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Antihistaminic Treatment, Allergen-Specific Immunotherapy, and Blockade of IgE as Alternative Allergy Treatments

Olga Lima Tavares Machado,
Débora Mothé de Campos-Mesquita and
Thais Pacheco-Soares

Additional information is available at the end of the chapter

Abstract

Allergies mediated by immunoglobulin E (IgE) are the most common immunological hypersensitivity diseases. The prevalence has been continuously increasing in recent decades, and more than 25% of the population is currently affected. Symptoms of allergies can be observed in the skin and respiratory and gastrointestinal tracts, and systemic manifestations include anaphylactic shock. If an allergy is not properly diagnosed and treated, it tends to progress to a severe and chronic debilitating disease. Understanding the mechanisms by which the immune system induces and controls allergic inflammation depends on knowing the structure of several allergens and identifying epitopes, which are critical for the design of new strategies for treating allergies. Strategies for immunotherapy will be reviewed. Allergen-specific immunotherapy has been used for nearly a century and remains one of the few antigen-specific treatments for inflammatory diseases. There is a strong rationale for improving the efficacy of allergen-specific immunotherapy by reducing the incidence and severity of adverse reactions mediated by IgE. Approaches to address this problem, including the use of modified allergens, synthetic peptides as vaccines, and alternative strategies for blocking IgE, will be discussed.

Keywords: IgE blocker, antihistaminic, immunotherapy

1. Allergic mechanism

An allergen is defined as a normally harmless substance, found in the environment or food, which can produce asthma, fever, eczema, or gastrointestinal discomfort upon contact with

a previously sensitized person. An allergy is commonly defined as an immediate or type I hypersensitivity reaction where symptoms appear rapidly and are caused by exposure to exogenous macromolecules known as antigens or allergens. The hypersensitivity reaction has two phases: sensitization, when the subject is first exposed to the antigen, and the subsequent reaction, when the subject is again exposed to the antigen [1]. **The first sensitization** of a body begins with the first contact with an antigen, which induces an allergy. The allergen penetrates the airways of the body or other tissues and is found by antigen-presenting cells (APCs) such as macrophages and/or dendritic cells, which encyst and proteolytically cleave the foreign substance. The peptide fragments generated, known as T cell epitopes, are directed to the outer membrane of the APC by the major histocompatibility class II (MHC II) complex in the form of a complex peptide-MHC class II [2]. The T-helper lymphocytes (Th1 and/or Th2) recognize these exposed epitopes and together with B cells initiate the immune response. The activation clones specific for the antigen, Th2 cells, are essential for the development of atopic diseases, because these cells activated by contact with APCs produce cytokines and interleukins 4 (IL-4) and 5 (IL-5). These interleukins act as signals, among other functions, for the biosynthesis of immunoglobulin E (IgE) by B lymphocytes. An immunoglobulin, IgE, binds to the surface of mast cells and basophils by FcЄRI receptors. A subsequent exposure to the same antigen, **the second sensitization**, leads to a substantial allergic response. The antigen-specific segments (IgE epitopes) are cross-linked to the IgE bound to the mast and/or basophil cells after interaction with the allergen, activating intracellular messengers, and the subsequent release of cellular mediators such as histamine and prostaglandins, which in turn induce physiological and anatomical changes that trigger the allergic symptoms of immediate hypersensitivity [3, 4].

IgE antibodies generated in response to a specific allergen interact with this allergen and trigger a series of intracellular reactions leading to the release of histamine and other inflammatory mediators. Histamine plays a key role in the allergic response. The release of histamine causes the smooth muscles of the gastrointestinal and respiratory tracts to contract, stimulates nerves, and dilates blood vessels [5, 6]. These effects of histamine include, among other clinical manifestations, erythema, flushing, nasal congestion, pruritus, headache, hypotension, tachycardia, and bronchoconstriction [5]. There are four main subtypes of histamine receptors: H1, H2, H3, and H4. These receptors are G-protein-coupled receptors that transfer extracellular signals via G proteins, acting as intermediates between cell-surface receptors and second intracellular messengers [6, 7]. The H1 receptor is the main mediator subtype of the allergic response causing allergic symptoms. In addition to its role in the immediate allergic response, histamine contributes to the late allergic response by stimulating the production of cell-adhesion molecules, class II antigens, and cytokines [6].

2. Tolerance induction

Immune tolerance can develop against any substance, and multiple mechanisms are involved. The lack of response of immune tolerance can lead to the development of various diseases such as:

- allergies

- asthma

- tumors

- chronic infections

- transplant organ rejection

- graft versus host disease

- many autoimmune diseases [8].

