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REVIEW

THE ANTIINFLAMMATORY EFFECT OF H1 ANTIHISTAMINES IN ALLERGIC RHINITIS

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Abstract. Allergic rhinitis is an immune inflammatory process, IgE mediated, which affects nasal mucosa. The immune allergic response presents 3 phases and involves many cells and mediators. Interleukins are involved both in producing and maintaining this process. Il-1, Il-6 and TNF-a increase allergic inflammation and are involved in producing the late phase of inflammation. The studies regarding unique or continuous exposure to specific allergens of the patients with allergic rhinitis revealed the increase of the proinflammatory cytokines level both in nasal secretion and in plasma. Histamine is the main mediator involved in allergic rhinitis through type 1 specific receptors. H1 antihistamines are first line treatment in all forms of allergic rhinitis. New generation antihistamines possess some anti-inflammatory properties, especially relevant in vitro studies and sometimes in vivo studies.
Keywords: H1 antihistamines, anti-inflammatory effect, interleukines

Introduction

Allergies are diseases with increasing incidence and prevalence, with multiple therapeutical and socio-economical problems. An atopic person could develop different clinical forms of allergies (food allergy, atopic dermatitis, bronchial asthma, allergic rhinitis). Allergies must be understood as lifetime systemic diseases[1]. Allergic rhinitis is an IgE mediated process which affects nasal mucosa. It is a chronic disease with acute episodes, that influences the patients' quality of life and reduces their school and profesional performances of them.[2, 3].

H1 antihistamines treatment is now the first line of treatment in allergic rhinitis[3]. These drugs improve allergic rhinitis specific symptoms, as nasal itching, rhinorrea, sneeze, with a low effect on nasal congestion. For the second generation H1 antihistamines (levocetirizine, fexofenadine and desloratadine) a high efficiency on nasal congestion was demonstrated, due to an additional anti-inflammatory effect[2].

Allergic rhinitis

The disease is underdiagnosed, in most of the cases being considered a normal situation by the patients[2]. Allergic rhinitis is a global health problem, affecting between 10 to 25% of the general population, but in some countries the prevalence is up to 40%[3, 5]. In many cases allergic rhinitis is a risk factor for asthma development[6].

ARIA consensus recently classified allergic rhinitis as intermmitent and persistent, dropping out to previous one in seasonal and perennial rhinitis. This classification was chosen because most of the patients are polisensitized and in some geographical regions pollen season is prolonged, so a seasonal

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allergic rhinitis may become a perennial one[3]. This modifies the type and duration of treatment.

Recent descoveries in cell and molecular biology have demonstrated that chronic inflammation is the key of allergic rhinitis pathogenesis. Allergic reaction involves a cascade of inflammatory processes which involve many cells and mediators. The immune response consists in 3 phases.

1. The first phase of allergic inflammation consists in allergen sensitization at first exposure to this. Th2 lymphocytes are activated after antigen presentation by antigen presenting cells (APC). Activated TH2 lymphocytes synthesize mediators, mainly IL-4 and IL-13. These will stimulate IgE synthesis from B lymphocytes. Antigen specific IgE will be fixed on target cells surface (mast cell and basophil), which present specific receptors.

2. The second phase starts at involved antigen reexposure and represents early allergic reaction. An interaction between antigen and fixed specific IgE takes place and this interaction produces mast cell and basophil degranulation with release of preformed (histamine) or de novo (interleukins, prostaglandins, kinines and leukotrienes) pro-inflammatory mediators. Histamine is resopnsable for acute inflammation and is considered the key mediator for allergic diseases. De novo mediators subsequently activate other interleukins and adhesion molecules, favorizing second phase pro-inflammatory cells migration.

3. In the 3rd phase there is a cellular inflammatory response which increases acute inflammation, changing it into a chronic one. In later phase the eosinophil is the primary cell, that releases cytokines responsible for chronic inflamation (IL-1, IL-3, IL-5, IL-6, IL-8, TNFα, TGFα and β)[7].

Histamine and specific receptors

Histamine is the primary mediator involved in allergic rhinitis acute symptoms appearance. This reaction is mediated through type 1 specific receptors[8].

Since 1966 to the present 4 types of histamine specific receptors were identified and cloned: H1, H2, H3 and H4. They belong to G coupled receptors family[9]. They are transmembrane molecules, formed by 7 helix, that convert extracelular signal using G proteins and intracellular second systems[9]. The receptors have different localizations and cell expresions, but also a different role. Regarding their role in immune system it has been observed that H1 receptors activation produces the stimulation of this system with enhancement of pro-inflammatory activity and cell migration to inflammatory site. The H2 receptors activation determines an anti-inflammatory effect with efficient suppresion of the functions[10, 11]. There are few inconstant data regarding types 3 and 4 involvement in allergic reaction[10].

