

Allergic Rhinitis/Asthma Interrelationships

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Introduction

The relationship between the upper and lower airways, specifically allergic rhinitis and asthma, has been a source of interest among clinicians and investigators for many years, dating back to at least 1919 when Sluder proposed a nasal reflex as a cause of asthma (1). Since then, extensive research has been done to link upper and lower airway diseases, and an association between allergic rhinitis and asthma has been shown epidemiologically, pathophysiologically, and therapeutically (see Table 1).

The epidemiologic relationship between allergic rhinitis and asthma includes the co-existence of both airway diseases, and similarities in natural history, triggers, and seasonal exacerbations. Commonalities in the inflammatory and structural elements of the airways, as well as similarities in the development and clinical manifestations of these diseases, support the pathophysiologic relationship. Therapeutically, prevention and relief of allergic rhinitis and asthma symptoms can be obtained with control of airborne allergens, the use of same or similar medications, and in certain instances immunotherapy.

Researchers have proposed many theories to explain the relationship between allergic rhinitis and asthma, including the existence of a nasal-bronchial reflex, nasal obstruction resulting in a shift in breathing patterns, systemic absorption of mediators, and aspiration of nasal contents. Yet, despite the evidence supporting a clinical relationship between allergic rhinitis and asthma, controversy exists as to the significance of rhinitis as a risk factor for asthma development and whether lower airway function is affected by nasal disease.

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Table 1
Epidemiologic and Therapeutic Association Between Rhinitis and Asthma

Epidemiologic:

- Distinct entities: majority of subjects with rhinitis do not have asthma
- Coincidental diseases: two- to fourfold more likely to have both diseases
- Interrelated conditions: rhinitis is clearly a risk factor for developing asthma
 - Brown University Study: threefold for college students
 - Tucson Study: twofold for infants

Therapeutic:

- Treatment of rhinitis with intranasal steroids improve asthma
 - Treatment with systemic agents improve both diseases
 - Theophylline
 - Antihistamines $\pm$ decongestants
 - Leukotriene modifiers $\pm$ antihistamines
 - Allergy vaccines (Immunotherapy)
 - Corticosteroids
 - Anti-IgE
 - Other experimental therapies
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Conversely, differences in the upper and lower airways have also been demonstrated. Epidemiologically, there is a greater incidence of allergic rhinitis than asthma in the general population. Pathophysiologically, the consequences of inflammation on the lungs vs the nose differ. The initial inflammation caused by exposure to allergens is similar in the upper and lower airways; however, manifestations differ according to structure and function of the upper vs lower airways. The key events leading to acute airway obstruction are different in the upper (mucosal edema) vs lower (smooth muscle contraction) airways. Although allergen-induced IgE-mediated mechanisms are common to both diseases, the role of basophils appears more important in upper vs lower airway responses, especially in the late phase (2). Thus, therapeutic modalities effective for disease management in the upper airways may not ameliorate symptoms in the lower airways.

Therefore, in order to understand and properly manage these diseases, we will review the commonalties and differences in the epidemiology, pathophysiology, and therapeutic approaches to upper and lower airway diseases.

Epidemiology

Asthma

The prevalence of asthma is on the rise, especially in the under-18 yr of age group (3) with an estimated 15 million people in the United States diagnosed with asthma. There is an associated rise in costs associated with asthma care with an increased rate of hospitalizations and

emergency room visits, especially in children up to 15 yr of age. Mortality rates due to asthma are, however, greatest in patients older than 64. Statistical reports of asthma incidence and prevalence rates vary because there is no set standard for the diagnosis of asthma; however, the current epidemiological definition being proposed is "airway hyperresponsiveness with wheezing"(4). In addition, studies frequently rely on patient self-reports for epidemiological data.

The increased prevalence and incidence rates for asthma can be attributed to changes in risk factors, poor access to medical care, and inadequate treatment. Maternal cigarette smoking, indoor allergens, and premature birth are potential risk factors in the development of asthma (4). Maternal and paternal physician diagnosed asthma continue to be strong independent risk factors for development of asthma in children. Asthma mortality rates are highest among urban, minority populations, supporting the role of inadequate access to appropriate health care on increased asthma morbidity and mortality rates (4).

Allergic Rhinitis

Approximately 40 million people in the U.S. are diagnosed with allergic rhinitis, a disease more commonly seen in childhood and young adulthood. Rhinitis is known to occur more frequently in atopic than nonatopic families and symptoms are related to skin-test positivity (4-7). The adverse effects of allergic rhinitis are seen in activities of daily living, emotional function, quality of life, and psychological problems in adolescents (8,9). In addition, chronic rhinitis has been associated with depression, fearfulness, fatigue, and cognitive impairments.

Allergic Rhinitis and Asthma Relationship

The association between allergic rhinitis and asthma has been extensively studied, most notably in the Tucson Children's Respiratory Study (10). In this study, children who were physician diagnosed with allergic rhinitis at age 1 had a higher incidence of asthma by age 6, as well as increased respiratory symptoms and increased medication usage. Additionally, hazard ratios were calculated and after adjustment for certain risk factors, it was found that physician diagnosed allergic rhinitis was associated with twice the odds of developing asthma by age 11.

