

Inflammatory mediators in allergic rhinitis

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Allergic rhinitis (AR) is part of a systemic disease complex. There is a close relationship between AR and asthma, which has led to the “one airway, one disease” concept. Both conditions share common immunopathology and pathophysiology. In patients with AR, allergen-triggered early and late responses are mediated by a series of inflammatory cells. Within minutes of contact with allergen, IgE-sensitized mast cells degranulate, releasing both preformed and newly synthesized mediators. Immunologic processes in both nasal and bronchial tissue involve T_H2 lymphocytes and eosinophils. Eosinophils are the predominant cell in the chronic inflammatory process characteristic of the late-phase allergic response. Eosinophils release an array of proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and might serve as a major source of IL-3, IL-5, GM-CSF, and IL-13. Neuropeptides also appear to contribute to the pathophysiology of AR symptoms. Both AR and asthma exhibit marked day-night variation in symptom severity. Acknowledging both the chronobiology of AR and circadian rhythm-dependent attributes of antiallergy medications might enhance the beneficial effects of allergy therapies. (*J Allergy Clin Immunol* 2004;114:S135-8.)

Key words: Allergic rhinitis, inflammation, inflammatory mediators, asthma, chronotherapy, chronobiology, unified airway

Allergic rhinitis (AR) is the most common atopic disease in the United States and is estimated to affect up to 25% of adults and more than 40% of children. Strikingly, close to 80 million individuals experience manifestations of AR, nasal-ocular symptoms, for more than 7 days a year. The associated socioeconomic costs are similarly significant because AR affects school performance, socialization, and work productivity.¹⁻⁴

PATHOPHYSIOLOGY OF ALLERGIC RHINITIS

As with the other atopic disorders such as asthma, eczema, and food allergy, AR is part of a systemic disease complex. Within minutes of exposure to allergen, sensitized mast cells release mediators that result in early symptoms, as well as the recruitment of additional inflammatory cells, causing later symptoms and maintaining the disease process. Even the term “hay fever”

Abbreviation used
AR: Allergic rhinitis

connotes the findings that the nasal-ocular symptoms of AR elicited by antigen are also associated with systemic manifestations, the consequence of mediator release.

There is a very close relationship between AR and allergic asthma. In fact, the 2 conditions are manifestations of one syndrome in 2 regions of the respiratory tract, leading to a “chronic allergic respiratory syndrome.” As stressed recently, AR and asthma can be considered “one airway, one disease.” It is well recognized that more than 80% of persons with allergic asthma have AR and that AR is a risk factor for the development of asthma. The 2 conditions also share a common immunopathology and pathophysiology.⁵⁻⁷ As outlined in Table I, they share similar immunologic processes, the findings in nasal and bronchial tissue are similar, and T_H2 lymphocytes, mast cells, and eosinophils are involved in both conditions. In both AR and asthma, early- and late-phase responses can be elicited, and hyperresponsive states, sensorineural in the nasal passages and in the airways in response to allergen challenge, can also be demonstrated.

Within minutes of contact with allergen, IgE-sensitized mast cells degranulate and release a series of preformed and newly synthesized mediators. Many of these mediators lead to the characteristic symptoms of AR, including sneezing, itchiness, rhinorrhea, and congestion. These early-phase responses have been attributed to the immediate release of cysteinyl leukotrienes, prostaglandins, histamine, and cytokines. Histamine has been shown to elicit virtually all of the early-phase responses, primarily through binding to the H_1 receptor.^{8,9}

In the second, or late, phase of the AR response, congestion becomes more prominent. As a result of cytokine or mediator release, the nasal mucosa becomes infiltrated with inflammatory cells, basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, further sustaining the nasal mucosal inflammatory reaction.^{5,10,11} Histamine acting through H_1 receptors, as well as through H_2 , H_3 , and H_4 receptors, might increase expression of adhesion molecules and increase production of a number of proinflammatory cytokines.¹²

Over the course of an allergy season, there might be a 10-fold increase in the numbers of nasal epithelial and submucosal mast cells.¹³ In fact, the number might correlate very well with pollen counts. These mast cells might not only play important roles during the initial AR response but also might be key to sustaining this response into a more chronic phase. One interesting possibility is

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TABLE I. Immunopathology and pathophysiology common to AR and asthma

Similar immunologic processes
Similar findings in nasal and bronchial tissue
Eosinophils, mast cells
T _H 2 lymphocytes
Early- and late-phase responses
Hyperresponsiveness: sensorineural in nasal passages and airways in response to allergen challenge

TABLE II. Cysteinyl leukotrienes in AR

Increased levels in nasal fluid after allergen challenge
Levels correlate with eosinophil cationic protein levels
Contribute to both early and late phase
Nasal congestion
Sneezing, rhinorrhea
Chemoattractant for eosinophils
Promote eosinophil adhesion
Decrease eosinophil apoptosis
Facilitate growth of eosinophil precursors (with GM-CSF, IL-5)

that mast cell–derived lipid mediators and histamine might be important in the recruitment of T_H2 lymphocytes to target organs.

