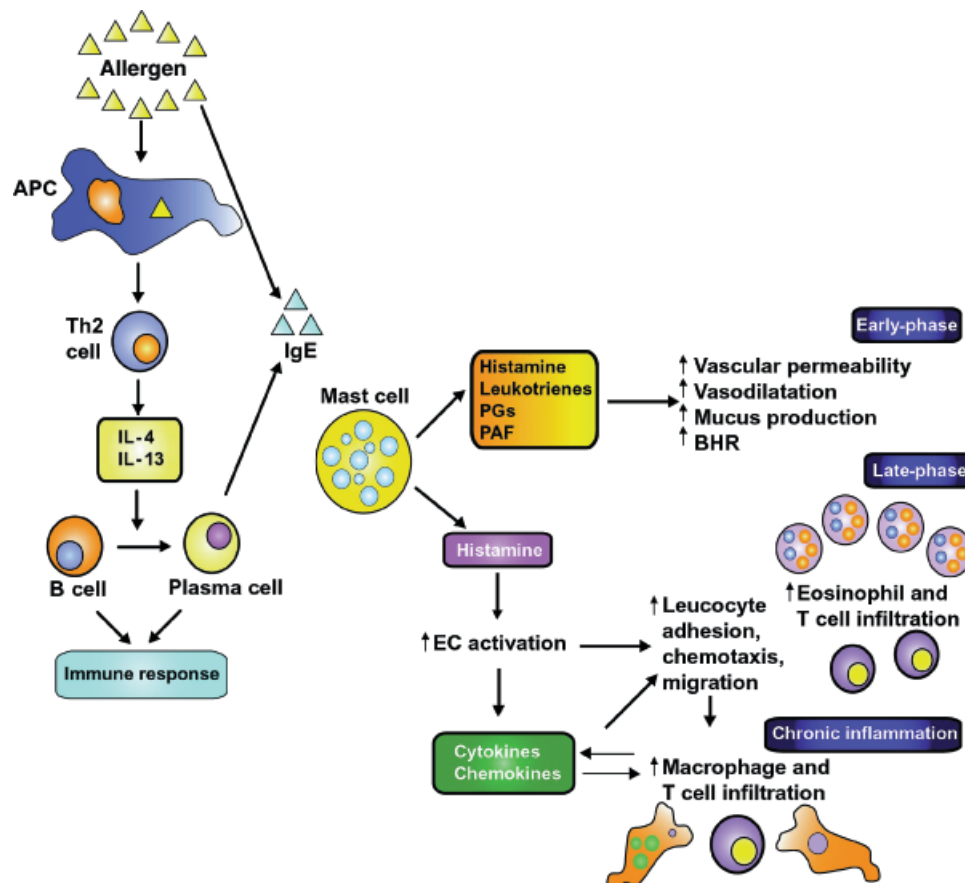


Fig. 1. The allergic inflammatory response: early- and late-phase reactions. APC, antigen-presenting cell; BHR, bronchial hyper-responsiveness; EC, endothelial cell; PAF, platelet-activating factor; PG, prostaglandin. Adapted with permission [2].

addition to histamine and newly synthesized molecules (e.g. PGD₂, LTC₄, platelet-activating factor (PAF), bradykinin), are released from mast cells and basophils [15]. The release of preformed and newly synthesized immune mediators has synergistic effects on upper and lower respiratory tissues [13]. Patients note symptoms within minutes of re-exposure to the allergen [2, 11]; symptoms associated with the early-phase response usually resolve spontaneously when the released mediators are metabolized and cleared from the nasal mucosa [2]. Once the early-phase response has been initiated, control of more downstream events becomes more challenging. This is demonstrated by the fact that about half of all patients who exhibit an early-phase allergic response experience a late-phase inflammatory reaction approximately 4–24 h following allergen exposure [2, 11].