In a study of Tecumseh, Michigan residents, there was a two- to four-fold higher incidence of asthma or rhinitis in residents who had a prior history of either disease (11). In a 23-yr follow-up study of Brown University students, 10.5% of allergic rhinitis subjects developed asthma, whereas only 3.6% of subjects without allergic rhinitis developed asthma (12). In a recent report from the American Academy of Allergy, Asthma and Immunology (13), it was estimated that as many

as 78% of asthma patients have nasal symptoms and 38% of allergic rhinitis patients have asthma. In most cases, allergic rhinitis appears to precede the development of asthma.

The association that is seen between allergic rhinitis and asthma is most likely due to a common alteration of an immune-system pathway. Epidemiologic data suggest that this consists of a relative imbalance between TH₁-like and TH₂-like cytokine responses (discussed below) in these subjects. The individual's pattern of response appears to exist before the development of allergic rhinitis and asthma. However, in order to develop asthma, an additional "lung factor" appears to be necessary. This factor appears to be multifaceted and reflects a genetic determination of bronchial hyperresponsiveness and an interaction between an altered immune system and a specific form of lung development that occurs in subjects who are exposed (or not) to certain factors present in the environment (4).

Pathophysiology

The discussion of similarities and differences in the pathophysiology of allergic rhinitis and asthma must first begin with a review of the key structural elements in the upper and lower airways. This will be followed by a review of important pathophysiologic factors.

The nasal mucosa is supplied by a very rich and complex microcirculation designed to meet the high metabolic demands of the epithelium and submucosal glands and to heat and humidify inspired air. Special venous sinusoids serve as capacitance vessels that play a major role in the expansion (congestion) and shrinkage of the nasal mucosa. Subepithelial and glandular capillaries are fenestrated, thus permitting the exudation of plasma into the submucosa, which in turn supplies the glands with the necessary fluid to produce copious amounts of secretions. These events lead to nasal congestion and rhinorrhea, two of the common symptoms of rhinitis (14).

In the lower airways, the airway smooth muscle is prominent and plays a key role in controlling airway patency. Airway smooth-muscle cells have been found to be secretory cells and, thus, part of the autocrine process. Because there is little smooth muscle in the nose, this represents a substantial difference between the upper and lower airways (4).

Other differences include airway geometry, surface area, and blood supplies. There is a large pulmonary surface area and dual pulmonary blood supplies. Another difference includes mechanisms that regulate the exposure of the airway to environmental insults and pollutants. The nose appears to be more capable of controlling exposure to airway cells.

Table 2
Similarities and Differences in the Pathogenesis of Asthma and Rhinitis

Characteristics	Similarities	Differences
Key events leading to airway obstruction Key immune effector cells	Mucosal edema, especially rhinitis	asm ^a contraction in asthma
	T lymphocytes (TH ₂), mast cells, eosinophils	Basophils in rhinitis
Role of smooth muscle	Effects on blood vessels	In asthma: controls airway geometry, part of auto-crine process, expresses critical adhesion molecules
Role of epithelium	Protective barrier	In asthma: greater heterogeneity, production of bronchoconstricting factors, sloughing
Effects of chronic disease Airway hyperresponsiveness	Inflammation with eosinophilia Occurs in both rhinitis and asthma, due to interaction of neurogenic and inflammatory pathways	"Airway remodeling" in asthma Role of neurotransmitters
Airflow and neural pathways	Little in common	In lung: decreased airflow (asm contraction), increased airflow (asm relaxation) In nose: decreased airflow (vasodilation), increased airflow (vasoconstriction)
Role of muscarinic receptors	M ₁ and M ₃ receptors present in both upper and lower airways	Importance of receptor subtypes in asthma: M ₁ enhances acetylcholine release, M ₂ decreases acetylcholine release, M ₃ mediates asm contraction

^aasm, airway smooth muscle.

Despite these fundamental structural differences, there are many similarities in the pathogenesis of allergic rhinitis and allergic asthma (see Table 2). The pathogenesis of allergic rhinitis and asthma begins with sensitization and the generation of allergen-specific IgE. Airborne allergens settle on airway mucosa where antigenic fragments are processed by dendritic cells and are presented to T-helper cells. Allergen-specific B cells switch to IgE antibody production under the influence of interleukin-4 (IL-4) and IL-13 produced by TH₂ and other cells. This

sensitization process is completed when allergen-specific IgE antibodies bind via high affinity Fcε receptors (FcεRI) to the surface of mast cells and basophils residing in the mucosal tissues of the respiratory tract (4,14).

