Histamine and Antihistamines

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SUMMARY

In recent years, there has been a steady increase in the prevalence of allergic diseases. Allergic immune response represents a complex network of cellular events involving numerous immune cells and mediators. It represents the interaction of innate and acquired immune response. The key role in the immune cascade is taken by histamine, a natural component of the body, which in the allergic inflammatory response is released by the mast cells and basophils. The aim of this study was to highlight the role of histamine in allergic immunological events, their effect on Th1 and Th2 subpopulation of lymphocytes and the production of the corresponding cytokines, as well as the role of histamine blockers in the treatment of these conditions.

Histamine achieves its effect by binding to the four types of its receptors, which are widely distributed in the body. Histamine blockers block a numerous effects of histamine by binding to these receptors. As a highly selective second-generation antihistamine, cetirizine not only achieves its effects by binding to H1 receptors, but also attenuates numerous events during the inflammatory process. Knowledge of the effects of histamine blockers, including cetirizine, may lead to the selection of proper therapy for the treatment of allergic diseases.

Key words: histamine, immune response, histamine blockers, cetirizine

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INTRODUCTION

Over the last 30 years, the prevalence of allergic diseases (asthma, allergic rhinitis, atopic dermatitis etc.) has been rapidly growing. The goal of treatment of these conditions represents a blocking effect of histamine release from basophils and mast cells and is considered to be the key cause of all the symptoms associated with allergic inflammatory response. Antihistamines are drugs that are widely used in dealing with this type of disease. The aim of this paper was to provide the insight into the mechanism of allergic immune responses and highlight the possibility of using histamine blockers, including cetirizine, a second generation antihistamine, in solving many problems in allergy caused by intracellular communication and numerous mediators.

ALLERGY

An immune cascade of allergic conditions is the interactions between numerous cell types and inflammatory mediators (1). Allergic inflammatory response has three distinct phases: sensitization, early-phase responses and late-phase responses. The sensitization phase begins with the production of allergen-specific IgE-antibodies that bind to the surfaces of mast cells, basophils and antigen presentation cells (APC), causing degranulation and subsequent mediator release. Just before that occurs a differentiation and clonal expansion of allergen-specific CD4+Th2 cells, with the capability of producing IL-4 and IL-13, which are the key events in induction of IgE. Engagement of IgE on effector cells leads to sensitization of patients to specific allergen (2). At the early stage of the reaction from the mast cells and basophils are released many inflammatory mediators such as tryptase, eosinophil chemotactic factor in addition to histamine as well as newly synthesized molecules (PGD2, LCT4, bradykinin). The process of secretion of these mediators is crucial characteristic of the early stages of the response. About half of all patients who exhibit an early-phase allergic response experience a late phase inflammatory reaction approximately 4-24 hours following allergen exposure. Late phase response is manifested by activation of endothelial cells and secretion of many inflammatory cytokines (TNF-α, granulocyte-macrophage colony-stimulating factor, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13) with strong inflows of inflammatory granulocytes (eosinophils, basophils, neutrophils and lymphocytes), except for eosinophils which have a particular role because they secrete several substances that promote the chronic late-phase inflammatory reaction. During the late phase of allergic inflammatory response, which is characterized by inflammation and tissue injury, there is a return of symptoms in the early stage.

