

# LEUKOTRIENE AS INFLAMMATION MEDIATORS IN THE PATHOGENESIS OF ALLERGIC RHINITIS IN CHILDREN: THE CURRENT STATE OF THE PROBLEM

O.K.Jonuzokov

Samarkand State Medical University, Samarkand, Uzbekistan

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## Abstract

**Objective:** To summarize current data on the role of cysteinyl leukotrienes and 15-lipoxygenase pathway products (in particular, 15-hydroxyeicosatetraenoic acid, 15-HETA) as inflammatory mediators in the pathogenesis of allergic rhinitis in children, as well as the importance of their determination in nasal secretions for objective diagnosis of the disease. **Material and methods.** We analyzed literature data on the biosynthetic pathways, cellular sources, receptor apparatus, and pathophysiological effects of cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>) and 15-GETC in allergic rhinitis, as well as clinical studies assessing the levels of these mediators in nasal secretions during natural and provocative allergen exposure, including depending on the phase of the disease (exacerbation/remission), the burden of family allergy history, and the nutritional status of the child.

**Results.** This paper systematizes data on the origin of cysteinyl leukotrienes (mast cells, basophils, eosinophils) and their receptor interaction (CysLT<sub>1</sub> receptor), as well as the contribution of leukotrienes to the development of nasal obstruction, rhinorrhea, and cellular infiltration of the nasal mucosa. Data on the role of the 15-lipoxygenase pathway and its metabolite 15-GETA as an additional marker of eosinophilic inflammation of the nasal mucosa are summarized. It is shown that the level of inflammatory mediators in nasal secretions increases regularly during an exacerbation compared to remission and can be modulated by concomitant factors, such as a positive family history of allergies and excess body weight in the child. This justifies the use of these biomarkers as an objective addition to the clinical and instrumental diagnosis of allergic rhinitis in children.

**Conclusion.** Cysteinyl leukotrienes and 15-lipoxygenase pathway products are pathogenetically significant and potentially informative biomarkers of allergic inflammation of the nasal mucosa in children. Their determination in nasal secretions can serve as an objective complement to traditional diagnostic methods for allergic rhinitis, as well as a rationale for the differentiated use of antileukotriene therapy.

**Keywords:** cysteinyl leukotrienes, 15-hydroxyeicosatetraenoic acid, allergic rhinitis, children, nasal secretion, inflammatory mediators.

## 1. Introduction

Allergic rhinitis (AR) in children is an IgE-mediated inflammatory disease of the nasal mucosa, in the

pathogenesis of which, along with histamine, an important role belongs to lipid inflammatory mediators - products of arachidonic acid metabolism via the cyclooxygenase and lipoxygenase pathways [1,2]. Among the latter, the most clinically significant are cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>), synthesized primarily by mast cells, basophils and eosinophils via the 5-lipoxygenase pathway of arachidonic acid metabolism [1,3]. Unlike histamine, the effects of which are realized mainly in the early phase of the allergic reaction and are short-lived, the action of cysteinyl leukotrienes is more prolonged and largely determines the late phase of the allergic response, including persistent nasal obstruction and cellular infiltration of the mucous membrane [2,4].

In addition to the 5-lipoxygenase pathway, eosinophils possess independent 15-lipoxygenase activity, the product of which is 15-hydroxyeicosatetraenoic acid (15-HETE) [5]. The significance of 15-HETE as a biomarker of allergic inflammation of the nasal mucosa has been studied to a lesser extent than cysteinyl leukotrienes; however, the available data indicate a consistent increase in its concentration in nasal secretions during an allergen challenge, which allows us to consider this metabolite as an additional, pathogenetically substantiated marker of the eosinophilic component of inflammation [6]. The study of both classes of mediators—cysteinyl leukotrienes and products of the 15-lipoxygenase pathway—in the nasal secretions of children with seasonal allergic rhinitis is of independent practical interest, since it can serve as an objective addition to the clinical and instrumental methods of diagnosing the disease used in routine otolaryngological practice.

## 2. Materials and Methods

An analysis of literature data, including basic and clinical studies on the role of leukotrienes and 15-lipoxygenase pathway products in the pathogenesis of allergic rhinitis, was conducted using the keywords "cysteinyl leukotrienes," "15-HETE," "allergic rhinitis," "nasal secretion," and "CysLT1 receptor." Data on the influence of clinically significant factors such as the disease phase (exacerbation/remission), family history of allergies, and the child's nutritional status on the levels of these mediators were separately analyzed, as these factors are considered potential modulators of the severity of the mediator response in allergic rhinitis in children.

## 3. Results

Biosynthesis and cellular sources of cysteinyl leukotrienes. Cysteinyl leukotrienes are formed from arachidonic acid in the cell membrane by its oxidation by 5-lipoxygenase to form the unstable intermediate LTA<sub>4</sub>, which is then conjugated with reduced glutathione by LTC<sub>4</sub> synthase to form LTC<sub>4</sub>, the progenitor of the entire group of cysteinyl leukotrienes [3,7]. Mast cells and basophils have the greatest capacity to synthesize cysteinyl leukotrienes, and the amount of leukotrienes produced by basophils can be more than 100 times higher than that of eosinophils; however, it is the eosinophils infiltrating the nasal mucosa in the late phase of an allergic reaction that ensure long-term and sustained production of the mediator at the site of inflammation [3].

Receptor apparatus and pathophysiological effects.