Upon re-exposure, the allergen binds to cell surface bound IgE, resulting in cross-linking of the IgE:FcεRI complexes, which activate mast cells and basophils. Activation results in degranulation with release of preformed mediators including histamine and various proteases and the synthesis and release of newly generated lipid-derived mediators and cytokines. These mediators affect nerve endings, blood vessels, submucosal glands and, in the lower airways, smooth muscle. This immediate response is followed by a more prolonged late phase response involving many cells and mediators (4,14).

The basic aspects of the machinery needed to produce an IgE-mediated inflammatory response in the lung and nose appear to be similar. CD4+ T cells play an essential role in allergic rhinitis and asthma, both as a part of the sensitization phase to antigen, providing help to B cells for IgE synthesis, and as part of the inflammatory cascade during the subsequent symptomatic phases of antigen exposure. The factors responsible for the accumulation of CD4+ T cells are many and include IL-16, which has been shown to have a role in both upper and lower airways (4).

Mast-cell accumulation in the airways, an event mediated in part through the release of cytokines by CD4+ T cells, is an important pathophysiologic element in both allergic rhinitis and asthma. Although the specific biochemical events resulting from mast cell degranulation are similar in the upper and lower airways, the physiologic consequences differ owing to the target organs affected. Mast cell mediator-induced mucosal edema is extremely important in inducing upper airway obstruction. Although playing a role in the lower airways, specific airway smooth-muscle contraction secondary to released mast-cell mediators is a more important event leading to lower airway obstruction. The mediators responsible for upper and lower airway obstruction are likely also different. For example, histamine plays a prominent role in inducing upper airway obstruction, but its role in inducing lower airway obstruction is less significant (4).

Subsequent to the immediate response to antigen-induced mast cell degranulation, there is often a later response occurring 4–8 h later. In the upper airways, this late response is characterized by nasal congestion, anosmia, mucus secretion, and nasal hyperresponsiveness to the same or another allergen, or to nonspecific irritants. In the lower airways, the late response is also characterized by airway obstruction and an increase in airway responsiveness. Experimental models of allergic rhinitis have documented that the same mediators released during

the early phase are recovered during the late phase with the exception of PGD₂. This suggests that basophils are important during the late phase, because PGD₂ is produced by mast cells but not basophils. Indeed, nasal biopsies from allergic rhinitics during symptomatic periods show increased mast cells and basophils. In the lower airways, the role of basophils has not been fully elucidated. Nonetheless, the late response in both the upper and lower airways is also manifested by an influx of inflammatory cells, especially eosinophils (4,14).

Endothelial Adhesion Molecules

Adhesion molecules, especially intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, are significantly important in the emigration of inflammatory cells during the inflammatory response. Adhesion molecules can be upregulated on endothelial and epithelial cells by cytokines such as IL-1 and tumor necrosis factor alpha (TNF- α) and lipopolysaccharide (2,4,14). ICAM-1 is expressed on the surface of vascular endothelial cells and airway epithelial cells and mediates the attachment of leukocytes to endothelial and epithelial cells. E-selectin is expressed on the cell surface of leukocytes. VCAM-1 supports the adhesion of leukocytes to endothelial cells and its expression can be selectively induced by IL-4 (15).

An increase in ICAM-1 and VCAM-1 was found on the vascular endothelium of nasal mucosal biopsy specimens of individuals with allergic rhinitis (16). In addition, Lee and colleagues (17) found that both VCAM-1 and E-selectin are upregulated 24 h postallergen challenge, whereas ICAM-1 was not. VCAM-1 may contribute to the selective recruitment of eosinophils into the nasal mucosa, as the counter ligand for VCAM-1, very late activation antigen-4 (VLA-4), is present on eosinophils, but not on neutrophils. VLA-4 is also present on lymphocytes and is an important factor in controlling lymphocyte migration into the airways.

Eosinophils

Although the prominence of eosinophils in upper and lower airway diseases has been documented, how eosinophil activation occurs is not well-understood. The mechanism of priming is likely similar in the upper and lower airways and is related to molecular adhesion. Eosinophils produce various cytotoxic proteins, oxygen radicals, neuropeptides, cytokines, and lipid mediators, which contribute to the pathophysiology of these diseases (4,18). Specifically, major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO) cause histamine release from mast cells and lead to epithelial damage. Furthermore, MBP may cause bronchoconstriction and airway hyperreactivity, as may EPO. Fibroblast proliferation has

been noted with eosinophil-derived neurotoxin (EDN), which acts as a mitogen. Toxic oxygen metabolites may contribute to smooth-muscle contraction with resultant pulmonary-tissue damage. Neuropeptides (substance P and vasoactive intestinal polypeptide [VIP]) may contribute to smooth muscle contraction, edema, vasodilation and mast cell degranulation. The cytokines released by eosinophils (e.g., IL-3, IL-5, GM-CSF, TNF- α , transforming growth factor [TGF], RANTES) promote activation of inflammatory cells and enhance granulocyte differentiation and survival. Platelet-activating factor (PAF) activates mast cells, neutrophils, and eosinophils, and is a putative mediator of mucus secretion, edema, and bronchial and vascular smooth-muscle constriction. Eosinophils also synthesize and release cysteinyl leukotrienes (LTC₄), which are important molecules in the pathogenesis of airway diseases.