Late-phase inflammatory response

The period comprising the end of the early-phase response and entry into the late-phase allergic response is characterized by endothelial cell activation and release of inflammatory cytokines (e.g. IL-3, IL-4, IL-5, IL-6, IL-13, TNF- α and granulocyte-macrophage colony-stimulating factor (GM-CSF)) (Fig. 2) [12, 16]. Several of these cytokines stimulate cellular release of chemokines (e.g. regulated upon activation, normal T cell expressed and secreted (RANTES), eotaxin) that attract eosinophils and basophils to activate tissue [16]. Up-regulation of endothelial cell adhesion molecules (e.g. E-selectin, P-selectin, ICAM-1, vascular cell adhesion molecule) is critical in facilitating the trafficking of eosinophils and basophils from the vascular lumen, through the vessel wall, and into inflamed respiratory mucosa.

The late-phase reaction is characterized by an intense influx of inflammatory granulocytes – predominantly eosinophils, along with basophils, neutrophils, and lymphocytes – into the nasal mucosa and other affected tissues [16]. Eosinophils secrete several substances that promote the chronic late-phase inflammatory reaction [13]. Eosinophil cationic protein and major basic protein appear to stimulate cellular disaggregation and epithelial desquamation, leading to cell death [13].

Eosinophil-derived protein and eosinophil peroxidase may inactivate mucosal nerves and lead to free radical damage of cells, respectively [13]. Numerous eosinophil-derived cytokines and chemokines (e.g. IL-3, IL-5, GM-CSF, eotaxin, RANTES) are secreted; these promote eosinophil survival and eosinophil chemoattraction [13]. The release of these eosinophil-derived pro-inflammatory substances ultimately disrupts the mucosal epithelium of the airway, resulting in clinical symptoms associated with the late-phase response.

Mast cell degranulation and the subsequent release of pro-inflammatory mediators (i.e. cytokines, chemokines, leukotrienes) provide chemoattractants for immune cells involved in the late-phase response. Release of TNF- α and IL-4 from activated T cells can result in the up-regulation of cellular adhesion molecules on the nasal endothelium and nasal mucosa. Increased expression of adhesion molecules of the nasal epithelium allows for the extravasation and entry of activated immune cells into the mucosal region. It is not uncommon for some patients to experience hyper-reactivity and bronchial hyper-responsiveness to allergic and non-allergic (e.g. cigarette smoke) stimuli during this phase [12]. Hyper-reactivity responses can persist for several days and may develop into a chronic inflammatory disease [2, 12].

Allergic inflammation: clinical consequences

The inflammatory mediators involved in the early- and late-phase responses are associated with the development of specific symptoms in patients with AR. The early-phase response is primarily caused by the release of preformed mediators (e.g. histamine, tryptase, bradykinin), which contribute to the pathophysiology of this disease.

Most acute symptoms associated with AR and allergic asthma are related to the rapid activity of histamine on the vascular endothelium and bronchial and vascular smooth muscle cells [14]. Histamine exerts its inflammatory effects by binding to neuronal H₁ receptors present on the epithelium and in submucosal regions. During the early-phase inflammatory reaction, histamine promotes vasodilatation and vascular

