

The unified immune system: Respiratory tract-nasobronchial interaction mechanisms in allergic airway disease

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Allergy is a systemic disorder that can affect the nose, lungs, eyes, skin, and gastrointestinal tract, simultaneously or in succession, during the course of a patient's life. The reason for the variety in clinical expression of allergic disease is not known. Genetic predisposition, as well as environmental factors, contribute to the development of the allergic phenotype. Local and systemic inflammatory processes also seem to play a role; however, their exact contribution to the clinical manifestation of airway allergy still remains to be clarified. Although it is clear that allergen exposure of a sensitized target organ is associated with immunopathologic changes at the level of other target organs, the mechanisms underlying this relationship are far from being resolved. Today, most data suggest a systemic link between mucosal sites, involving the bloodstream, bone marrow, and mucosa-associated lymphoid tissue. This review will focus on the interaction between the nose and lungs in allergic disease and the possible implications for the gastrointestinal mucosa. (J Allergy Clin Immunol 2005;115:142-8.)

Key words: Allergic rhinitis, asthma, interaction mechanisms, mucosal inflammation, gastrointestinal tract

Although anecdotal descriptions of asthma and allergic rhinitis date from earlier times, it was not until the 19th century that a pathophysiologic association between these 2 allergic airways diseases was recognized. In 1873, Charles Blackley was the first to establish a relationship between grass pollen exposure and the subsequent development of nasal and bronchial complaints.¹ Because allergic rhinitis and asthma are increasing health problems in the industrialized world, there is a renewed interest in the interaction between the 2 disorders. Not only is allergic rhinitis a risk factor for the development of asthma, it also aggravates ongoing bronchial inflammation. Moreover, mucosal inflammation is not restricted to the airway mucosa in patients with allergic rhinitis and asthma; the

Abbreviation used

BHR: Bronchial hyperresponsiveness

gastrointestinal mucosa also seems to participate in the systemic allergic reaction.

EPIDEMIOLOGY

Prevalence rates of atopic diseases, such as asthma, rhinitis, and eczema, vary throughout the world.² In Europe the prevalence of asthma and rhinitis has doubled during the last 2 decades.³ Epidemiologic studies strongly suggest an association between allergic rhinitis and asthma.^{4,5} Almost 40% of patients with allergic rhinitis have lower airways involvement, whereas more than 80% of the patients with allergic asthma have concomitant rhinitis symptoms.^{6,7} The latter percentage reaches nearly 95% according to more recent data.⁸ Moreover, in the same study it was shown that the relationship between rhinitis and asthma symptoms was stronger for animal and mite sensitization than for pollen sensitization.

ETIOLOGY

Allergic disorders, such as allergic rhinitis and asthma, have a multifactorial origin (Fig 1). Family cohort studies and studies in twins demonstrate that atopic disorders are, at least partially, inheritable.⁹⁻¹¹ Several candidate genes implicated in the expression of allergic disease have been identified in the past years, among which are the *IL4* gene cluster, the HLA-D region, the high-affinity IgE receptor gene (*FCER1B*), and, more recently, genes encoding transcription factors and mediators of inflammation.¹² However, even in monozygotic twins, concordance numbers do not exceed 70%, which indicates that other factors are also involved.¹³

Atopic diathesis requires appropriate allergen exposure to result in the production of specific IgE in a genetically susceptible host. The initial sensitization typically occurs in childhood and depends on lifestyle influences, such as indoor allergen exposure,¹⁴⁻¹⁷ breast-feeding,¹⁸ and maternal smoking.¹⁹ Reduction of exposure to indoor

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Concept chronic airway disease

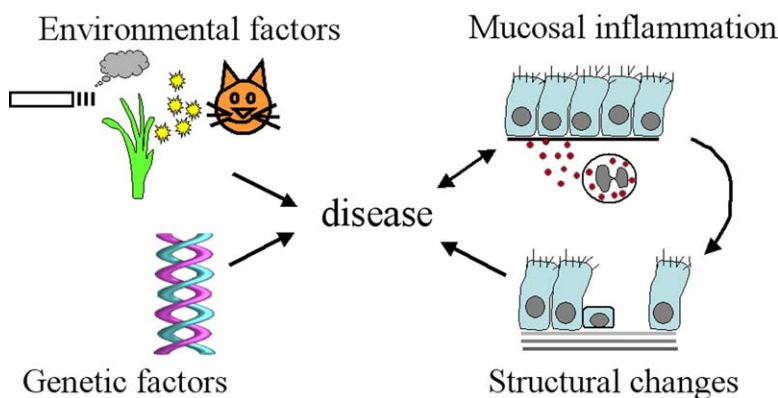


FIG 1. Concepts of chronic airway disease. Local and systemic factors involved in the continuation of allergic airway disease.