The importance of the eosinophil as a key element in the pathophysiology of allergic rhinitis and asthma is supported by the presence of an increased number of eosinophils hours after allergen challenge in nasal secretions, sputum, and peripheral blood (19). Chanez and colleagues (20) examined eosinophilic infiltrates in the nasal and bronchial mucosa of untreated asthmatics vs controls and reported greater eosinophilic inflammation in the nose and bronchi of the asthmatics. However, they noted significantly higher eosinophilic infiltration in the bronchial vs nasal mucosa in untreated asthmatics with perennial rhinitis.

Leukotrienes

There has been an increased interest in the pathophysiologic role of leukotrienes in upper and lower airway diseases, including their contribution to early and late allergic responses. Leukotrienes have been shown to be chemotactic for eosinophils and to be released by eosinophils. A key enzyme in the synthesis of LTC₄ is 5-LO (lipoxygenase), and inhibition of 5-LO has been associated with a decrease in allergic rhinitis and asthma symptoms (4), which supports the relationship between upper and lower airways. Furthermore, leukotrienes contribute to increased mucus production and mucosal edema and assist in the recruitment of eosinophils (21). Cysteinyl leukotrienes have been shown to be 3,000–10,000 times more potent than histamine or methacholine in inducing bronchoconstriction.

Leukotrienes further demonstrate the relationship between the upper and lower airways with similarities in the cells that are responsible for synthesis, including mast cells, basophils, eosinophils, monocytes, and macrophages. The degree to which leukotrienes contribute to upper vs lower airway diseases, however, is not yet clear and warrants further investigation (4). Nonetheless, there is mounting evidence that leukotrienes are important mediators in the pathogenesis of allergic rhinitis and asthma. In vivo, both spontaneous and induced rhinitis

and asthma episodes are accompanied by increases in cysteinyl leukotrienes, which are associated with inflammation and symptoms. Furthermore, as discussed below, leukotriene modifiers have been shown to be effective therapy for both allergic rhinitis and asthma.

Epithelium and Airway Remodeling

The primary functions of the upper and lower airway epithelial cells are the same: to lubricate, humidify, and circulate air; to waterproof; and to provide suitable conditions for ciliary movement. Cilia and ciliary motion have important functions including: adherence of microbes, irritants, and cell debris to the mucous film; provision of a surface for immunoglobulin and enzymatic action; neutralization of toxic gases; and clearance of inhaled debris. In addition to acting as a barrier, research has supported the contribution of the epithelium to the allergic inflammatory process in both the upper and lower airways, including the production of key chemotactic factors and mediators (2,4,14).

Differences in the upper and lower airway epithelium with regard to rhinitis and asthma include the degree to which epithelium is shedding and a greater degree of epithelial heterogeneity in the lung, factors that could influence the degree of inflammation in the lung vs the nose. Epithelial shedding, which during asthma occurs to a variable degree at various times and locations in the conducting airways of the lung, does not occur to the same degree in the nose. A comparison between nasal and bronchial inflammation in untreated asthmatic subjects with perennial rhinitis showed that the extent of eosinophilic inflammation, reticular basement membrane thickening, and epithelial shedding was greater in bronchial than in nasal mucosa. This study supports differences in the upper and lower airways (20).

Another common feature described as part of "airway remodeling" (i.e., in addition to epithelial shedding and basement-membrane thickening) is changes in smooth muscle. Asthma has been associated with both airway smooth-muscle hypertrophy and hyperplasia. Because there is little smooth muscle in the nose, this represents another substantial difference between allergic rhinitis and allergic asthma. As indicated earlier, airway smooth muscle can produce a number of factors including RANTES, eotaxin, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prostaglandins (4). Evidence indicates that adhesion molecules on smooth muscle have counter ligands corresponding to those on inflammatory cells. Thus, airway smooth muscle could conceivably upregulate the constrictor response by enhancing inflammatory cell influx to this important target organ.

Thus, although both the upper and lower airways have airway epithelium that may function in a similar capacity, there are important

differences as well. Furthermore, the importance of airway remodeling as a hallmark of long-standing or significant asthma is not as apparent in patients who have rhinitis.

Neurogenic Pathways in Asthma and Rhinitis

Inhalation of irritants into the upper and lower airways can cause similar neurogenic symptoms, with bronchoconstriction in patients with asthma and nasal obstruction in patients with allergic rhinitis and some patients with nonallergic rhinitis. These nociceptive reflexes and parasympathetic pathways may contribute to the worsening of asthma when rhinitis is active.