Allergic diseases represent complex innate and adaptive immune responses to environmental antigens leading to inflammatory reactions with a T-helper-2 type cell and allergen-specific IgE predominance (3,4). Allergy is essentially an inflammatory disease. Our knowledge of the cells and mediators that are involved in the allergic inflammation has increased immensely during the last decade. This knowledge provides the basis of a more rational way for the development of therapeutic principles and prevention of allergic symptoms. The allergic inflammation involves a large number of cells. However, three types of cells seem to be of particular importance. These are the eosinophil granulocyte, the mast cell and the T-lymphocyte of the Th2-type. The cytokines and other molecules and the cells present in the microenvironment are the main factors which determine differentiation of naive T cells into distinct subsets such as Th1, Th2, Th9, Th17 and Th22 type memory and effector cells (5). In conditions of allergic diseases, effector Th2 cells produce not only traditional Th2 cytokines such as IL-4, IL-5, IL-9 and IL-13 (6,7), but also novel cytokines such as IL-25, IL-31 and IL-33 which have proinflammatory functions (8-14). These cytokines induce eosinophilia, mucus production, producing of allergen-specific IgE and the recruitment of inflammatory cells to inflamed tissues. Th2 cells are the leader of the process. The main effector cells are the eosinophils and mast cells. Predominance of Th2 cells might be caused by an increased tendency to activate induced cell death of high IFN-gama producing Th1 cells as it is commonly observed in patients with atopic disorders (15). Th1 cells induce apoptosis of keratinocytes in atopic dermatitis and epithelial cells and/or smooth muscle cells in asthma in the effector phase of these allergic diseases (16-20). As the major consequences of the activation of mast cells, the release of histamine and other mediators occur, which leads to acute allergic reaction. Activation of eosinophils lead to the extracellular release of a number of potent cytotoxic
proteins. These proteins play a very important role in the development of subacute and chronic symptoms of allergy. Macrophages, epithelial cells, neutrophil granulocytes and endothelial cells also play an important role in allergic diseases. Antigen-induced immunological cascade is presented in Figure 1. Treatment of allergic diseases still has stereotyped character and consists of international and national recommendations.

This treatment shows varying degrees of success and there are many reasons for this variability. One of the very important reasons for this may be the fact that we are not seeing the mechanisms that underlie the individuality of the patient. It is clear that there are large differences in terms of inflammatory cells and mediators that are crucial for allergic diseases.

Figure 1: The allergic cascade. Mast cell mediators, including cytokines, cause degranulation and contribute to the bidirectional messaging with other inflammatory cells or their precursors, leading to lymphocyte activity, and migration of immune cells to inflammatory sites (21) (source: Canonica GW, Blaiss M. Antihistaminic, anti-inflammatory, and antiallergic properties of the nonsedating second-generation antihistamine desloratadine: a review of the evidence. World Allergy Organ J 2011;4(2):47-53.)
HISTAMINE

Histamine (2,4-imidazol-ethylamine) was first identified as a mediator of biological functions in the early 20th century. It was identified in 1911, owing to vasoactive properties by Barger and Dale, and drugs that work on the principle of binding to histamine receptor have been clinically used for more than 60 years. It is one of the most extensively studied molecules in medicine, of which synthesis, metabolism, receptors, signal transduction, physiological and pathological effects there is a large number of collected evidence. It has a wide range of both physiological and pathological effects, whereby the width of the spectrum has continuously been increasing by new research. Histamine is a low-molecular-weight amine, a natural body constituent, synthesized from L-histidine by histidine decarboxylase, an enzyme that is expressed in many types of cells throughout the body, including the central nervous system neurons, gastric-mucosa parietal cells, Mast cells, basophils, lymphocytes, and enterophromaphiles cells. Histamine plays an important role in human health, exerting its diverse biological effects through four types of receptors. It plays a key role in the hematopoiesis, proliferation of cells, differentiation of cells, regeneration and wound healing, embryonic development. Histamine is produced in neurons of the central nervous system which have cell bodies located exclusively in the tuberomamillary nucleus of the posterior hypothalamus. Their axons perform transmission of histamine to the frontal and temporal cortices of the brain. In the phylogenetically old part of neurotransmitter systems, histamine has a role in the regulation of basic body function through the H1-receptor such as the cycle of sleeping and waking, appetite, cognition and memory, energy and endocrine homeostasis. Histamine also has anticonvulsant activity (22, 23).

The roles of histamine in inflammation, gastric acid secretion and as a neurotransmitter are the best described roles in the human body. Mast cells and basophils release histamine during inflammation. Smooth muscle cells and endothelial cells are the target places of action of histamine. This leads to vasodilatation and increase in vascular permeability. In the skin, histamine results in the triple response, which is an immediate local reddening due to vasodilatation, a wheal due to increased vascular permeability and a flare due to indirect vasodilatation via the stimulation of axonal reflex. Histamine has an essential role in the gastrointestinal system for gastric acid secretion. Gastrin and vagal stimulation induce enterochromaffine cells to release histamine. Then histamine can act on the H+K+ATPases, which results finally in the secretion of H+, a key element for synthesis of HCl in the stomach.