allergens during early childhood offers some, but not total, protection against the development of respiratory symptoms in a high-risk population.²⁰ Moreover, there is compelling evidence that exposure to endotoxins during the first years of life reduces the risk of allergic rhinitis²¹ and asthma.²² Viral infections in early childhood might also affect allergen sensitization and the development of asthma, depending on the nature of the virus.²³ An increase in the prevalence of rhinitis and atopic sensitization was observed among East German children between 1991 and 1996. However, no increase in the prevalence of asthma was noticed in this population.²⁴ Therefore genetic predisposition and early-life influences might be more important for the development of childhood asthma, whereas allergic rhinitis might also be affected by environmental factors occurring later in life.

IMMUNOLOGIC ASPECTS

It has been well established that allergic rhinitis and asthma are characterized by a similar inflammatory process in which multiple inflammatory cells and mediators are involved. Allergic mucosal inflammation is the result of several sequential events. The primary response to an allergic²⁵ or irritating²⁶ stimulus takes place in the target organ and is generally more severe in patients with allergic rhinitis and asthma than in patients with only rhinitis.²⁵ Several mechanisms are involved, including antigen presentation by dendritic cells to T lymphocytes, resulting in the generation of cytokines and other chemotactic factors^{27,28} and mast cell degranulation, leading to release of histamine and proteases.²⁹⁻³¹ Antigen-presenting cells also transport allergens to the draining lymphoid tissue. They present their contents to T lymphocytes, which will become activated and enter the circulation. These cells will not only home at the primary site of the allergic

reaction but also migrate to other possible target organs. Both mast cells and T lymphocytes orchestrate the late-phase reaction in which eosinophils and basophils migrate from the circulation toward the mucosa, depending on adhesion molecule expression and chemotactic factors, such as IL-5, eotaxin, and cysteinyl leukotrienes.³²⁻³⁴

Although eosinophilia in bronchial mucosa is regarded as one of the hallmarks of allergic asthma,^{35,36} this might not be a very specific finding. Lower airway eosinophilia is also present in allergic rhinitis^{37,38} and not related to clinical severity.³⁹ Likewise, eosinophilic infiltration has been demonstrated in the upper airways of asthmatic patients without nasal complaints.⁴⁰ In fact, the presence of bronchial inflammation in nonasthmatic atopic patients, even in the absence of any airway symptoms at all, challenges the direct relationship between the presence of inflammatory cells, particularly eosinophils, and clinical expression.³⁹ The presence of inflammatory cells per se in mucosal tissue might therefore only be an indication of a systemic atopic disease.

Therefore the threshold above which an allergic response is initiated in the bronchi in daily life is probably higher in patients with allergic rhinitis than in those with clinical asthma. In a bronchoprovocation model Beckey Kelly et al⁴¹ demonstrated that the dose required to initiate comparable clinical responses was significantly lower in patients with asthma than in patients with allergic rhinitis without asthma. The response to inhaled allergen also depends on the degree of bronchial hyperresponsiveness (BHR), which is often less pronounced in patients with allergic rhinitis than in those with asthma.⁴²

Apparently, allergic inflammation affects the entire airway in patients with allergic rhinitis and asthma without necessarily influencing symptomatology and airway patency. However, some patients with allergic rhinitis and asthma have such a poor perception of nasal⁴³ and bronchial⁴⁴ symptoms that this might also partly explain