One of the mechanisms postulated for rhinitis-associated asthma is a common neurogenic pathway with upper airway stimulation directly leading to reflex-mediated bronchoconstriction (4). A subpopulation of patients with asthma have active nasobronchial and sinobronchial reflexes that produce an ~10–12% fall in FEV₁. Cold-air nasal provocation can also activate a reflex decrease in FEV₁. Conversely, histamine bronchial provocation can increase nasal airflow resistance, suggesting modulation of central reflexes affecting both organs (4). Viral infections may affect both upper and lower airways, leading to the common association of rhinitis followed by an asthma exacerbation. Production of IL-11 during rhinovirus infections may promote neural and other mechanisms of airway inflammation (22)

Nerves containing the tachykinins, neurokinin A and substance P, VIP and other neurotransmitters innervate upper airway submucosal glands, blood vessels, myoepithelium, and epithelium (23). In sensitized animals or humans, the application of allergen to the nasal mucosa can result not only in the immediate- and late-phase response, but also in neuropeptide release. It is postulated that these peptides alter secretion, airway smooth muscle tone, vasodilation, and possibly cellular recruitment, leading to changes in nasal airway conductance. Similar events are postulated to occur in the lower airways, contributing to the pathogenesis of asthma (4).

In the upper and central airways, inflammation-induced regulation of neuronal function is most obviously evidenced by conscious reflexes such as coughing and sneezing. In peripheral airways, immunologic alteration of neuronal activity occurs at a subconscious level, and consequently receives relatively little attention from those interested in the pathogenesis of airway disease. Yet, the innervation of the small airways serves to regulate the function of cells relevant to asthma, including smooth-muscle, glandular, vascular, and interstitial cells.

Anatomical, pharmacological, and physiological studies support the hypothesis that virtually all aspects of airway inflammation may be

influenced by autonomic and/or afferent neurons. The participation of afferent nerve fibers in inflammation may occur as a result of axon reflexes, whereby action potentials travel not only centrally, but also back down collateral branches of the axon to evoke neuropeptide release into the airway wall (24,25). Released afferent or efferent neurotransmitters may then interact with receptors on nearby airway cells to influence their function. Both rhinitis and asthma are associated with airway hyperresponsiveness, and this physiologic feature is due to an interaction of the neurogenic and inflammatory pathways.

As indicated previously, mast cells are important in the pathogenesis of allergic rhinitis and asthma. There is evidence indicating a preferential growth of neurites toward mast cells (26). Furthermore, inflammatory mediators released from mast cells and other inflammatory cells, including bradykinin, PGE₂, and leukotriene D₄ (LTD₄), all appear capable of enhancing the release of tachykinins (4,23,24,27). In addition, neurotrophins, such as nerve growth factor (NGF) and IL-6 and IL-11, also increase nociceptive nerve activity, and may have potent effects on airway inflammation induced by allergic, viral, irritant, and pollutant stimuli. Other cytokines such as IL-1 β and IL-8 can depolarize sensory nerves (4,28).

Proinflammatory cytokines such as IL-1 can be induced by substance P acting on epithelial cells and macrophages, setting the stage for a circuit involving nerves and inflammatory pathways. Indeed, epithelial cells can synthesize both proinflammatory cytokines as well as neurotrophic factors, thus further potentiating and enhancing the outgrowth of nerves, neuropeptide formation and release, and inflammation in response to activation of the epithelium. The role of NGF, in particular, as both mast cell and neuronal differentiation factor, highlights the intricate connections of these two systems within mucosal tissues. The effects of NGF in conjunction with the other hematopoietic cytokines on stimulation of the growth and differentiation of eosinophils and basophils (29), the characteristic cells of the late-phase allergic inflammatory response in the airway, suggest that NGF may also play an important role in the recruitment and differentiation of these cells in a variety of airway diseases such as asthma, allergic and nonallergic rhinitis, sinusitis, and nasal polyposis. Over the years, studies have also emphasized a role for hematopoietic pathways, and NGF, in synergy with either GM-CSF or IL-5, in the elicitation of eosinophil and basophil progenitors from the bone marrow through the blood and into the airway tissues (29).

Thus, there are many similarities in the neurogenic pathways and their effects, including their interactions with key inflammatory and structural cells, in the upper and lower airways.

Neurogenically mediated inflammation is regulated by enzymes that break down many of the neuropeptides. The most important enzymes in controlling the inflammatory response are neutral endopeptidase (NEP) (30) and angiotensin-converting enzyme (ACE). Inhibiting these enzymes markedly potentiates the inflammatory response to both endogenous and exogenous tachykinins. Furthermore, levels of these enzymes are decreased by viral infections (31), and by exposure to cigarette smoke and oxidants (32), suggesting that the potentiation of neurogenic inflammation may contribute to exacerbations of airway diseases caused by these stimuli. Conversely, the activity of these enzymes is increased *in vivo* after treatment with dexamethasone, and this decreases neurogenic inflammatory responses in the airways (33).

Differences in the function of neurotransmitters in the upper and lower airways are also apparent, and as with inflammatory pathways, depend in part on dissimilarities in the upper and lower airway anatomy. For example, in the lower airways, neurokinin A mediates bronchoconstriction through NK2 receptors on smooth muscle. However, its effects on upper airway functions contributing to rhinitis are less clear owing to the lack of airway smooth muscle in nasal tissue.