The generation of regulatory T (Treg) cells initiates tolerance. Peripheral tolerance is initiated by the secretion of IL-10 and TGF-β by allergen-specific Treg cells during continuous exposure. The induction of allergen-specific tolerance is associated with an increase in FOXP3+CD25+CD3+ cells in the nasal mucosa [9]. Atopic individuals have a reduced capacity to proliferate CD25+ and CD4 Treg cells, which indicates the mechanisms of failure of tolerance allergens. A clonal shift occurs during tolerance fromTh1, Th2 to Th1 (**Table 1**). B cells are stimulated by the action of IL-10 to produce IgG (particularly IgG4) and to suppress IgE production, which prevents the development of allergic symptoms in the tolerogenic individual [9–11] (**Table 2**).

If an allergy is not properly diagnosed and treated, it tends to progress to a severe and chronic debilitating disease.

Many treatments have been developed to circumvent the symptoms of allergic diseases, most of which use histamine inhibitors that mask the symptoms of the allergy. Allergen-specific immunotherapy (ASIT), however, is the only long-term preventive and long-term treatment for allergic diseases. ASIT involves the administration of a specific allergen, so it induces a specific immunological tolerance to the allergen. ASIT has been used for more than 100 years, but the mechanism of action has only recently been resolved [12].
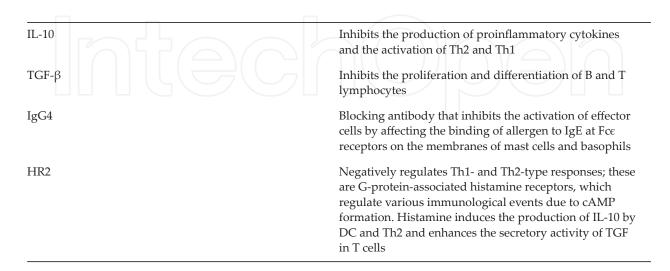
IL-10	Inhibits the production of proinflammatory cytokines and the activation of Th2 and Th1
TGF-β	Inhibits the proliferation and differentiation of B and T lymphocytes
IgG4	Blocking antibody that inhibits the activation of effector cells by affecting the binding of allergen to IgE at Fcε receptors on the membranes of mast cells and basophils
HR2	Negatively regulates Th1- and Th2-type responses; these are G-protein-associated histamine receptors, which regulate various immunological events due to cAMP formation. Histamine induces the production of IL-10 by DC and Th2 and enhances the secretory activity of TGF in T cells

Table 1. Molecules with effector functions in allergen tolerance.

Treg	Secretors of TGF-β and IL-10; induce Foxp3 expression, Th2 suppression; direct, and indirect suppression of mast cells, basophils, and eosinophils; stimulate B lymphocytes in IgG4 production and IgE suppression
Breg	Expression of IL-10 and IgG4
Eosinophils	Decrease the activity of inflammatory mediator secretion (histamine and leukotrienes) by the action of IL-10 and TGF secreted by regulatory cells
Basophils	
Mast cells	

Table 2. Roles of cells in allergen tolerance.

In this chapter, we will describe the most common allergy treatments using antihistamines and emphasize the new methodologies of allergen-specific immunotherapy (ASIT) as a prophylactic treatment and IgE blockade as a therapeutic treatment.

3. Approaches for allergy treatment

3.1. Antihistaminic treatment

Researchers have devoted their efforts for many years to the development of effective and safe strategies for the treatment of allergy to alleviate the symptoms triggered by the body's responses to allergens [1, 13, 14]. Antihistamines are currently the most commonly used treatment. These drugs are used to alleviate allergic symptoms, that is, they are based on the consequences of the allergy [5]. First-generation antihistamines, or H1-receptor antagonists, may have undesirable side effects on the central nervous system, even at therapeutic doses, due to their ability to cross the blood-brain barrier rather than to their lack of selectivity. Side effects include sleepiness, sedation, and fatigue that may lead to reduced cognitive, memory, and psychomotor performance [7, 15]. First-generation antihistamines include doxepin, diphenhydramine, pyrilamine, chlorpheniramine, hydroxyzine, promethazine, and cyproheptadine [6].