The biological action of cysteinyl leukotrienes is realized through a specific CysLT1 receptor expressed on the vascular endothelium of the nasal mucosa, smooth muscle cells, eosinophils, mast cells and monocytes/macrophages [3]. The interaction of leukotrienes with this receptor leads to three main pathophysiological effects: (1) dilation of nasal mucosal vessels and increased vascular permeability with the development of edema, which is clinically manifested by nasal obstruction; (2) stimulation of mucus secretion by goblet cells, which underlies rhinorrhea; (3) chemotactic recruitment of eosinophils and other inflammatory cells from the bloodstream into the mucosal tissue, which maintains and enhances the inflammatory process [3,4]. Unlike histamine, the administration of cysteinyl leukotrienes is not accompanied by itching and sneezing, but causes severe and prolonged nasal obstruction, which persists significantly longer than the histamine-mediated reaction [8].

15-lipoxygenase pathway and 15-GETK.

In addition to the 5-lipoxygenase pathway, human eosinophils possess 15-lipoxygenase activity, which ensures the formation of 15-GETA and a number of dihydroxy derivatives of eicosatetraenoic acid [5]. Data from early clinical studies with a provocative intranasal test with a house dust allergen showed a significant increase in the level of 15-GETA in nasal secretions already during the early phase of the allergic reaction, along with an increase in the level of peptide leukotrienes and other metabolites of

arachidonic acid, which confirms the involvement of the lipoxygenase metabolic pathway as a whole (not only the 5-, but also the 15-lipoxygenase branch) in the formation of the pathophysiological response of the nasal mucosa to an allergen challenge [6]. Activation of the 15-lipoxygenase pathway is also associated with increased eosinophilic infiltration and expression of eosinophil chemoattractants in the mucous membrane of the upper respiratory tract, which allows us to consider 15-GETK not only as a marker, but also as an independent, although less studied compared to cysteinyl leukotrienes, participant in the pathogenesis of allergic inflammation [9].

Clinical and diagnostic significance.

Determination of the level of cysteinyl leukotrienes and 15-HETC in nasal secretion obtained by nasal lavage is considered a minimally invasive and well-tolerated method for objectifying allergic inflammation of the nasal mucosa in children, suitable for repeated use in the dynamics of observation [1]. A higher level during a clinical exacerbation compared to a remission period is typical for this group of mediators, which reflects the relationship between the concentration of mediators and the current activity of the allergic process, and not only with the fact of sensitization as such. Clinically significant modulators of the severity of the mediator response are considered to be a burdened family history of allergy, associated with a higher initial level of the mediator response, as well as the nutritional status of the child: overweight and obesity are associated with proinflammatory secretion of adipokines, potentially increasing the severity and severity of allergic inflammation of the nasal mucosa [10].

#### 4. Discussion

The totality of the presented data justifies the consideration of cysteinyl leukotrienes and 15-HETC not as two isolated, but as complementary links of the same lipoxygenase cascade of arachidonic acid metabolism, reflecting different cellular sources and, probably, different temporal phases of the inflammatory response of the nasal mucosa in allergic rhinitis in children [3,5,6]. The practical significance of these data for pediatric otolaryngology lies in the possibility of using the level of these mediators in nasal secretion as an objective, pathogenetically substantiated addition to traditional clinical-instrumental and laboratory-immunological methods of diagnosing allergic rhinitis (anterior rhinoscopy/endoscopy, skin allergy tests, determination of specific IgE), especially in cases where the clinical picture of the disease is nonspecific and requires differential diagnosis with other causes of difficult nasal breathing in frequently ill children.

The clinical significance of cysteinyl leukotrienes is also confirmed indirectly, through the proven effectiveness of antileukotriene drugs (CysLT1 receptor antagonists, in particular montelukast) in allergic rhinitis in children, especially with a concomitant broncho-obstructive component, which makes biomarker determination of leukotriene levels not only diagnostic, but also a therapeutically oriented study, potentially capable of justifying differentiated choice of antileukotriene therapy in addition to the standard regimen [11,12].

A limitation of most of the cited studies is the relatively small sample size and heterogeneity of the methods for obtaining and analyzing nasal secretions (provocative tests versus the natural course of the disease, differences in lavage methods and sampling points), which complicates direct comparison of absolute values of mediator concentrations between individual studies and emphasizes the need for standardization of methods when introducing these biomarkers into routine clinical practice.

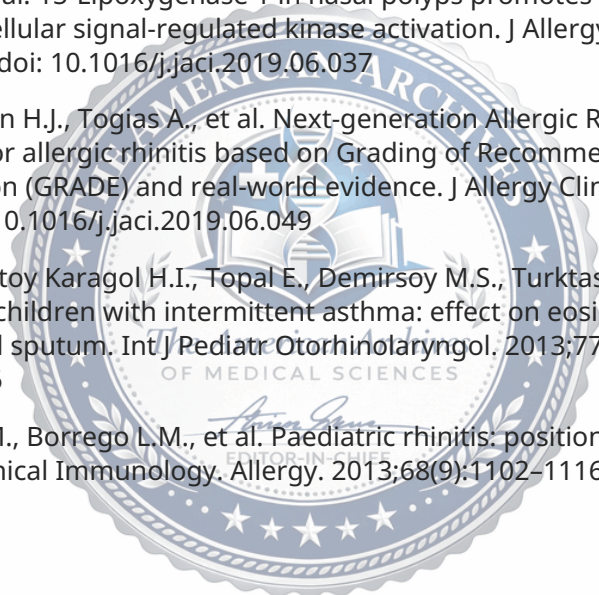
#### 5. Conclusion

Cysteinyl leukotrienes and 15-lipoxygenase pathway products, primarily 15-GETA, are pathogenetically significant mediators of nasal mucosal inflammation in children with allergic rhinitis. Their levels in nasal secretions consistently increase during exacerbations and are modulated by a positive family history of allergies and the child's nutritional status. Determination of these biomarkers can be considered a promising objective complement to traditional diagnostic methods for allergic rhinitis in children and a basis for the differentiated use of antileukotriene therapy in the complex treatment of the disease.

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