Indeed, vasodilation mediated by sensory and parasympathetic nerves is the most important factor contributing to nasal airflow resistance. However, in the lower airways, bronchoconstriction mediated by tachykinins, and to a greater extent, parasympathetic mechanisms, is one of the most important factors in regulating lower airway resistance.

Parasympathetic and muscarinic receptor subtypes are important in controlling lower airway patency. No analogous roles for these receptors in rhinitis have been found. The parasympathetic nerves release acetylcholine, which binds to M₃ muscarinic receptors, causing contraction of the muscle and airway narrowing. The bronchoprotective effects of M₂ muscarinic receptors may be dysfunctional in asthma. M₂ receptors have been found to be dysfunctional after exposure to ozone, parainfluenza viruses, and antigen (34–39). Eosinophils, through major basic protein, have also been found to cause dysfunction of M₂ receptors (40,41).

Thus, although there are many similarities, some substantial differences also exist in the roles of neurogenic pathways and neurotransmitters in the pathogenesis of asthma and rhinitis (42,43). The interactions between these neurotransmitters and inflammatory cells are important factors in the immunobiology of asthma and rhinitis. However, much is yet to be learned about the relative roles of neurogenic pathways controlling upper and lower airway responses under normal conditions and in asthma and rhinitis.

Treatment

As the understanding of the steps involved in the pathophysiologic processes in asthma and rhinitis has increased, novel therapies to interrupt specific components of the inflammatory cascade have evolved. Therapeutic interventions for asthma and/or rhinitis have been useful to further examine the link between upper and lower airway diseases. For example, if an antagonist of a specific mediator or pathway common in the allergic inflammatory cascade for both rhinitis and asthma were to be effective for both diseases, this would imply a stronger link between these two diseases.

To better elucidate the interrelationships between asthma and allergic rhinitis, one must first define the effects of various treatments on both diseases. Specifically, three questions should be asked: 1) Do drugs primarily used to treat asthma improve allergic rhinitis? 2) Do drugs primarily used to treat allergic rhinitis improve asthma? and 3) Are there systemic agents that are beneficial to both allergic rhinitis and asthma? The answer to all three questions is yes, but not unequivocally. There is some ambiguity in defining which drugs are more effective for asthma vs rhinitis, as well as how treatment of one disease affects the other disease. Nonetheless, many lines of investigation have indicated that the therapy of either or both of these diseases can impact positively on allergic rhinitis and asthma, lending further support for a link between the upper and lower airways.

Theophylline

A classic example of a drug primarily used to treat asthma that has in some instances been shown to improve allergic rhinitis is theophylline. Theophylline has been used for a number of years for the therapy of asthma. Originally, theophylline's efficacy was attributed to its bronchodilating effect, however, it is clear that phosphodiesterase inhibitors such as theophylline also have anti-inflammatory effects.

There is limited information available about the effect of theophylline on allergic rhinitis. In earlier studies, theophylline had been shown to reduce the release of mediators from mast cells and to decrease sneezing after nasal antigen challenge (44). Theophylline has also been demonstrated to have a protective effect on increases in bronchial responsiveness in patients with allergic rhinitis (45). More recently, Aubier and colleagues demonstrated that after 3 wk of treatment with theophylline, antigen challenges of the nose resulted in less nasal symptoms, including nasal obstruction, and no increase in eosinophil cationic protein vs placebo (46). These three studies indicate that a drug primarily used to treat asthma may in fact have some benefits for patients with allergic rhinitis. The mechanism of action of this protec-

tive effect for allergic rhinitis and asthma most likely involves anti-inflammatory effects of theophylline.

Topical Corticosteroids

Topical corticosteroids have been the mainstay of therapy for both allergic rhinitis and asthma for many years. Corticosteroids have been shown to have anti-inflammatory effects in both disorders. The specific effects of inhaled corticosteroids on allergic rhinitis and asthma have been reviewed elsewhere (47) and are beyond the scope of the present article. Nonetheless, some generalities can be described. Topical corticosteroids have been shown to decrease the cellular infiltrate important for both allergic rhinitis and asthma and to influence the release of mediators and the effects of critical cells important in both allergic rhinitis and asthma (47).

Several investigators have conducted studies on patients with both allergic rhinitis and asthma to evaluate the effectiveness of topical corticosteroids applied intranasally on lower airway events. The data from these studies showed that intranasal corticosteroids reduced nasal symptoms significantly and concurrently reduced asthma symptoms or bronchial hyperresponsiveness (48–50). Interestingly, orally inhaled corticosteroids have been shown to improve allergic rhinitis (51). Whether or not the beneficial effects of topically applied intranasal corticosteroids on lower airway functions and vice versa are due to systemic absorption of the corticosteroid is unclear. However, the same dose of corticosteroid administered intranasally had a greater effect on bronchial hyperresponsiveness than when administered directly into the lower airways (52). This suggests that there is truly a therapeutic link between these two diseases.