A new class of antihistamine has been developed. Second-generation H1 antagonists cannot cross the blood-brain barrier as easily and have a greater affinity to H1 receptors, decreasing their sedative effects compared to the first-generation drugs [7]. These antihistaminic agents include cetirizine, ebastine, epinastine, fexofenadine, loratadine, desloratadine, levocetirizine, and rupatadine. The second-generation antihistamines cause fewer adverse effects, but some drugs, for example, levocetirizine, may cause drowsiness, and fexofenadine has a brief effect and may require more than one daily dose. Treatment with antihistaminic drugs does not address the cause of allergic responses but only alleviates their symptoms [7, 14, 16].

3.2. Allergen-specific immunotherapy (ASIT)

Immunotherapy was first conceived in 1911, from which a type of therapy was developed that used allergens as a tool for the development of immunological tolerance in sensitized individuals [17]. The term "desensitization" was replaced with "hypo-sensitization." The term "immunotherapy" became popular only in the 1980s and "specific immunotherapy" is a

commonly used term. When immunotherapy involves the direct use of allergens as immunotherapeutics, the appropriate term is ASIT [12]. ASIT has been used for more than a century and remains one of the few antigen-specific treatments for inflammatory diseases.

ASIT consists of the gradual administration of doses of a specific allergen or part of that allergen to reduce the sensitivity and consequently to decrease the symptomatic reactions to a future exposure of the allergic individual to the causative natural agent [1, 18]. ASIT is a widely used therapeutic strategy for treating allergic rhinitis, venom-induced hypersensitivity, some drug allergies, and mild bronchial asthma [13]. The mechanisms of ASIT are not yet clear but include modulating both T and B cell responses, thereby reducing the incidence and severity of IgE-mediated adverse reactions [19]. Some of the immunological changes that occur during ASIT have been elucidated [1]. ASIT increases the level of allergen-specific IgA and IgG4 antibodies and decreases the level of allergen-specific IgE antibodies. Oral, sublingual, and subcutaneous immunotherapies are used the most in the treatment of hypo-sensitization in various types of allergies. These three mechanisms of immunotherapies, however, are specific to particular allergens, so the therapy is effective only for the particular allergen.

Approaches to improving ASIT include the use of modified recombinant allergens, novel adjuvants, and alternative routes of administration. Recombinant allergens are similar to wild-type allergens, generally equivalent in structure and properties, but with alterations in their epitopes that do not guarantee their ability to trigger an allergic response [20].

3.2.1. Recombinant hypoallergenic peptides for immunotherapy

Valenta et al. using purified recombinant allergens and derivatives of recombinant hypoallergenic allergens has identified the induction of the production of IgG-specific allergen-blocking antibodies as one of the main mechanisms of ASIT [21]. Blocking IgG, however, may also inhibit the presentation of antigen in APCs to antigen T cells and therefore suppress the activation of T cells induced [22]. ASIT can also alter the balance of specific helper T cells from a Th2 profile to an allergen-specific Th1 immunity profile and can induce the secretion of immunoregulatory cytokines such as interleukin (IL)-10, and regulatory T cells [23]. The induction of allergen-specific tolerance is thus the essential immune mechanism of ASIT.

Recombinant hypoallergenic from variants have been produced. Linhart constructed, purified, and characterized two hybrid hypoallergenic recombinant proteins from *Brassica rapa* allergens, Der p 2 (rder p 2)/1 C and rder p 2/1S [19]. Mutations in aspartic acid residues in these allergens decreased the cross-linking of IgE in the membrane of sensitized mast cells by decreasing the allergenic potential of the protein [24].

Patients immunized in 2016 with a variant Bet v1 (birch allergen) hypoallergen did not develop a local allergic response, as observed by histopathological tests of skin contact. Rats immunized with the same recombinant hypoallergen demonstrated that a profile of tolerogenic responses with proinflammatory cytokine production was possible [25].

3.2.2. Synthetic peptides

Immunotherapy using peptides has some advantages over immunotherapies fusing recombinant allergens. Vaccines using peptides with T cell epitopes can induce regulatory T cells.

The use of synthetic peptides derived from allergens containing T cell epitopes is an alternative to the production of allergen-specific T cells in ASIT. These peptides are formed from linear sequences representing fragments of small allergens that bind to the allergen-specific T cell receptor and do not react with IgE antibodies, which give them an advantage because they do not trigger the classic allergic symptoms measured by IgE. The treatment may induce T cell tolerance by the secretion of the immune cytokine regulator IL-10 from regulatory T cells. The diversity of T cell epitopes is a possible disadvantage of vaccines based on T cell epitopes, making treatment with only one or a few peptides difficult. This treatment can cause secondary systemic symptoms and lacks the ability to induce IgG blocking [2].