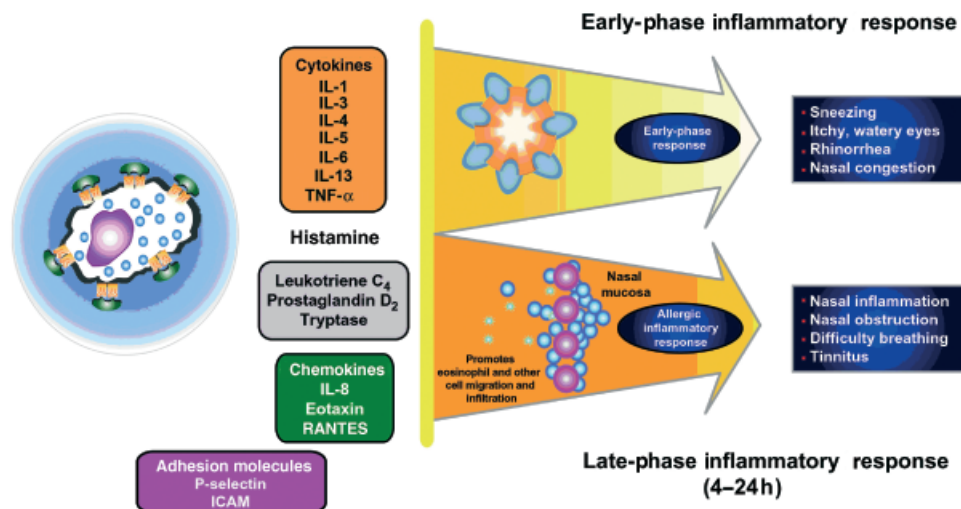


Fig. 2. Cytokines, chemokines, and endothelial adhesion molecules associated with early- and late-phase reactions. ICAM, intercellular adhesion molecule; RANTES, regulated upon activation, normal T cell expressed and secreted.

permeability, hypersecretion of mucus, oedema, and bronchoconstriction [2]. Specifically, itching and sneezing result from the binding of histamine to nerve endings, triggering a reflex arc [13]. Histamine-induced increases in vascular permeability and increased glandular secretions can lead to rhinorrhea. The binding of histamine to H_1 receptors on nociceptive type C nerves releases a variety of inflammatory mediators, causing stimulation of parasympathetic reflexes and, ultimately, increased secretion of mucus and nasal congestion [13]. Non-nasal symptoms, including itchy, red, watery eyes and itchy palate, also occur during the acute-phase response. Collectively, the mast cell-derived mediators cause many of the acute-phase clinical symptoms associated with AR.

During the late-phase response, patients experience a recurrence of early-phase symptoms. However, nasal congestion is the predominant symptom of the late-phase response [2, 11]. Nasal congestion during the late-phase response is caused, in part, by an influx of activated inflammatory cells migrating into the mucosa following allergen exposure; eosinophils are believed to play a critical role in establishing nasal congestion [16]. In addition to histamine, LTC_4 and PGD_2 cause increased vascular permeability, increased production of mucus, bronchoconstriction, and vasodilatation, resulting in airway oedema, sneezing, nasal congestion, and rhinorrhea [12, 13]. Patients with allergic skin disease typically exhibit signs and symptoms of erythema, pruritus, and oedema as part of a late-phase reaction [2].

Desloratadine: potent inhibitor of the immune cascade

Clinical trials have demonstrated the efficacy of desloratadine 5 mg for the treatment of seasonal AR (SAR) and chronic idiopathic urticaria [17–20]. Although these trials reported a significant reduction in classic symptoms typically attributed to histamine (e.g. sneezing, rhinorrhea), desloratadine 5 mg has also effectively reduced nasal congestion [21]. These observations suggest that desloratadine might target both early- and late-phase mediators of the allergic cascade. Therefore, it is suggested that the efficacy of desloratadine may be due, in part, to its potent anti-inflammatory properties. Indeed, numerous *in vitro* studies have demonstrated that desloratadine possesses anti-inflammatory properties at pharmacologically relevant concentrations (10^{-9} – 10^{-7} M) [22].

Potent H_1 -receptor antagonist

Desloratadine possesses greater affinity and avidity for H_1 receptors compared with many currently available antihistamines [23, 24]. Anthes et al. [25] demonstrated that the association of desloratadine with the H_1 receptor was significantly greater than that of other antihistamines – 63% of drug remained bound after 6 h. Collectively, these data provided the first evidence that desloratadine had potent antihistaminic activity and favourable H_1 -receptor dynamics.

Anti-allergic effects of desloratadine

Mast cell/basophil histamine stabilization Although many mediators and cells are involved in the allergic inflammatory

response, inhibition of the effects and release of histamine remains important for the relief of signs and symptoms of AR and related allergic conditions. Desloratadine has been shown to inhibit the release of preformed histamine from human mast cells and basophils induced by both IgE-dependent and IgE-independent mechanisms [26, 27]. The effect of desloratadine on histamine release was studied in human basophils challenged with a variety of stimuli [27]. Desloratadine inhibited IgE-mediated histamine release from leucocytes in a concentration-dependent manner [27]. Another study demonstrated that desloratadine suppressed histamine release from human peripheral blood basophils and tissue mast cells ($Fc\epsilon RI^+$) by 10–40% following allergen challenge [26]. It has been proposed that desloratadine prevents histamine release from mast cells by directly inhibiting the release of free intracellular calcium [28]; others have suggested that desloratadine exerts its effects following the influx of calcium into the cell [26]. In addition, desloratadine inhibits the release of other preformed mediators (i.e. tryptase and PGD_2) from human mast cells *in vitro*, demonstrating its effects on more than one mediator associated with the early-phase reaction [26].