Eosinophils are the predominant cell in the chronic inflammatory process characteristic of the late-phase response. The influx of eosinophils correlates with the development and progression of symptoms.¹⁴⁻¹⁶ Eosinophils release an array of proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and might serve as a major source of IL-3, IL-5, GM-CSF, and IL-13.¹⁷ The cysteinyl leukotrienes have many activities that are linked to the symptomatology of AR, as well as the recruitment and activation of eosinophils (Table II).¹⁸⁻²⁶

Our understanding of the role of neuropeptides in AR is limited and is an area of growing interest. The nasal mucosa is highly innervated, and neuropeptides are involved in the pathophysiology and contribute to many of the symptoms of AR (Tables III and IV).

The nasal and bronchial mucosa are very similar, with columnar ciliated cells positioned over a basement membrane. The inflammatory infiltrate in asthma and AR is also very similar, as are the triggers to a large extent.²⁷⁻³⁰ There are also important differences (Table V). The embryonic development of the upper and lower airways differs, suggesting that the genes governing repair or remodeling are different.³¹ Smooth muscle is only present in the bronchi. In the nose there is a large supply of subepithelial capillaries, arterial systems, and venous cavernous sinusoids.

Together, these differences are most obvious when remodeling in the upper and lower respiratory tract is considered (Table VI). Remodeling is much more prominent in the lower airways, whereas the nasal mucosa has a much higher capacity for epithelial regeneration and protection.³²

TABLE III. Action of neuropeptides in AR

Vasoconstriction and decreases in nasal airway resistance result from sympathetic nerve stimulation.
Parasympathetic nerve stimulation promotes secretion from nasal airway glands and nasal congestion.
Nasal mucosa contains nerves of the nonadrenergic, noncholinergic system.

TABLE IV. Role of neuropeptides in AR

Substance P, neurokinin A, neurokinin K, calcitonin gene-related peptide
Vasodilation
Mucus secretion
Plasma extravasation
Neurogenic inflammation
Mast cell–nerve interactions

TABLE V. Differences between the upper and lower airways

Nose (ectodermal) and bronchial (endodermal) airways have a different embryologic origin.
Genes governing repair-remodeling might be different.
Smooth muscle is only present in the bronchi.
Nose contains a large supply of subepithelial capillaries, arterial systems, and venous cavernous sinusoids.

CHRONOBIOLOGY OF ALLERGIC RHINITIS

Within the context of homeostasis, biologic functions are not consistent over time, especially during different parts of the day-night cycle. Chronobiology is the science studying biologic rhythms. Circadian rhythms are critically important in medicine. Whether endogenous or exogenous, the activity of biologically important molecules is dependent on circadian rhythmic phenomena that can affect pharmacokinetics and pharmacodynamics. Many diseases are affected by circadian time structure, including asthma and AR. For asthma, peak flows are best around 4 PM and worst at 4 AM. The worsening of lung function in the early morning hours is associated with increased inflammatory cell infiltration of the airways.³³

There is also a striking day-night pattern in AR. Patients with seasonal and perennial AR complain of disturbed sleep at night, as well as symptoms on awakening in the morning. In fact, the earliest description of the chronobiology of AR was by Trousseau in 1865, who described the prominent morning manifestations and intensity of nasal symptoms.³⁴ Since then, many studies have examined day-night variation and intensity of AR. Generally, all show that symptom severity peaks at approximately 6 AM.³⁵⁻³⁷

This circadian rhythm for symptoms of AR is intertwined with the pharmacokinetics and dynamics of many medications, which are similarly circadian rhythm

TABLE VI. Remodeling differs in asthma and AR

Magnitude of inflammatory response might differ.
Epithelial disruption and desquamation is a feature of the bronchial epithelium in asthma but is less marked in the nasal epithelium with rhinitis.
Thickness of the reticular basement membrane is greater in bronchial mucosa than in nasal mucosa.

dependent. The need for medication might not be consistent throughout the 24-hour cycle. Thus chronotherapy of AR with H₁ receptor antagonists might be an important consideration. When examined, these mediations were least effective when most of or all of the daily dose was taken in the morning at breakfast. Evening administration was especially effective, considering the usual peaking of symptoms at 6 AM.^{38,39}

CONCLUSIONS

AR, like other atopic diseases, is the result of allergen-triggered early and late or chronic responses mediated by a series of inflammatory cells and mediators. Although the nasal mucosa is derived from a different embryologic origin, much of the immunopathology is shared between the upper and lower respiratory tracts. Similar to asthma, AR exhibits a marked day-night variation, which currently is often in conflict with administration of, for example, antihistamines in a single dose at breakfast. Failure to acknowledge both the chronobiology of the disease and the circadian rhythm-dependent attributes of the medications will clearly compromise or limit the beneficial effects of many of these therapies.

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