Antihistamines

Antihistamines plus or minus decongestants used orally have been a mainstay for the treatment of allergic rhinitis for many years. In allergic rhinitis, the primary effect of antihistamines is on the H₁ receptors on the sensory nerves of the nose, causing a reduction in sneezing and rhinorrhea. Nasal stuffiness and late-phase allergic symptoms may continue to persist despite treatment with antihistamines (14).

Antihistamines may be effective in the treatment of asthma by inhibiting H₁-induced smooth-muscle contraction, vascular permeability, and nerve activation. Antihistamines can also alleviate asthmatic symptoms through their attenuation of both early- and late-phase reactions. They have also been shown to ameliorate exercise- and histamine-induced bronchoconstriction. Antihistamines can be used safely in most patients with asthma. However, histamine is not the only mediator

responsible for asthma symptoms and, therefore, antihistamines, if used, should be considered adjunctive therapy in the treatment of asthma.

Nonetheless, there are many studies to suggest that antihistamines have a positive therapeutic effect for both allergic rhinitis and asthma. Most of these studies involved the newer second-generation antihistamines, including cetirizine, loratadine, terfenadine, and azelastine. In doses used to treat allergic rhinitis, these agents have been shown to decrease asthma symptoms and in some instances, improve lung function and reduce requirements for bronchodilator use (52–55). In addition, the combination of loratadine plus pseudoephedrine improved morning and evening peak expiratory-flow rates, spirometry results, and asthma-specific quality of life measures in 193 patients with allergic rhinitis and asthma (56).

There is a strong clinical impression that, in patients who have concomitant allergic rhinitis and asthma, improvement of upper respiratory symptoms may facilitate the treatment of lower respiratory symptoms. Whether or not the effects of antihistamines on asthma are due primarily to improvement of allergic rhinitis vs those attributable to antagonizing histamine's effects on the lower airways is unclear. The data do suggest that antihistamines can be an effective adjunctive therapy for patients who have both diseases. However, to date, antihistamines as monotherapy have not proven to be an important therapeutic agent for asthma. Nonetheless, these studies do again point to a link between the therapeutic effects of agents used to treat allergic rhinitis and asthma.

Leukotriene Modifiers

Leukotrienes are important mediators and have been shown to be released both spontaneously and subsequent to specific challenges in allergic rhinitis and asthma. In both instances, leukotrienes have been associated with an influx of inflammatory cells and airway symptoms. Furthermore, recent studies suggested that leukotriene modifiers, both as monotherapy and in combination with antihistamines, were effective in the therapy of allergic rhinitis and asthma (57–59). For example, a recently published abstract showed the benefits of the LTD₄ antagonist, zafirlukast, in both upper and lower respiratory responses to acute cat challenge. Eighteen subjects with cat-induced asthma and allergic rhinitis were enrolled in a double-blind, placebo-controlled, crossover study. Zafirlukast significantly attenuated the drop in FEV₁. In addition, the overall change in nasal patency as assessed by acoustic rhinometry was significantly reduced with zafirlukast. Zafirlukast also significantly reduced both upper and lower airway symptom scores (57).

Concomitant treatment with an antihistamine and leukotriene modifier appears promising for both allergic rhinitis and asthma. In a study by Roquet et. al. (60) the combination of zafirlukast 80 mg b.i.d. and loratadine 10 mg b.i.d. was more effective than either agent alone or placebo in inhibiting early- and late-phase lower airway obstruction. Zafirlukast was significantly more effective than loratadine during the early but not during the late allergic response to allergen broncho-provocation. The combination, however, reduced the area under the curve for FEV₁ during the early and late airway responses and was significantly more effective than either drug alone during the late allergic response. Similarly, the combination of montelukast and loratadine improved allergic rhinitis symptoms to a much greater degree than either therapy alone (59).

Thus, the studies with leukotriene modifiers point to the importance of cysteinyl leukotrienes as mediators in both allergic rhinitis and asthma. Furthermore, the data indicate that leukotriene modifiers with and without antihistamines might improve the symptoms of both allergic rhinitis and asthma, again implying an interrelationship between these two diseases.

Immunotherapy

Allergy immunotherapy is an example of a systemic therapy that has proven to be beneficial for both allergic rhinitis and asthma. Much of the data supporting the use of immunotherapy for allergic rhinitis and asthma, as well as the recommendations for the specific use in these disorders have been summarized in the World Health Organization (WHO) Position Paper on allergen immunotherapy (61). Overall, there is more data suggestive of a positive effect for allergen immunotherapy for allergic rhinitis and asthma than there is negative data.

Perhaps more intriguing than the treatment of allergic rhinitis and asthma is the prevention of the development of asthma and new sensitization to allergens in patients who have allergic rhinitis. Preliminary results from the Preventative Asthma Treatment (PAT) Study in children 7–13 yr of age suggested that immunotherapy impeded the progression from allergic rhinoconjunctivitis to asthma (62). Furthermore, in a prospective case-controlled study in 44 asthmatic children aged 2–6 yr who were monosensitized to domestic mite, immunotherapy inhibited the development of new sensitizations by approx 50%. These studies suggest that immunotherapy may alter the natural course of allergy and allergic rhinitis progression by preventing sensitization to new allergens and the development of asthma (63).