Although sufficient evidence has demonstrated the effects of desloratadine on H_1 receptors and mast cell/basophil-derived histamine release, these actions cannot account for all of the clinical benefits of desloratadine in patients with AR and other allergic conditions. Because of the complexity of the immune response that is involved in an allergic reaction, it cannot be assumed that blockade of histamine alone is sufficient to allay all of the symptoms associated with this disease. Therefore, it is possible that desloratadine provides beneficial effects that are independent of H_1 -receptor binding and mast cell histamine release [29].

Other H_1 -receptor-independent mechanisms of desloratadine

Eosinophils Eosinophils are critically involved in the late-phase allergic response; they contribute to the development of AR and bronchial asthma. Accordingly, antihistamines that interfere with eosinophil recruitment and function (i.e. secretion of inflammatory mediators and proteins) are likely to minimize mucosal inflammation in the airways and contribute clinical benefits. Agrawal [30] evaluated the effects of desloratadine on the chemotaxis, adhesion, and superoxide production of human blood eosinophils *in vitro*. With the use of purified eosinophils obtained from patients with AR or allergic asthma, desloratadine (10^{-7} – 10^{-5} M) was shown to significantly down-regulate PAF-induced chemotaxis by up to 36% ($P < 0.02$) (Fig. 3). In a separate experiment, TNF- α -induced eosinophil adhesion to human umbilical vein endothelial cells was also significantly reduced by desloratadine in a concentration-dependent manner; maximum attenuation of 27% was observed at 10^{-5} M of desloratadine ($P < 0.02$) (Fig. 4) [30]. In the same cell line, desloratadine in concentrations of 10^{-5} M inhibited the generation of spontaneous and phorbol myristate acetate (PMA)-stimulated superoxide radicals. Notably, the effect of desloratadine on chemotaxis, adhesion, and superoxide production was similar in cells obtained from patients with AR and allergic asthma [30].

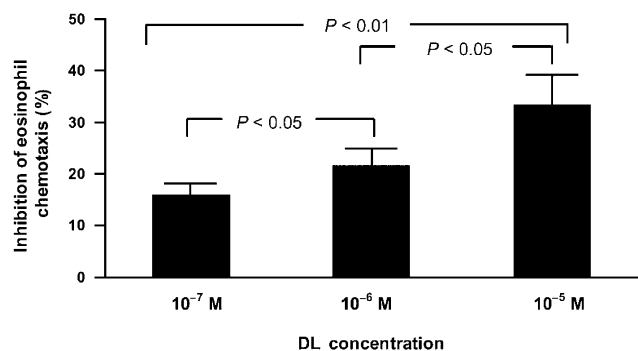


Fig. 3. Effect of desloratadine (DL) on platelet-activating factor-induced eosinophil chemotaxis. Adapted with permission [30].

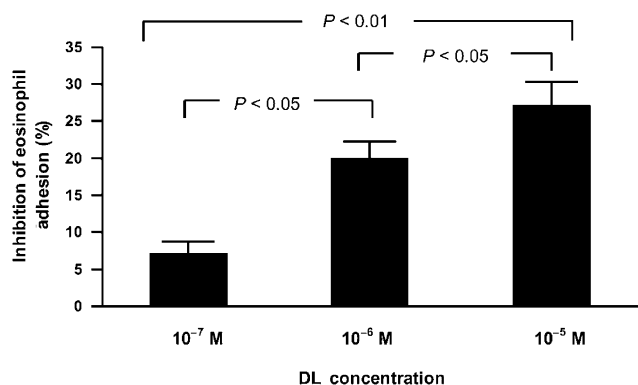


Fig. 4. Effect of desloratadine (DL) on eosinophil adhesion to human umbilical vein endothelial cells (HUVEC). Adapted with permission [30].