Interaction mechanisms

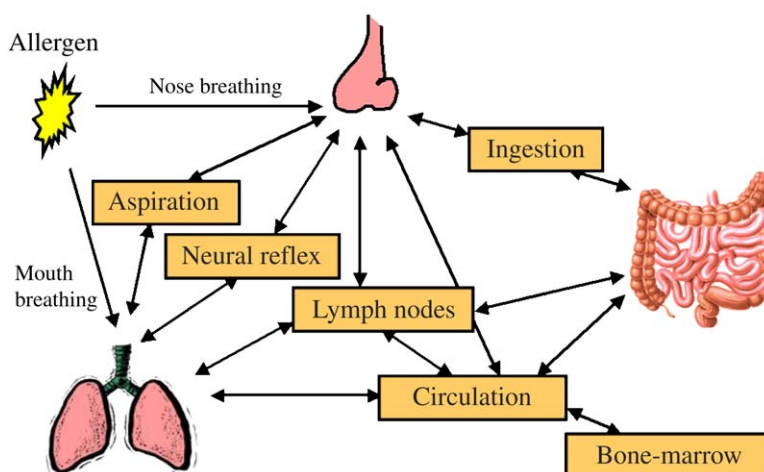


FIG 2. Interaction mechanisms. The possible pathways of nasobronchial interaction in allergic rhinitis and asthma.

the discrepancy between mucosal inflammation and clinical expression.

NASOBRONCHIAL INTERACTION

Allergic rhinitis and asthma often coexist in the same patient.^{6,8,45} Patients with rhinitis have a 3 times higher risk of asthma development than healthy people, irrespective of the presence of atopy, suggesting that rhinitis by itself is an important risk factor for the development of asthma.^{46,47}

Pathophysiologically, the relationship between nasal malfunction and subsequent bronchial airway involvement is obvious. The nose protects the lower airways through filtering and air conditioning of the inhaled air. However, the efficacy of the nose filter depends on the size of the inhaled particles.⁴⁸ Small molecules, such as molds and cat dander, are associated with an increased risk for asthma, whereas larger molecules, such as tree and grass pollen, are associated with upper airway symptoms.^{49,50}

Inhalation of cold and dry air was associated with a decreased FEV₁ value in asthmatic patients,⁵¹ indicating that air conditioning is also of major importance. In allergic rhinitis these functions are impaired, which also has consequences for lower airway function.⁵² A clear relationship has been found between the severity of allergic rhinitis and lower airway symptoms.⁵³ Treatment of allergic rhinitis in patients with concomitant asthma significantly reduced the risk of severe asthma exacerbations and hospitalization.⁵⁴

Several mechanisms have been held responsible for the interaction between the upper and lower airways (Fig 2), such as the nasal bronchial reflex and migration of inflammatory cells.⁵⁵ On the basis of airway anatomy and physiology, 3 different pathways could be involved in nasobronchial cross-talk: the respiratory pathway, the neural pathway, and the circulatory pathway.

RESPIRATORY PATHWAY

The first publication mentioning aspiration of nasal secretions as a provocative factor in the development of asthma dates from 1883.⁵⁶ Although later studies confirmed a clear relationship between postnasal drip and coughing,^{49,57,58} no direct contact has been proved between nasal secretions and bronchial mucosa. In contrast, Bardin et al⁵⁹ and Corren et al⁶⁰ demonstrated, after nasal application, deposits of radioactive labeled allergen in the digestive tract but not in the respiratory tract. Stimulation of pharyngolaryngeal receptors is more likely to be responsible for a postnasal drip-related cough.⁶¹ Aspiration might play a role in patients with depressed consciousness and impaired cough reflex, such as mechanically ventilated patients.⁶² Under normal conditions, however, this mechanism does not seem to have a contributory effect on nasobronchial interaction.⁵⁹

In patients with allergic rhinitis, the nose can be blocked, and mouth breathing is favored. The reduced filter and air-conditioning function of the nose leads to increased exposure of the lower airways to allergens. In susceptible persons this might lead to inflammatory changes and an increase in BHR.⁶³ However, nasal allergic inflammation increased the ability of the nose to condition inhaled air by changing the perimeter of the nasal cavity.⁶⁴ Also, in patients with cat allergy, blocking the nose with a nose clip did not lead to an enhanced asthmatic response.⁶⁵ Moreover, changes in BHR were not related to the degree of nasal blockage after nasal allergen provocation.⁶⁰ Therefore the role of preferential mouth breathing in the development of asthma still remains unclear.