Histamine receptors can be found in both active and inactive status, these two being in balance. Type 1 receptors are mainly involved in producing hypersensitivity reaction and allergic inflammatory response[9, 10]. Binding histamine to receptors stabilizes its active form of this with pro-inflammatory effect[12]. Following this mast cells and basophils

	H1 Receptor	H2 Receptor	H3 Receptor	H4 Receptor
Structure	487 aa, 56 kDa	359 aa, 40 kDa	445 aa, 70 kDa; splice variants	390 aa,
Role of histamine in allergic inflammation	↑ histamine and other mediators release; ↑ adhesion molecules expression and Eo and N chemotaxis; ↑ APC activity, co-stimulatory effect on B cell; ↑ cellular immunity (Th1); ↑ IFNγ; ↑ auto-immunity; ↓ humoral immunity and IgE synthesis	↓ Eo and N chemotaxis; ↓ IL-12 produced by DC; ↑ IL-10 induces Th2 response or tolerance-inducing DC; ↑ humoral immunity; ↓ cellular immunity; supress Th2 cells and specific cytokines; role in allergies, auto-immunity, malignancy, graft rejection	Probably involved in control of neurogenic inflammation; ↑ pro-inflammatory activity and APC activity	↑ calcium flux in Eo; ↑ Eo chemotaxis; ↑ IL-16 production
Inverse agonists	> 40, loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine	Ranitidine, famotidine, nizatidine	There are some drug in clinical studies for treatment of dementia, schizophrenia, narcolepsy, other CNS disorders	Medications in development for allergic rhinitis treatment

Table I. Histamine receptors and the histamine involvement in allergic inflammation

Legend: *Histamine=His, dendritic cell=DC, lymfocit= Ly, eosinophil=Eo, neutrophil=N, antigen presenting cell=APC, (Adapted to Estelle F, Simons R, Akdis CA. Histamine and H1-Antihistamines. In Adkinson NF, Yunginger JW, Busse WW, et al. Middleton's Allergy Principles and Practice, 2008).*

release pro-inflammatory cytokines, like IL-1α, IL-1b, IL-6 and IL-8[13, 14, 15]. A part of this cytokines regulates following histamine synthesis and release and histamine receptors expression on cells surface. On the other hand it has been demonstrated that histamine is involved in lymphocytes Th1/Th2 balance and therefore immunoglobulins synthesis, favorizing Th1 response after H1 receptors activation. H2 receptor activation produces a negative regulation of both types of lymphocytes, involving different intracellular mechanisms.[16] Data regarding histamine involvement in Th1/Th2 balance are unsteady, because histamine effects depends on receptors exxpression, which is variable according to cytokines synthesis[14].

H1 antihistamines and the anti-inflammatory effect

H1 antihistamines are the largest class of medications used in allergic diseases treatment, since now there are more than 40 drugs available worldwide[10]. 1st generation H1 antihistamines are widely used in some countries, but because they pass blood brain barrier they may produce nervous central side effects, even in usual doses, like sedation and impairment of psychomotor performance[10, 11].

H1 antihistamines competitively block type 1 receptors and stabilize inactive form of them, blocking histamines effect[9]. For this reason they are called invers agonist. These drugs are first line treatment in all forms of allergic rhinitis, in monotherapy or associated with other drugs[3, 17]. This recommendation is given by symptomatic effect of H1 antihistamines, because they mainly controlle symptoms like sneeze, rhinorrea, nasal itching, with low effect on nasal congestion.

Recent studies have shown that new generation of antihistamines also influence nasal congestion, probably due to an additional anti-inflammatory effect[4, 8, 18]. Levocetirizine, desloratadine and fexofenadine possess some anti-inflammatory properties, which determine decrease of nasal congestion, presented especially in the late phase of allergic inflammation[8].

Fexofenadine is active carboxylic acid metabolite of terfenadine, with the same pharmacodynamics properties as that, by blocking H1 receptors. The affinity for H1 receptors is lower compared to levocetirizine and desloratadine[14]. But fexofenadine does not present cardiac side effects of terfenadine (QT prolongation)[19]. Levocetirizine is a potent antihistamines, the active R enantiomer of cetirizine. It has two fold affinity for H1 receptors compared to cetirizine[20]. Desloratadine is major biologically active metabolite of loratadine[21]. It has the highest affinity for H1 receptors compared to the above mentioned H1 antihistamines[14].

Fexofenadine

A study from 2001 demonstrated that fexofenadine inhibits Il-6 release from human macrophage, in concentration dependend fashion. The inhibitory effect was significant at 10^{-6} mol/L[22]. Later they demonstrated that fexofenadine in higher concentration inhibits ICAM-1 expression, but also inhibits Rantes chemokines and eotaxin release from nasal polyps fibroblasts in same concentrations which inhibits Il-6 release(14). Hoda et al showed that fexofenadine inhibits TNF- α dependent cell activation[23].