The *in vitro* effects of desloratadine on eosinophils that were described earlier have also been demonstrated *in vivo*. The study by Cyr et al. [31] was based on the well-recognized concept that the number of eosinophil and basophil progenitors in the circulation declines during the peak allergy season in sensitized patients because of trafficking to inflamed nasal/airway mucosal tissues. In a 4-week, randomized, double-blind study conducted during a ragweed pollen season, 45 symptomatic patients with SAR were randomly assigned to receive desloratadine 20 mg or placebo daily. Peripheral blood eosinophil/basophil progenitors declined significantly in patients who were administered placebo compared with desloratadine, suggesting an increased eosinophil influx into the nasal mucosa following placebo treatment ($P = 0.013$) [31]. Eotaxin levels in nasal lavage fluids were also significantly lower in desloratadine-treated patients. Although the administered dose of desloratadine was greater than the recommended dose, the results demonstrated that desloratadine could alter aspects of the immune response through mechanisms other than H_1 -receptor blockade.

Recently, Agrawal and Berro [32] demonstrated a novel anti-inflammatory effect of desloratadine on human blood eosinophils *in vitro*. The main finding of this study was that desloratadine significantly induced apoptosis of human blood eosinophils in a concentration-dependent manner (10^{-7} – 10^{-5} M); significant apoptotic effect was observed in concentrations that are therapeutically relevant. Although the mechanism for desloratadine-induced eosinophil apoptosis remains to be elucidated, this is the first study to demonstrate

the apoptotic effect of a new-generation antihistamine. Very recently, Domae et al. [33] reported the effect of oxatomide, an anti-allergic drug, in promoting apoptosis in human blood eosinophils. However, the effect of oxatomide on eosinophil apoptosis was observed in concentrations much higher than those seen in clinical doses ($> 20 \mu\text{M}$).

Adhesion and adhesion molecule expression It is well recognized that accumulation of inflammatory cells at tissue sites depends, in part, on the up-regulation of specific endothelial adhesion molecules. It is well established that desloratadine can down-regulate cell adhesion molecule expression (i.e. ICAM-1 and P-selectin) *in vitro* [34–36]. Following stimulation with histamine (10^{-4} M), P-selectin expression was reduced by desloratadine (2.3×10^{-8} – 1.3×10^{-8} M) in human umbilical vein endothelial cells [36]. Additional studies have demonstrated the effects of desloratadine on cell adhesion molecule expression, albeit at greater than pharmacologically relevant concentrations of the drug. Vignola et al. [34] evaluated the inhibitory effects of desloratadine on histamine-induced activation of nasal epithelial cells obtained from non-allergic patients. Another study reported that rhinovirus-induced ICAM-1 expression on cultured primary bronchial and transformed (type II) respiratory epithelial cells was down-regulated following pretreatment with desloratadine [35]. It is interesting to note that desloratadine (10^{-7} – 10^{-5} M) inhibited ICAM-1 mRNA expression in a concentration-dependent manner and blocked rhinovirus-induced ICAM-1 promoter activation. This latter study, which was conducted in a histamine-free environment, further indicated that desloratadine has activity beyond H_1 -receptor blockade.

T-helper type 1 (Th1) and Th2 cytokines *In vitro* studies have demonstrated that desloratadine modulates the release of Th2 cytokines [9, 37, 38]. Desloratadine inhibited IL-4 and IL-13 release (~ 40 – 80%) from anti-IgE-stimulated human basophils to a much greater extent (6-fold) than the release of histamine and LTC₄ [38]. IL-4 mRNA expression was also significantly inhibited (up to 80%) by desloratadine, suggesting that desloratadine may interfere with cytokine gene transcription [38].