NEURAL PATHWAY

It is also possible that a nasal bronchial reflex mechanism accounts for the interaction between nose and lungs. A

complex neural network involving the trigeminal and vagal nerves⁶¹ might facilitate a fast-working mechanism, explaining reactions that take place after the nose is exposed to cold air.^{51,66,67} Mechanical or chemical stimulation of receptors in the nose, trachea, larynx, or elsewhere in the respiratory tract might produce sneezing, coughing, or bronchoconstriction to prevent deeper penetration of allergens or irritants into the airways.⁶¹

Although nasal exposure to cold, dry air resulted in immediate bronchoconstriction and BHR in asthmatic patients,^{51,66,67} others were not able to reproduce these results. In contrast, McLane et al⁶⁸ showed that as long as nasal breathing was maintained, no decrease in FEV₁ values could be detected. Others have suggested that facial cooling, and not nasal exposure, was responsible for the bronchoconstrictive effect of cold air.⁶⁹ Also, after nasal allergen provocation, no changes in FEV₁ values could be measured in patients with allergic rhinitis and asthma.^{60,70} Nasal provocation with methacholine⁷¹ and allergen^{60,72} in patients with allergic rhinitis and asthma resulted in impaired airway function. The progression of the events, however, suggests a more delayed response mechanism than would be expected following a nasobronchial reflex. Although a neural reflex mechanism certainly contributes to the bronchoconstrictive effect after exposure to cold air, the role after allergen exposure has not yet been confirmed.

CIRCULATORY PATHWAY

In the early 20th century, von Pirquet⁷³ found that repeated vaccination with horse streptococcal antitoxin serum induced increased reactivity in susceptible persons, for which he proposed the term *allergy*. Many years later, IgE was identified as the major immunoglobulin involved in allergic disease.^{74,75} Studies in animals^{76,77} and patients with allergic rhinitis, asthma, and other atopic diseases^{33,78,79} have consequently shown an increase in circulating inflammatory cells and progenitors after allergen inhalation, followed by recruitment to sites of allergic inflammation.

Allergen provocation studies are a good model to study nasobronchial cross-talk in allergic airway disease. In patients with allergic rhinitis, segmental bronchial provocation, as well as nasal provocation, induced allergic inflammation in both the nasal and bronchial mucosa.^{72,80} Furthermore, allergen provocation resulted in an increase in circulating inflammatory cells and mediators. Although the clinical response was more severe after segmental bronchial provocation,⁸⁰ patients with allergic rhinitis had pulmonary symptoms and decreased airway function after nasal provocation as well.⁷²

Presumably, absorption of inflammatory mediators (eg, IL-5 and eotaxin) from sites of inflammation into the systemic circulation results in the release of eosinophils, basophils, and their progenitor cells from the bone marrow.⁸¹⁻⁸³ The systemic allergic response is further characterized by increased expression of adhesion molecules,

such as vascular cell adhesion molecule 1 and E-selectin, on nasal and bronchial endothelium, which facilitates the migration of inflammatory cells into the tissue.⁷²

Increases in CD34⁺ cells capable of eosinophil differentiation, as well as other circulatory mediators (IL-5, eotaxin, and cysteinyl leukotrienes), are associated with impaired lung function parameters and enhanced mucosal inflammation in asthmatic patients,^{34,78,84} as well as in nonasthmatic patients with rhinitis.⁸⁵ Efforts to translate this concept into clinical practice have been disappointing until now because depletion of eosinophils by means of anti-IL-5 therapy did not have a significant effect on lung function in patients with mild asthma.⁸⁶ Therefore other immunoregulatory agents, apart from IL-5 and eosinophils, need to be evaluated as well.

In conclusion, these studies demonstrate that allergic rhinitis is not a local disease but that the entire respiratory tract is involved, even in the absence of clinical asthma. Systemic factors, such as the number of blood eosinophils and atopy severity, are indicative of more extensive airway disease.^{39,87,88}

GASTROINTESTINAL INVOLVEMENT

Traditionally, the lung and the gut are considered to be part of a common mucosal system. Atopic sensitization and asthma frequently occur in patients with inflammatory bowel disease, particularly ulcerative colitis.⁸⁹ It has been shown that there is a greater prevalence of BHR in nonasthmatic patients with food allergy.⁹⁰