Level of histamine is increased in bronchoalveolar lavage fluid in patients with allergic asthma and this increase negatively correlates with airway function (24-29). An increase in histamine levels has been noted in the skin and plasma of patients with atopic dermatitis (30,31) and in chronic urticaria (32, 33). Histamine levels are also increased in multiple sclerosis (34) and in psoriatic skin (35). Both plasma and synovial fluid of patients with rheumatoid arthritis and plasma of patients with psoriatic arthritis have increased histamine levels (36, 37). It is know that the diverse biological effects of histamine are mediated through different types of histamine receptor in treatment. Histamine can have varying and sometimes counteracting effects on a particular cell depending on the concentration used, and which histamine receptors are activated. Receptor levels may change during different stages of cell development or under pathophysiological conditions and could vary among species.

HISTAMINE RECEPTORS

There are four major types of histamine receptors: H1, H2, H3 and H4 receptors which differ in their expression, signal transduction and function (38-45). Expression of H1 and H2 receptors are widely expressed in contrast to H2 and H4 receptors. H1, H2 and H4 receptors are expressed on the surface of many cells involved in inflammatory reactions, with the H1-receptor playing a major role in potentiation of proinflammatory immune cell activity and effector responses fundamental to an allergic reaction. The H1 receptors have been associated with many actions in relation to allergic inflammation, such as rhinorhea, smooth muscle contraction and many forms of itching (pruritus). This is mediated by the transduction of extracellular signals through G protein and intracellular second messengers (inositol triphosphate, diacylglycerol, phospholipase D and A2, and increases in intracellular calcium concentration).
Making of H1 receptors is encoded by genes, localized on chromosome 3. The H2-receptor, in contrast, appears to suppress inflammatory and effector functions, while data regarding the role of the H4-receptor in immune response is limited. Evidence of the existence of a third histamine receptor groups (H3) was based on the activity of histamine, which could not be blocked by antagonists of H1 or H2-receptor antagonist (46). The histamine H3 receptor has been identified in the central and peripheral nervous systems as pre-synaptic receptors controlling the release of histamine and other neurotransmitters. The local concentration of histamine and predominant type of histamine receptor undergoing activation determines the type of effector response that is elicited.

All four types of histamine receptor are heptahelical transmembrane molecules that transduce extracellular signals by way of G proteins to intracellular second-messenger systems. The classic model of receptor activation requires binding by a specific ligand, or agonist and binding of inverse agonist (antagonist in the older literature) leads to the inactivation, blockade of these receptors. Aspartic acid located in the third transmembrane domain of the human receptor is crucial for the affinity of histamine and histamine antagonists; this amino acid is a hallmark of G-protein-coupled receptors. All types of receptor have constitutive activity, which is defined as the ability to trigger events even in the absence of ligand binding. It can be said that there is a balance between active and inactive states of the receptor. H1-receptor polymorphisms have been described, although it is not yet clear how they influence the clinical response to H1-antihistamines (47). Target disruption of the genes encoding the H1 receptor, is applied in mice which results in CNS function disorders, such as memory, learning, locomotion and aggressive behavior. H1 receptor deficiency also leads to numerous immunological abnormalities such as weakening of antigenic-specific response of T and B cells (48,49).

The presence of histamine leads to upregulation of H1 receptors. It was experimentally proven that antagonists cause blockade of upregulation.

The concept of constitutive activity has led to a reclassification of drugs acting at the H1-receptor. For example, the H1-receptor promotes NF-kB in both a constitutive and agonist-dependent manner and all clinically available H1-antihistamines inhibit constitutive H1-receptor-mediated NF-kB production (50, 51).

Histamine can also be linked to one type of intracellular histamine receptor (Hic), which was described several years ago in the microsomes and nucleus. These types of receptors are comprised of the cytochrome P450 and cytochrome c (52). This type of receptor cannot yet be discussed with absolute certainty, because it is not yet clear which type of reactions are induced by histamine binding to this receptor. Localization of histamine receptors as well as the mechanism of their activation are presented in Table 1.

**Table 1. Histamine receptors, the localization of their expression and mechanism of action**
(source: Akdis CA, Simons FER. Histamine receptors are hot in immunopharmacology. Eur J Pharmacol 2006; 533:69-76.)