Following treatment with desloratadine, reductions in release of the pro-inflammatory cytokines IL-6 and IL-8 from human lung and skin mast cells and basophilic cell lines have been described in three *in vitro* studies [9, 36, 37]. Pre-incubation with desloratadine (10^{-14} – 10^{-5} M) dose dependently suppressed IL-6 release by up to 40% and IL-8 secretion by up to 50% following exposure to various stimuli [37]. Similar findings were obtained by Molet et al. [36], who reported that desloratadine inhibited IL-8 mRNA levels. Another report compared the suppression of IL-6, IL-8, IL-3, TNF- α , and GM-CSF secretion from stimulated human mast cells incubated with various antihistamines [9]. Desloratadine (10^{-9} M) was almost as effective as dexamethasone, a potent corticosteroid, and more potent than cetirizine (10^{-9} M) in inhibiting cytokine secretion [9]. Collectively, these data demonstrate that desloratadine interferes with many cell types and immune mediators involved in an allergic response (Fig. 5).

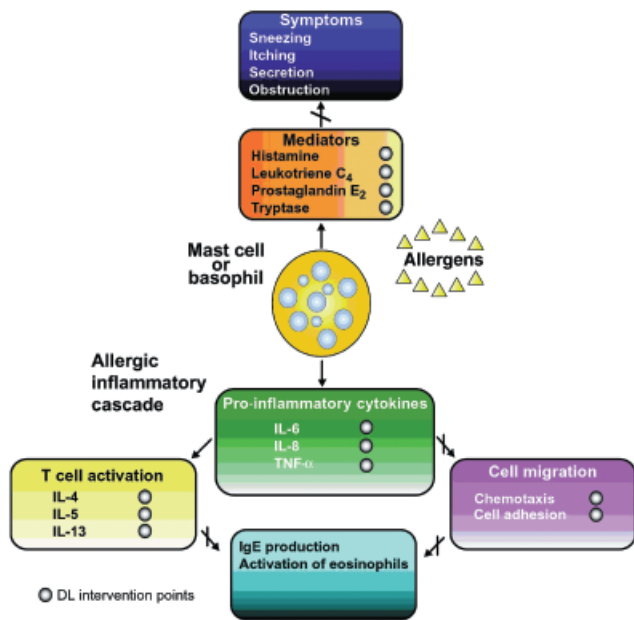


Fig. 5. Effect of desloratadine (DL) at multiple points during the allergic cascade.

Novel mechanism of action

The anti-inflammatory effects of desloratadine have been demonstrated in numerous studies. However, the mechanism by which desloratadine blocks key immune effector molecules has remained elusive. Recently, two separate research groups have proposed that desloratadine targets a key molecule involved in the transcription and subsequent expression of cytokines and cell adhesion molecules [35, 39]. Papi et al. [35] provided initial data demonstrating that desloratadine inhibits rhinovirus-induced nuclear factor-kappa B (NF-κB) activity. Recent evidence has further extended these findings by demonstrating the inhibitory effects of desloratadine on NF-κB activation *in vitro* [39]. Whether inhibition of NF-κB is responsible for the anti-inflammatory effects of desloratadine is unclear. Future work towards a better understanding of the molecular mechanisms by which desloratadine inhibits key inflammatory processes is currently under way.

Conclusions

Over the past decade, much has been learned about the pathophysiology that governs allergic conditions. Signs and symptoms associated with allergy-based diseases are the consequence of a complex and highly integrated immune network of effector cells and chemical mediators. It is now appreciated that, although histamine is a key mediator of both early- and late-phase responses, many other mediators and cells are vital to the inflammatory process. As such, drugs that solely neutralize histamine may not be completely effective in the treatment of many allergic conditions.

In vitro and *in vivo* data have demonstrated that desloratadine, a newer-generation H₁-receptor antagonist, attenuates numerous critical pathways of the allergic inflammatory response. Although *in vitro* results do not necessarily correlate with clinical efficacy, the anti-inflammatory properties of

desloratadine may contribute to its efficacy in patients with AR, allergy-induced asthma, and other related allergic conditions. Administration of antihistamines that modulate the mast cell–eosinophil axis of the immune system may optimize treatment of allergic disease.