Vaccines for allergies based on B cell epitopes of approximately 20–40 amino acids use peptides that lack the ability to bind IgE. The peptides must be covalently linked to a protein transporter that is unrelated to the T allergens in order to render these peptides immunogenic, capable of inducing the production of IgG, which blocks the binding of IgE to the corresponding allergen. Valenta et al. demonstrated the use of carrier-linked allergenic peptides to induce IgG antibodies to the main pollen allergen of thyme grasses, Phl p 1, and to the main birch pollen allergen, Bet v 1. These conjugates decreased allergenic activity even more than the recombinant hypoallergens, because the non-IgE-reactive peptides were selected from the IgE-binding sites [21].

3.3. Allergen-nonspecific therapy

3.3.1. Anti-IgE antibodies

The new approaches for the treatment of allergic diseases have two main strategies using nonspecific allergens [26]. The first strategy is to bind IgE to high-affinity receptors (FcϵRI) in mast cells and basophils, and the second strategy is to interfere with the signaling generated by receptor binding (FcϵRI) [26, 27]. Knowledge of the pathophysiological role of IgE antibodies has allowed the development of new drugs against many allergic diseases.

3.3.2. Anti-IgE receptor antibodies

A currently promising therapeutic approach has been the use of antibodies against the region of the IgE molecule that interacts with specific IgE receptors. The interaction of IgE molecules with high- and low-affinity receptors may be inhibited by the use of anti-IgE for reducing the induced allergic responses, preventing the activation of mast cells and consequently the release of allergic mediators [2, 26]. Omalizumab is a murine anti-human IgE monoclonal antibody that binds to the same receptor site (Cϵ3) to which IgE binds, thereby inhibiting the binding of IgE-to-IgE receptors [2, 8]. Omalizumab does not bind to fixed IgE in cells, because the IgE epitope (specific fragment) against which omalizumab is targeted is already fixed to the receptors and is therefore hidden. Anti-IgE therapy is most commonly used to treat bronchial asthma but is also effective for treating allergic rhinoconjunctivitis, but therapy must begin before the pollen season [26]. The anti-IgE therapy is currently being studied for use in food allergies, but the cost has limited its use for this purpose [1].

3.3.3. IgE blocker

A new proposal has been studied by Deus-de-Oliveira et al. for blocking IgE-allergen binding. The identification of the IgE-binding epitopes and the amino acids involved in these interactions are fundamental steps. Deus-de-Oliveira et al. found that two glutamic acid residues in the main allergens of *Ricinus communis*, Ric c1 and Ric c 3, are involved in IgE binding, triggering an allergic response. They also found that the *Ricinus* allergens cross-reacted with aeroallergens and food allergens from several sources. Free glutamic acid can bind to castor-allergen-specific IgE, occupying the epitope-interaction site and preventing the binding of the allergens in a second exposure to the IgEs fixed in the mast cells. IgE blockade may be a safe approach for the treatment of allergy but will depend on determining the structures of allergens and on identifying epitopes and cross-allergen responses.

A summary of strategies for treating allergies is presented in **Table 3**.

Method	Advantages	Disadvantages
Antihistamines	• Alleviate the symptoms triggered by the body's responses to allergens • Effective and safe	• May cause undesirable side effects on the central nervous system • Side effects include sleepiness, sedation and fatigue that may lead to reduced cognitive, memory, and psychomotor performance
Allergen-specific immunotherapy	• Reduces the sensitivity and consequently decreases symptomatic reactions	• Specific to particular allergens
Allergen-nonspecific therapy (*anti-IgE antibodies*)	• Reduces the induced allergic responses preventing the activation of mast cells and consequently the release of allergic mediators	• Does not bind to fixed IgE in cells because the IgE epitope (specific fragment) against which omalizumab is targeted is already fixed to the receptors and is therefore masked
IgE blocker	• Blockade of IgE sites involved in the interaction with allergenic epitopes	• Under development

Table 3. Summary of strategies for treating allergies.

Author details

Olga Lima Tavares Machado*, Débora Mothé de Campos-Mesquita and Thais Pacheco-Soares

*Address all correspondence to: olga@uenf.br

Laboratory of Chemistry and Function of Proteins and Peptides, Center for Biosciences and Biotechnology, Northern State University of Rio de Janeiro - Darcy Ribeiro (CBB/UENF), Rio de Janeiro, Brazil

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