Mucosal inflammation

Mucosal inflammation of the gastrointestinal tract might accompany allergic airways disease. Eosinophilic inflammation in the esophagus,⁹¹ stomach,⁹² and small intestines⁹³ has been associated with simultaneous allergic manifestations in the airway. Increased numbers of lymphocytes and eosinophils were present in the intestinal mucosa of atopic patients with and without asthma but not in nonatopic control subjects.⁹³ In contrast to lung T lymphocytes, gut mucosa lymphocytes did not express immunoreactivity for IL-3, IL-5, and GM-CSF, suggesting that, unlike bronchial inflammation in asthma, T_H2 responses do not contribute to intestinal eosinophilic inflammation.⁹³ Despite this airway-like inflammation of gut mucosa, these atopic patients were without any gastrointestinal symptoms.

Eosinophil recruitment

In an experimental murine model nasal administration of aeroallergens resulted in eosinophil recruitment to the esophagus,⁹¹ depending on the presence of IL-5 and eotaxin.⁹⁴ In contrast, eosinophil levels in the gastric and intestinal mucosa did not significantly increase after allergen challenge in this study. Furthermore, airway exposure appeared to be crucial in the process of sensitization because oral and intragastric allergen exposure alone

were not sufficient to elicit eosinophilia in mice.⁹¹ As with human esophagitis, eosinophil accumulation led to epithelial changes, such as epithelial cell hyperplasia.⁹¹

T-lymphocyte trafficking

Both the lung and the gut possess mucosa-associated lymphoid tissues that communicate through selective traffic of lymphocytes. T lymphocytes are dynamic cells that circulate from blood to tissue and vice versa. Migration to regional lymph nodes plays an important role in the process of allergen sensitization. Memory T cells preferentially return, or home, to the initial site of allergen exposure. Campbell et al⁹⁵ demonstrated that lung-derived T cells express a different set of adhesion and chemokine-homing receptors than T cells found in other organs, such as the skin and gut. Mice challenged with intranasal OVA, which is known to induce bronchial and blood eosinophilia, did not experience significant esophagitis. Systemic T_H2 responses might therefore not always lead to eosinophilic esophagitis.⁹¹

Mechanisms

What are the mechanisms for this intestinal inflammation in atopy and asthma? Several possibilities have been proposed. First, inhalation of an allergen might lead to ingestion of a large proportion of it entering the gastrointestinal tract. In animal experiments it has been demonstrated that, in response to an inhaled allergen, induction of IgE-secreting cells was observed in both the lung and gut.⁹⁶ Moreover, nasal application of radioactive allergen in patients with rhinitis and sinusitis showed primarily gastrointestinal uptake 24 hours later.^{59,60} Second, inflammation of intestinal mucosa might also result from a bronchus-to-gut flow of inflammatory cells involving the mucosa-associated lymphoid tissue and circulation. Finally, the pathologic abnormalities of gut mucosa are probably related to a primary dysfunction of the mucosal immune system, as is seen in both allergic rhinitis and asthma. The fact that atopy alone is sufficient to elicit an intestinal mucosal inflammation in the absence of symptoms supports the hypothesis that systemic trafficking of cells is involved rather than ingestion of allergen.

CONCLUSION

Allergic rhinitis and asthma frequently occur together. The epidemiologic, pathophysiologic, and clinical data are so compelling that the concept of "one airway, one disease" is now generally accepted. Genetic and environmental factors contribute to the clinical expression in allergic disease. The clinical manifestations of the atopic syndrome might vary during a lifetime and depend on complex interactive mechanisms between the nose, lung, skin, and gastrointestinal tract. Allergic rhinitis and asthma are characterized by generalized airway inflammation, which even extends to the gut mucosa. Direct contact between allergen and mucosa is not necessary to elicit allergic inflammation. Trafficking of inflammatory

cells, as well as upregulation of cytokines and adhesion molecules at mucosal sites, might lead to recruitment of these cells in the tissue. The circulatory pathway, involving bloodstream, mucosa-associated lymphoid tissue, and bone marrow, plays an important role in cross-linking the target organs of atopic disease. Whether allergic inflammation depends on local allergen contact or a pre-existing hyperreactive state of the tissue to result in the subsequent development of clinical manifest disease remains to be elucidated.

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