<table>
<thead>
<tr>
<th>Histamine receptors</th>
<th>Expression</th>
<th>Activated intracellular G proteins</th>
<th>signals</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 receptors</td>
<td>Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, dendritic cells (DC), T and B cells</td>
<td>Ca²⁺, cGMP, phospholipase D, phospholipase A2, NF-kB</td>
<td>Gq/11</td>
</tr>
<tr>
<td>H2 receptors</td>
<td>Nerve cells, airway and vascular smooth muscle, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, dendritic cells, T and B cells</td>
<td>Adenylate cyclase, cAMP, c-Fos, c-Jun, PKC, p70S6K</td>
<td>Gas</td>
</tr>
<tr>
<td>H3 receptors</td>
<td>Histaminergic neurons, eosinophils, DC, monocytes, low expression in peripheral tissues</td>
<td>MAP kinase, inhibition of cAMP, Ca²⁺</td>
<td>Gi/o</td>
</tr>
<tr>
<td>H4 receptors</td>
<td>High expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DC, T cells, basophils, mast cells; low expression in nerve cells, hepatocytes and peripheral tissues</td>
<td>Ca²⁺, inhibition of cAMP</td>
<td>Gi/os</td>
</tr>
</tbody>
</table>
THE ROLE OF HISTAMINE IN ALLERGIC INFLAMMATION AND IMMUNE MODULATION

Histamine plays a key role in allergic inflammation, which is a complex network of cellular events that involve many cells and mediators. Histamine is released from the mast cells and basophils together with tryptase and other preformed mediators such as prostaglandins, leukotrienes, after the cross-linking of surface IgE by allergen or through mechanisms that are independent of IgE. After allergen challenge in sensitized persons, the local concentration of histamine is much higher compared to leukotrienes and other mediators. The concentration of histamine can then be measured in micrograms, whereas the concentration of leukotrienes, and other mediators may be measured in picograms.

Most of the changes in allergic disease occur as a consequence of binding histamine to H1 receptor (38-40, 54). Hypotension, tachycardia, flushing and headache occur through both the H1 and H2 receptors (55), whereas irritation of the skin in the form of itching and nasal congestion can be caused by the activation of H1 and H3 receptors (56, 57). The role of histamine can be discussed also as a stimulatory signal for the production of cytokines and the expression of cell adhesion molecules in the late-phase of allergic reaction (55, 56, 58, 59).

Histamine may have proinflammatory or antiinflammatory effects, depending on the predominance of the type of histamine receptor.

Through the H1-receptor, histamine has proinflammatory effect, which activation can be greatly involved in several aspects of antigen-specific immune response, including maturation of dendritic cells and the modulation of the balance of Th1 cells and Th2 cells. Histamine may induce an increase in the proliferation of Th1 cells and in the production of interferon γ, which may result in blocking humoral immune responses by means of this mechanism. Histamine has the capacity to influence the activity of basophils, eosinophils and fibroblasts.

The binding of histamine to histamine H1 receptor leads to many effects that are associated with symptoms of anaphylaxis and other allergic diseases (60), however, increasing evidence suggests that this process also affects a number of immune /inflammatory and effector functions (38,59).

Under the influence of histamine occurs secretion of proinflammatory cytokines such as IL-1α, IL-1β, IL-6 as well as chemokines such as regulated activation (RANTES) or IL-8. This process takes place in several types of cells and tissues and leads to the progression of allergic-inflammatory responses.

Histamine H1 receptor and histamine H2 receptor are found on the surface of endothelial cells. Histamine through H1 receptor leads to increased expression of adhesion molecules such as vascular cellular adhesion molecule (VCAM-1), intracellular adhesion molecule (ICAM-1) and P-selectin.

Histamine regulates granulocyte accumulation in tissues in distinct ways. Allergen-induced accumulation of eosinophils in the skin, nose and airways is inhibited by histamine H1 receptor antagonists. The effect of histamine on eosinophil migration may differ according to the concentration. Whereas high concentrations inhibit eosinophil chemotaxis via histamine H1 receptor, low concentrations enhance eosinophil chemotaxis via histamine H1 receptor. One study has shown that histamine H4 receptor is the histamine receptor responsible for the selective recruitment of eosinophils. Histamine possesses all the properties of a classical leukocyte chemoattractant, including: alteration in cell shape, mobilization of intracellular calcium and up-regulation of adhesion molecule expression.