Anti-IgE

Finally, another example of a systemic therapy that links allergic rhinitis and asthma is anti-IgE monoclonal antibody (MAb).

Because of the central role that IgE plays in allergic reactions, an emerging concept in allergy therapy is to inhibit IgE-mediated responses through the use of anti-IgE antibodies. RhuMAB-E25, a recombinant humanized monoclonal anti-IgE antibody, binds to IgE on the same Fc site as Fc ϵ RI and decreases free serum IgE by forming biologically inactive immune complexes with free IgE. Because rhuMAB-E25 does not bind to IgE on mast cells and basophils, it is not anaphylactogenic. Given the fundamental role of IgE in the pathogenesis of allergic rhinitis and asthma, decreasing total serum IgE in these patients would be expected to decrease the available amounts of antigen-specific IgE to bind to and sensitize tissue mast cells and basophils. This reduction in available IgE should therefore lead to a reduction in IgE-mediated symptoms and improve control of allergic rhinitis and asthma.

Several studies have now indicated that anti-IgE therapy is effective for both allergic rhinitis and asthma, indicating a central role for IgE in the pathogenesis of these diseases and a link between allergic rhinitis and asthma (64–67).

Conclusion

There are many important features of the immunobiology of asthma that overlap with rhinitis. This has led some investigators to ask whether asthma and rhinitis fit into a “one airway/one disease” paradigm (Table 3). Furthermore, the epidemiology of these diseases suggests many common factors involved in their high coincidental occurrence. Data suggest that both allergic rhinitis and asthma appear to be risk factors for the development of each other. Therapy of either disease appears to improve the other. However, it is not clear whether this is related to local effects on one airway improving the other or whether there is a systemic effect from the treatment of one disease leading to improvement of the other (e.g., leukotriene modifiers plus antihistamines). Newer studies with systemic therapies, however, indicate that treatment of one disease might prevent or alter the course of the other. This is especially true in the case of allergen immunotherapy for allergic rhinitis in preventing the development of asthma. However, much about these diseases remains unknown, such as whether treating or neglecting to treat rhinitis ultimately affects the course of asthma. With the advent of newer therapeutic modalities, better knowledge about the control and interrelatedness of both diseases should be forthcoming.

Table 3
Airway Disease Paradigm

For One Airway/One Disease:

1. Similar pathogenic mechanisms
2. Stimulation of UAW^a causes LAW^b obstruction
3. Inhalation of irritants to UAW and LAW cause similar neurogenic symptoms
4. Diseases are linked epidemiologically
5. One therapy can treat both

Against One Airway/One Disease:

1. Different airway geometry, surface-area blood supply, exposures to triggers
2. Different mechanisms of airway obstruction
3. Epithelial shedding and airway remodeling important in asthma only
4. Physiology of airway obstruction is different
5. Role of neural pathways and transmitters are distinct
6. Does not take into account different rhinitis and asthma phenotypes

Alternate Viewpoint:

Allergic rhinitis and asthma represent a systemic disease clinically affecting two organs, the nose and lung.

- TH₂ paradigm is universal
 - Elevated IgE, eosinophils not organ-specific
 - Hyperresponsiveness occurs in gut as well as airways
 - Autonomic nervous system abnormalities are systemic
 - Therapy that works best for both diseases is systemic
 - Common genetic predisposing factors
-

^aUAW, upper airway. ^bLAW, lower airway

One view that should be considered is that allergic asthma and rhinitis represent a systemic disease affecting two organs, the lung and the nose (4). Asthma and allergic rhinitis share many of the same pathogenic factors, but they operate in different parts of the airway. Inflammatory cells and mediators are often the same and there may be common alterations that occur in the immune system. An elevated IgE level occurs not only in asthma and allergic rhinitis, but in other allergic conditions as well. Neurotransmitters are the same, although they have different effects in the upper and lower airways. Data suggest that people with atopic disease also have similar hyperresponsiveness in the gut as in the airways. There appears to be common genetic predisposing factors for the development of both allergic rhinitis and asthma. Both have been associated with abnormalities in the autonomic nervous system, many of which have been shown to be systemic in nature. For example, cholinergic hyperresponsiveness has been shown not only in the lung, but in the skin and eyes of patients with asthma and allergic rhinitis (42). Patients with allergic rhinitis and asthma have peripheral blood eosinophilia, not just lung or nasal eosinophilia. Finally, therapy that works for both diseases tends to be more systemic in

nature. Thus, one might view allergic rhinitis and asthma as a continuum of allergic diseases rather than as distinct or interrelated airway diseases. Viewed in this way, new approaches for the management of these common comorbid conditions will likely result in improved care (see Table 3).

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