MEDIATOR'S IMPLEMENTATION NASAL ALLERGIES

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Summary. The ability to determine and quantify mediators in nasal secretions after specific challenge or during natural challenge, has greatly contributed to our current understanding of allergic rhinitis. We can consider allergic rhinitis to be an inflammatory disease of the nasal airways, initially triggered by an immunoglobulin E mechanism and perpetuated through the action of T2 lymphocytes and eosinophils. Upon contact with the nasal mucosa, the allergen interacts with immunoglobulin E bound to the surface of nasal mast cells and also of some basophils present in the nasal mucosa, leading to cellular activation and release of a wide array of molecules. These molecules have a direct action on the nasal mucosa, inducing the appearance of immediate symptoms, which can start minutes after exposure and have a variable duration. Mediator detection and quantification in nasal secretions have contributed to the understanding of some aspects of the pathophisiology of allergic rhinitis.

Keywords: allergic rhinitism, inflammatory response, mast cells, eosinophils, prostaglandins, leukotriene, cytokines.

Allergic rhinitis may be defined as an inflammation of the nasal mucous membranes caused by immunoglobulin E (IgE)-mediated (allergic) reaction to aeroallergens. He has become the most common allergic or immunologic disorder and is acknowledged as a significant health challenge on a global scale. Allergic rhinitis is a major cause of patient visits to physicians, commonly complicates management of other conditions (e.g., asthma, chronic sinusitis), and if untreated or undertreated can lead to considerable morbidity including missed work or school, sleep disruption, diminished daytime performance, and impaired quality of life. The prevalence of allergic rhinitis has been steadily increasing, justifying a growing interest in the understanding of the pathophysiologic mechanisms involved, in order to develop new therapeutic strategies. In this regard, the ability to determine and quantify mediators in nasal secretions after specific challenge or during natural challenge, has greatly contributed to our current understanding of allergic rhinitis. Nevertheless, the subject remains complex; not only it is an inflammatory reaction in which multiple cell types, multiple cytokines and other molecules are involved but also these reactions can present different patterns with different allergens and with different exposures to the same allergen (unique, short-lived, prolonged or daily exposures; natural or provoked exposures).

Hyperreactivity or hyperresponsiveness in the upper and lower airways refers to an increased sensitivity to non-specific stimuli or irritants. In case of hyperreactivity of the nasal mucosa the most prominent symptoms of rhinitis patients are sneezes, rhinorrhoea and nasal blockage on exposure to low doses of stimuli which do not induce symptoms in healthy subjects. The inflammatory response in allergic rhinitis starts with an assymptomatic sensitisation period, followed by symptomatic immediate and late-phase reactions. During sensitisation the allergen is presented to T0 lymphocytes, which differentiate by mechanisms not yet fully understood to T2 lymphocytes, with the ability to produce and release an array of cytokines including Interleukins IL-4 and IL-13 which shift the humoral response towards IgE, Interleukins IL-3 and IL-5 which are important to the maturation and tissue survival of eosinophils and Interleukin IL-10 which tends to inhibit the Tl differentiation.

We can therefore consider allergic rhinitis to be an inflammatory disease of the nasal airways, initially triggered by an immunoglobulin IgE mechanism (type I hypersensitivity reaction) and perpetuated through the action of T2 lymphocytes and eosinophils (type IVa2 hypersensitivity reaction). Additionally, mast cells produce and release upon activation Type 2 cytokines [2] and also Interleukin IL-16, which helps to attract CD4+ lymphocytes to the site of the allergic reaction.

Clinically allergic rhinitis is characterised by an increase in nasal reactivity whether to immune/specific allergenic stimuli or to non-immune, non-specific challenges.