ANTIHISTAMINES

More than 45 types of antihistamines are widely used around the world, thus representing the largest group of medicines used in the treatment of allergic conditions.

Traditionally, this group of drugs is classified in six chemical groups: ethanolamines, ethylenediamines, alkylamines, piperazines, piperidines and phenothiazines. If antihistamines are classified according to function, then we distinguish two generations of antihistamines: first and second generation antihistamines, which are distinguished by the fact that first generation antihistamines penetrate the blood-brain barrier and have a sedative effect, while the second generation antihistamines do not possess these qualities. They are very different in terms of chemical structure, pharmacology and toxic potential. Representative of the first and second generation of antihistamines are given in Figure 2. Consequently, knowledge of their pharmacokinetic
and pharmacodynamics characteristics is important for the correct usage of such drugs, particularly in patients belonging to extreme age groups, pregnant women, or subjects with concomitant diseases.

Figure 2: Drugs of the first and second generation of antihistamines (61) (source: Simons FER, Simons KJ. The pharmacology and use of H1-receptor antagonist drugs. N Engl J Med 1994; 330: 1663-1670)

After oral application, most antihistamines show a good degree of absorption. The effective concentration of antihistamines is achieved three hours after application, which confirms the above thesis. These molecules have the characteristic of liposolubility, which enables them to pass through cell membranes with extreme ease. Concomitant administration with food can change the plasma concentrations of these drugs, which can be explained by the presence of P glycoprotein across cell membranes and the organic anion transporter polypeptides. These proteins function as active transport systems for other molecules, showing affinity for them. Antihistamine shows a good degree of binding to plasma proteins (78% to 99%).

The group of enzymes belonging to the P450 cytochrome system performs metabolism and detoxification of most antihistamines. Only acrivastine, levocetirizine, desloratadine and fexofenadine (62) avoid this metabolic passage through the liver to an important degree, which makes them more predictable in terms of their desirable and undesirable effects. Fexofenadine is eliminated in stool, while cetirizine and levocetirizine are eliminated in urine. Fexofenadine is eliminated without metabolic changes while cetirizine and levocetirizine are eliminated in unaltered form. Other antihistamines undergo the transformation in the liver, thereby resulting in metabolites which may be active or inactive. Their concentrations in plasma depend on the activity of the P450 enzyme system. Metabolism of antihistamines and drug interaction are given in Table 2.
Table 2: Antihistamines, their metabolism and interaction with other drugs (63) (modified from del Cuvillo A, Mullol J, Bartra J, Davila I et al. Comparative pharmacology of the H1 antihistamines. J Investig Allergol Clin Immunol 2006; 16(1):3-12.)

<table>
<thead>
<tr>
<th>Generation of antihistamines</th>
<th>Drug</th>
<th>Liver metabolism</th>
<th>Drug interactions</th>
</tr>
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<tbody>
<tr>
<td>First</td>
<td>Chlorpheniramine</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Second</td>
<td>Acrivastine</td>
<td>&lt;50%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cetirizine</td>
<td>&lt;40%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Loratadine</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Ebastine</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Fexofenadine</td>
<td>&lt;8%</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Mizolastine</td>
<td>Yes</td>
<td>Yes (P glycoprotein)</td>
</tr>
<tr>
<td></td>
<td>Levocetirizine</td>
<td>&lt;15%</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Desloratadine</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Rupatadine</td>
<td>Yes</td>
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</table>

Antagonists of H1 receptors are used in treatment of allergic rhinoconjunctivitis and relieve sneezing nasal and ocular itching, rhinorrhea, conjunctival erythema and early phase of inflammatory response, but they are less effective in the treatment of late phase of inflammatory response (64).

Pretreatment with H1 antagonists may provide some protection against bronchospasm induced by histamine, exercise, hyperventilation of cold and dry air, hypertonic or hypotonic saline, distilled water, adenosine 5 monophosphate, or allergen. The amount of protection varies with the dose of H1 antagonists and stimulus used (65-68).