In vivo studies do not always confirmed the anti-inflammatory effect of fexofenadine observed in vitro ones. Bensch et al studied fexofenadine effect in patients with seasonal allergic rhinitis to grasses and weeds, after antigen specific nasal provocation test. They observed that 2 doses of 60 mg fexofendine /day, 7 days before nasal provocation test has no influence on the level of IL-4, Il-10, TNF-α, MIP-1α and GM-CSF, so it does not reduce allergic inflammatory response after nasal challenge(19). A previous study demonstrates that fexofenadine decreases eosinophils and GM-CSF induced release of IL-8 and ICAM-1 from nasal epithelial cells in patients with seasonal allergic rhinitis[24]. Ciprandi et al studied fexofenadine effect in single dose of 120 mg on pro-inflammatory cytokines IL-1, IL-6 and TNF- α in patients with allergic rhinitis after antigen specific challenge test. They observed that fexofenadine significantly inhibits only IL-6 and TNF- α release compared to placebo, while mizolastine inhibits all 3 cytokines release, and also decreases symptoms score[25].

Levocetirizine

In vitro studies reported that levocetirizine inhibits eotaxin induced transendothelial migration of eosinophils, in dose dependent fashion, both in lung and derm endothelial cells[26]. Levocetirizine also inhibits ICAM-1 and VCAM-1 adhesion molecules in activated keratinocytes and nasal polyps derivated fibroblasts and IFN-g induced release of GM-CSF and Rantes from keratinocytes, in dose dependent fashion[27]. Levocetirizine inhibits eotaxin release from endothelial cells in concentrations similar to those observed in vivo studies (10^{5}-10^{9} M). The effect is significant if they used a mixture of histamine, IL-1 and TNF- α as activator of eotaxin release regulation, suggesting other involved mechanisms than H1 receptors blocking one[28]. Arnold et al also confirm this observation and demonstrated that cetirizine and levocetirizine inhibit neutrophil release of Il-8 and TNF- α[29].

Levocetirizine also inhibits histamine induced IL-8 release from monocytes and macrophages in dose dependent manner[30] Another study revealed that levocetirizine reduces IL-1b, IL-7 synthesis in lipopolysaccharides stimulated human eosinophils[31].

Levocetirizine's effect on pro-inflammatory cytokines was also studied in patients with seasonal allergic rhinitis. In vivo studies showed that levocetirizine 5 mg/day for 2 weeks significantly reduces neutrophils and eosinophils number in nasal lavage fluid in patients with seasonal allergic rhinitis after treatment. Levocetirizine also reduces IL-4 and IL-8 level, while desloratadine reduces only Il-4 level[18]. These observations were also demonstrated in previous studies for cetirizine[32]. The authors continue this study in patients with persistent rhinitis and noticed that both antihistamines reduce Il-4 level after 4 weeks of treatment[33].

Desloratadine

In vitro the study showed that desloratadine inhibits IgE and non IgE mediated IL-4 and Il-13 synthesis by human basophils[34]. Desloratadine also inhibits pro-inflammatory mediators release by human eosinophils, which is typically linked to late phase of allergic inflammation[35]. Desloratadine inhibits IL-6 and IL-8 release by isolated lung and skin mast cells and basophils in a concentration dependent manner[36]. Other authors compared inhibitory effect of desloratadine and other antihistamines and corticosteorids, showing that desloratadine has the same potency as dexamethasone to inhibit IL-6, IL-8, IL-3, TNF- α and GM-CSF secretion from activated mast cells[37]. In some cases the mentioned effects are observed in supratherapeutic concentrations, but in others the effects are obtained in smaller concetrations with potential clinical utility (10^{-8} mol/L)[35, 36, 37].

Not all in vivo studies confirmed the antiinflamatory effect of desloratadine, probably because some of these were noticed in smaller concentration in vitro, which are not obtained after therapeutic doses. Deruaz et al compared the effect of a single dose of 5 mg levocetirizine and 5 mg desloratadine in patients with grass pollen allergic rhinitis. The patients were evaluated after antigen specific nasal challenge test They were noticed symptoms score and the level of Il-4, IL-5, IL-8, eotaxin and ECP in nasal lavage fluid. No used antihistamines influenced cytokines level, but this observation does not exclude a possible anti-inflammatory effect after their long time administration[38]. Ciprandi et al observed that desloratadine influence only Il-4 level, but Il-8 level is unchanged in nasal lavage fluid of patients with seasonal allergic rhinitis after 2 weeks treatment with 5 mg/day desloratadine[18]. This study was continued in patients with persistent rhinitis and the authors observed that desloratadine reduces Il-4 level in nasal fluid after 4 weeks treatment[33]. Other studies demonstrated that desloratadine 5 mg/day, 4 weeks treatment has no influence on IL-4, IL-10, IL-18 and TGF-b plasmatic levels.[39]

Conclusions

Allergic rhinitis is an inflammatory process caused by exposure to specific antigens, in which many immune cells and mediators are involved. IL-1, IL-6 and TNF-a are involved still in early phase of allergic inflammation, while Il-8 is involved only in its late phase. New generation antihistamines, like levocetirizine, desloratadine and fexofenadine possess some anti-inflammatory properties, especially relevant in vitro studies especially and in some in vivo studies. The anti-inflammatory effects are still a controversial issue which requires future studies.

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