Upon contact with the nasal mucosa, the allergen interacts with IgE bound to the surface of nasal mast cells and also of some basophils present in the nasal mucosa, leading to cellular activation and release of a wide array of molecules, including pre-formed mediators, newly-formed mediators and cytokines. Several of these molecules have a direct action on the nasal mucosa, inducing the appearance of immediate symptoms, which can start minutes after exposure and have a variable duration. Others have proinflammatory actions, with chemotactic or cellular activating properties, including the up-regulation of adhesion molecules expression. Several studies have been conducted in order to identify cell types and mediators, in blood or nasal secretions, related to induction, duration and intensity of nasal symptoms (pruritus, sneezes, rhinorrea, nasal blockage) [5].

Regarding mast cells, mediators such as histamine, chimase, kinins, Platelet-activating factor, Prostaglandin PgD2, Leukotriene LTC4 and Tryptase - extensively used as mast cell marker since it is exclusively produced by these cells [18] - have been commonly related to the appearance of immediate symptoms.

Tissue mast cells have a widespread distribution throughout the body but are particularly numerous in nasal mucosa and pulmonary tissues. Activation and degranulation of nasal mast cells is a consistent finding in all allergic rhinitis patients and elevated levels of histamine and tryptase can be detected in nasal lavage fluid after allergen challenge. The rise in tryptase in nasal secretions is relatively brief and in parallel with a rise in Prostaglandin PgD2, which is also released by mast cells but not by basophils. It is interesting to note that some authors have not found any elevation of tryptase levels in nasal secretions of patients with seasonal allergic rhinitis during the pollinic season, despite elevated levels of Leukotriene LTC4, eosinophil cationic protein (ECP) and histamine, a finding which reflects mainly a chronic state of allergic inflammation of the nasal mucosa [27]. The pathogenic role of tryptase in allergic rhinitis is not perfectly clear, being also debatable if tryptase levels correlate or not with the intensity of nasal symptoms induced by allergen exposure. Despite the importance of tryptase as a mast cell marker, histamine is undoubtedly the most important mediator in the induction of immediate nasal symptoms, as proven by nasal provocations with histamine or by the therapeutic efficacy of antihistamines. However, mast cells release other mediators such as the leukotrienes which can also induce symptoms. Leukotrienes can be detected in nasal secretions in just a few minutes after allergen challenge [19]. However, correlation between the release of a single mediator and the presence of a specific symptom has not yet been fully established.

Late-phase reactions occur some hours after allergen exposure and the main clinical symptoms relate to nasal obstruction. There is an important contribution of cells which have been recruited and activated by mediators of the immediate phase; these cells in turn release their own mediators and proinflammatory molecules, contributing to the chronicity of the process. Eosinophils and also basophils are considered the main players of this phase. It has been discussed if a second histamine peak, that is sometimes observed, is due to a re-release from mast cells or to the release of histamine from basophils. Several studies and our own data, from a study with allergic rhinitis patients in which no tryptase was detected in nasal secretions since one hour to 24 hours after nasal challenge, point to the basophil as the origin of this second histamine peak.

Eosinophil activation is associated with surface expression of EG2 (a secreted form of eosinophil cationic protein - ECP), release of granule proteins: ECP, major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin EDN) with cytotoxic potential and increased production of phospholipids such as Prostaglandins, Platelet-activating factor or

Leukotrienes. Resting blood eosinophils normally do not produce significant amounts of Leukotriene LTC4 but activated tissular eosinophils do produce and release significant quantities of this mediator; levels of Leukotriene LTC4 correlate well with the presence of ECP and eosinophils in secretions, suggesting a role for the eosinophils as a source of LTC4 in an ongoing allergic rhinitis [19].