In patients with chronic urticaria, H1 antagonists relieve pruritus and reduce the number, size and duration of urticarial lesions (69-75).

In patients with anaphylactic or anaphylactoid reactions, the initial drug of choice is epinephrine; however, H1 antagonists are useful in the ancillary treatment of pruritus, urticarial and angioedema. For anaphylaxis, H2 antagonists are used concurrently with H1 antagonists to reduce the effects of histamine on the peripheral vasculature and the myocardium (76,77).

**CETIRIZINE**

Cetirizine is a highly selective, long-acting, peripheral H1 antagonist of the second generation, carboxylated metabolite of hydroxyzine, which represents a combination of the two enantiomers levocetirizine (R enantiomer) and dextrocetirizine (S enantiomer). It has very low affinity for the number of types of receptors such as α1-adrenergic, dopaminergic (D2 receptors), muscarinic and serotonergic receptors. Cetirizine also shows a low degree of affinity for calcium channels. Owing to some of its properties in the allergic response to antigenic stimulus, cetirizine shows antiallergic, anti-inflammatory and antihistamine effect. It exists as a zwitterion (has a separate positive and negative charged groups). The absorption of cetirizine is good after the oral administration of this drug. After oral application of cetirizine in a dosage of 10 to 20 mg, the maximum plasma concentration (Cmax) is attained for 1h and it is 257μg/L to 580μg/L. There is no difference in action of this medication if it is administered in the form of tablet or in the form of syrup. Ninety percent of the drug binds to plasma albumin. Cetirizine is widely distributed throughout
the body, although it does not pass the blood-brain barrier easily. 70% of the cetirizine is eliminated via urine, and about 10% through the digestive tract in the feces. This H1 antagonist has a low degree of interaction with other drugs, since it avoids the metabolic pathway through the liver.

The consensus of the British Society for Allergology and Clinical Immunology confirmed the anti-allergic and anti-inflammatory properties of cetirizine in vitro and in vivo. Antihistamine agents such as cetirizine do not act only through H1 receptors, but may attenuate many events during the inflammatory process. Cetirizine shows some modulation effects on the inflammatory response. It leads to reduction of the migration of eosinophils that is induced by inflammatory mediators in atopic and nonatopic individuals (78-87). In addition to the classic role in antagonizing the H1 receptor, cetirizine induces reduction of the expression of adhesion molecules associated with the migration of eosinophils and eosinophil cells in vitro studies (88-90) and in atopic patients (91-94), so that the recipients and the effect of cetirizine consists of the inhibition of eosinophil infiltration into tissues. It has a lipophilic and ionizing properties enabling it to act directly on the cell membrane leading to its stabilization. Cetirizine inhibits binding of NF-kB, inhibits the expression of adhesion molecules (ICAM-1) on immune cells and endothelial cells. It also inhibits migration of inhibitory factor (MIF) (95) as well as the production of IL-8, and leukotriene B4 production of two very potent chemoattractants. Cetirizine leads to the release of PGE2, suppressors of expression of antigen and presentation of MHC class II on monocytes and reducing macrophages (96), reducing the chemotaxis of monocytes and T lymphocytes (97). Cetirizine reduces the number of tryptase-positive mast cells at sites of inflammation (98). An increasing number of data points to the importance of fibroblasts in many organs.

CONCLUSION

Knowledge of the mechanisms underlying the allergic reaction, records a constant growth and tells us about the complex network of cells and mediators, which are at the core of allergic inflammatory response. Through its receptors, histamine as an important chemical messenger plays an important role in the physiological response, including neurotransmission, allergic inflammation and immunomodulation. Drugs that have the histamine receptors as target for their activity can be considered as a very good choice for the treatment of allergic conditions. Pharmacodynamic and pharmacokinetic differences between the first and second generation of antihistaminics should be well known, because it can help when choosing the right drug. Cetirizine is a potent second-generation antihistamine which shows remarkable immunoregulatory properties. It influences the interaction of mediator cells with all systems. It affects the interaction of eosinophils, mast cells and fibroblasts and thus may participate in the regulation of the internal environment.

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Histamin i antihistamini

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SAŽETAK


Ključne reči: histamin, imunski odgovor, blokatori histamina, cetirizin