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References

- 1 Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99:S805–28.
- 2 Salmun LM. Antihistamines in late-phase clinical development for allergic disease. *Expert Opin Invest Drugs* 2002; 11:259–73.
- 3 Nathan RA, Meltzer E, Selner JC, Storms WW. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99 (6 Part 2):S808–14.
- 4 Allergic rhinitis: diagnosis and complications. *Patient Care*, Fall 2000; 8–16.
- 5 Bousquet J, Van Cauwenberg P, Khaltaev N, ARIA Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108:S147–334.
- 6 Van Cauwenberg P, Bachert C, Passalacqua G et al. Consensus statement on the treatment of allergic rhinitis. *Allergy* 2000; 55:116–34.
- 7 Branco-Ferreira M, dos Santos MC, Palma-Carlos ML, Palma-Carlos AG. Antihistamines and serum adhesion molecule levels. *Allergy Immunol (Paris)* 2001; 33:233–6.
- 8 Sedgwick JB, Busse WW. Inhibitory effect of cetirizine on cytokine-enhanced *in vitro* eosinophil survival. *Ann Allergy Asthma Immunol* 1997; 78:581–5.
- 9 Lippert U, Moller A, Welker P, Artuc M, Henz BM. Inhibition of cytokine secretion from human leukemic mast cells and basophils by H₁- and H₂-receptor antagonists. *Exp Dermatol* 2000; 9:118–24.
- 10 Abdelaziz MM, Devalia JL, Khair OA, Bayram H, Prior AJ, Davies RJ. Effect of fexofenadine on eosinophil-induced changes in epithelial permeability and cytokine release from nasal epithelial cells of patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1998; 101:410–20.
- 11 Assanasen P, Naclerio RM. Antiallergic anti-inflammatory effects of H₁-antihistamines in humans. *Clin Allergy Immunol* 2002; 17:101–39.
- 12 Pearlman DS. Pathophysiology of the inflammatory response. *J Allergy Clin Immunol* 1999; 104:S132–7.
- 13 Baraniuk JN. Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 1997; 99:S763–72.
- 14 Gelfand EW. Role of histamine in the pathophysiology of asthma: immunomodulatory and anti-inflammatory activities of H₁-receptor antagonists. *Am J Med* 2002; 113 (Suppl. 8):2–7.
- 15 Scadding GK. Desloratadine in the treatment of nasal congestion in seasonal allergic rhinitis. Preclinical and clinical evidence. *Clin Drug Invest* 2002; 22 (Suppl. 2):21–32.
- 16 Meltzer E. Allergic rhinitis: a systemic inflammatory process. *Patient Care* 2002; Spring:7–15.
- 17 Meltzer E, Prenner B, Nayak A, Desloratadine Study Group. Efficacy and tolerability of once-daily 5 mg desloratadine, an H₁-receptor antagonist, in patients with seasonal allergic rhinitis: assessment during the spring and fall allergy seasons. *Clin Drug Invest* 2001; 21:25–32.