Interestingly, nasal provocation with leukotrienes induces nasal congestion but it does not induce significant sneezing, itching or rhinorrea, in opposition to histamine provocation. This finding can be due to the lack of stimulatory action of leukotrienes on nasal nerve endings [19]. Leukotriene receptor antagonists have demonstrated, in some experimental studies, clinical benefit in the therapy of rhinitis. In two studies in guinea pigs, pranlukast (a cysteinil leukotriene antagonist) did not affect immediate symptoms induced by allergen provocation but significantly inhibited the late phase response and mucosal infiltration by eosinophils [13] with inhibition of changes in nasal permeability and nasal airway resistance. Since nasal blockage is a most disturbing symptom and generally difficult to treat, the introduction of this new anti-mediator strategy may become very useful as an adjunct to topical nasal steroids or as a possible alternative in steroid-phobic patients.

Eosinophil cationic protein measurements in biological fluids such as blood, nasal secretions, bronchoalveolar lavage fluid or even in synovial fluid, have been used as markers of local eosinophil activation, although kinetics of this activation have been less well studied. Many studies confirm eosinophil as a main cell in late-phase reactions and in the evolution to chronicity, with few or no contribution to the early-phase reactions after allergen challenge. However, some studies also show that in some patients there is a detectable ECP rise in the early-phases after nasal allergen challenge. These discrepancies can be found between individuals subjected to the same allergen provocation procedure but are even more evident when we compare between different allergen types. As it is rare to find papers where the kinetics of cell activation have been studied for more than one allergen, it is difficult to analyse comparatively data from different authors because methodological differences are very significant. It is always important to stress that the technical aspects involved are very important and can account for huge differences in results [5]. Differences start immediately in the technique used for the collection of samples; these can be obtained by nasal lavages, embedding filter paper in the nasal secretions, collecting nasal secretions by forceful blowing of the nose, using microsuction techniques, cytological methods such as brushing or scraping or even by biopsing the nasal mucosa. In the laboratory analysis of mediators there are also different methods which can be employed; currently fluorescent enzymatic methods are convenient and easy to execute but radioimunoassays, High Performance Liquid Chromatography, Spectrofluorometry, ELISA or others can also be performed, with advantages and disadvantages, which are beyond the scope of this paper.

We have recently observed that specific nasal provocation out-of season, with standardised allergen extracts, in patients with grass pollen allergic rhinitis, induced a rise in ECP which was more pronounced at 24 hours, in agreement with data from several other authors [21,22]. However, using exactly the same methodology regarding nasal challenge, collection of nasal lavage fluid and quantification of ECP in nasal lavage, we could demonstrate that patients with mite-allergic rhinitis presented much earlier peaks of ECP - at four and even at one hour after challenge - with significantly higher pre-provocation values, when compared to pollinic patients. These results point to different contributions of the same cells in different allergies, probably as a result of a chronic state of activation in the case of mite-allergic patients. This early activation of eosinophils (which probably reflects the presence in the nasal mucosa of some eosinophils already in a primed state) also raises the possibility of direct activation of the eosinophils by the allergen itself (via IgE bound to low and high affinity IgE receptors) or, alternatively, an increase of eosinophil releasability (a concept which has been applied mainly to mast cells and basophils) in response to stimuli from

other cells, namely mast cells.

Measurement of serum ECP has not been consistently useful in rhinitis patients although in some studies it has been shown to be elevated in allergic rhinitis. In one interesting study there were significant reductions in serum ECP during specific immunotherapy to Dermatophagoides farinae, when compared to untreated D. farinae allergic rhinitis patients, reaching after 3 years of specific immunotherapy values not significantly different from the non-atopic control group [12].

Mediator detection and quantification in nasal secretions have contributed to the understanding of some aspects of the pathophisiology of allergic rhinitis and they will probably remain a useful research tool during the next years. In clinical practice they can be used in nasal challenges as a quantitative complementary method, allowing one other form of valorisation of a doubtful challenge and also allowing to monitor the evolution during therapy, namely during immunotherapy. In drug or other therapeutic trials, mediator measurement can also allow to reach statistical significance with the analysis of a smaller number of patients than other methods. Nevertheless, it should also be emphasised that optimal standardisation of the many technical aspects of mediator analysis is required.

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