- 18 Berger WE, Schenkel EJ, Mansfield LE. Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. *Ann Allergy Asthma Immunol* 2002; 89: 485–91.
- 19 Ring J, Hein R, Gauger A, Bronsky E, Miller B, The Desloratadine Study Group. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Int J Dermatol* 2001; 40:1–5.
- 20 Monroe E, Finn A, Patel P, Guerrero R, Ratner P, Bernstein D. Efficacy and safety of desloratadine 5 mg once daily in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2003; 48:535–41.
- 21 Nayak AS, Schenkel E. Desloratadine reduces nasal congestion in patients with intermittent allergic rhinitis. *Allergy* 2001; 56:1077–80.
- 22 Geha RS, Meltzer EO. Desloratadine: a new, nonsedating, oral antihistamine. *J Allergy Clin Immunol* 2001; 107:751–62.
- 23 Kreutner W, Hey JA, Anthes J, Barnett A, Young S, Tozzi S. Preclinical pharmacology of desloratadine, a selective and non-sedating histamine H₁ receptor antagonist. 1st communication: receptor selectivity, antihistaminic activity, and antiallergenic effects. *Arzneimittelforschung* 2000; 50:345–52.
- 24 Anthes J, Richard C, West RE et al. Functional characterization of desloratadine and other antihistamines in human histamine H₁ receptors. *Allergy* 2000; 55 (Suppl. 63):277–8.
- 25 Anthes J, Gilchrist H, Richard C et al. Biochemical characterization of desloratadine, a potent antagonist of the human histamine H₁ receptor. *Eur J Pharmacol* 2002; 449:229–37.
- 26 Genovese A, Patella V, De Crescenzo G, De Paulis A, Spadaro G, Marone G. Loratadine and desethoxycarbonyl-loratadine inhibit the immunological release of mediators from human FcεRI⁺ cells. *Clin Exp Allergy* 1997; 27:559–67.
- 27 Kleine-Tebbe J, Jostes C, Frank G et al. Inhibition of IgE- and non-IgE-mediated histamine release from human basophil leukocytes *in vitro* by a histamine H₁-antagonist, desethoxycarbonyl-loratadine. *J Allergy Clin Immunol* 1994; 93:494–500.
- 28 Berthon B, Taudou G, Combettes L et al. *In vitro* inhibition, by loratadine and descarboxyethoxyloratadine, of histamine release from human basophils, and of histamine release and intracellular calcium fluxes in rat basophilic leukemia cells. *Biochem Pharmacol* 1994; 47:789–94.
- 29 Leurs R, Church MK, Taglialatela M. H₁-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002; 32:489–98.
- 30 Agrawal DK. Pharmacology and clinical efficacy of desloratadine as an anti-allergic and anti-inflammatory drug. *Expert Opin Invest Drugs* 2001; 10:547–60.
- 31 Cyr MM, Baatjes AJ, Hayes LM, Crawford L, Denburg JA. The effect of desloratadine on eosinophil/basophil progenitors and other inflammatory markers in seasonal allergic rhinitis: a placebo-controlled randomized study. *J Allergy Clin Immunol* 2002; 109:S117.
- 32 Agrawal DK, Berro A. Effect of desloratadine (DL) on the apoptosis of human blood eosinophils. *Ann Allergy Asthma Immunol* 2003; 90:100–1.
- 33 Domae M, Sagara H, Sakaue M, Fukuda T, Kamikawa Y. The antiallergic drug oxatomide promotes human eosinophil apoptosis and suppresses IL-5-induced eosinophil survival. *Allergy Clin Immunol* 2003; 111:567–72.
- 34 Vignola AM, Crampette L, Mondain M et al. Inhibitory activity of loratadine and descarboethoxyloratadine on expression of ICAM-1 and HLA-DR by nasal epithelial cells. *Allergy* 1995; 50:200–3.
- 35 Papi A, Papadopoulos N, Stanciu L, Degitz K, Holgate S, Johnston S. Effect of desloratadine and loratadine on rhinovirus-induced intercellular adhesion molecule 1 upregulation and promoter activation in respiratory epithelial cells. *J Allergy Clin Immunol* 2001; 108:221–8.
- 36 Molet S, Gosset P, Lassalle P, Czarlewski W, Tonnel AB. Inhibitory activity of loratadine and descarboxyethoxyloratadine on histamine-induced activation of endothelial cells. *Clin Exp Allergy* 1997; 27:1167–74.
- 37 Lippert U, Krüger-Krasagakes S, Möller A, Kiessling U, Czarnetzki BM. Pharmacological modulation of IL-6 and IL-8 secretion by the H₁-antagonist descarboethoxy-loratadine and dexamethasone by human mast and basophilic cell lines. *Exp Dermatol* 1995; 4:272–6.
- 38 Schroeder JT, Schleimer RP, Lichtenstein LM, Kreutner W. Inhibition of cytokine generation and mediator release by human basophils treated with desloratadine. *Clin Exp Allergy* 2001; 31:1369–77.
- 39 Wu R, Anthes JC, Kreutner W et al. Desloratadine exhibits inverse agonism and inhibits NFκB activity. *J Allergy Clin Immunol* 2003; 111:283.