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**Understanding the inflammatory processes in
upper allergic airway disease and asthma**

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The conducting upper and lower airways have similarities and differences in their structure. The mucous membranes of the upper and lower airways are covered by a pseudostratified, columnar, ciliated epithelium with a continuous basement membrane. They contain a sub-epithelial capillary system; tubuloalveolar, seromucous glands; goblet cells; parasympathetic and sympathetic innervation; and immunohistochemical evidence for a nonadrenergic, noncholinergic nervous system.¹⁻⁵ The major differences are the absence of smooth muscle (except around vessels) in the upper airway and the lack of a cavernous vascular network in the lower airways. Gas exchange in the alveoli does not occur in the conducting airway but rather in its own unique histologic environment, which will not be covered in this review. This report highlights similarities in allergen-induced inflammation in the upper and lower airways.

Whereas inflammation initiated by allergen is probably similar in the upper and lower airways, the consequences of this inflammation differ, based on the structure and function of the airway involved (e.g., sneezing versus coughing, nasal congestion versus breathlessness, rhinorrhea versus sputum production). In addition, allergic rhinitis and asthma are not synonymous. Allergic rhinitis implies IgE-mediated disease, whereas asthma can be triggered by many factors besides allergens. Many asthma triggers, such as infection, drugs (e.g., aspirin), pollutants (e.g., ozone), and chemicals (e.g., sulfites),

Abbreviations used

CDA:	Cold, dry air
ICAM:	Intercellular adhesion molecule
RH:	Relative humidity
T _{H1} , T _{H2} :	T-helper cells
VCAM:	Vascular cell adhesion molecule
VIP:	Vasoactive intestinal peptide

also cause rhinitis, but not through an IgE-mediated mechanism.

PATHOPHYSIOLOGIC RESPONSE

IgE response

Researchers have investigated the pathophysiology of inflammation with lavage, scrapings, and biopsies after antigenic stimulation. Biochemical and cytologic information on such inflammation is relatively easy to obtain, and pharmacologic manipulations can be monitored reliably.

After repeated low-dose exposure to allergens, atopic individuals develop specific IgE antibodies to the allergens. Subsequent exposure initiates a secondary humoral response. The latter has been shown to occur after seasonal exposure to an allergen and after nasal antigenic challenge (Fig. 1).^{6,7}

Early response

Within minutes after exposure of an allergic subject to an antigen, an immediate (early) response follows. In the upper airway, sneezing begins, followed closely by an increase in nasal secretions.⁸ After approximately 5 minutes, mucosal swelling develops, leading to reduced airflow. These physiologic changes are associated with increases in levels of histamine, leukotrienes, prostaglandins, tryptase, and other proinflammatory sub-

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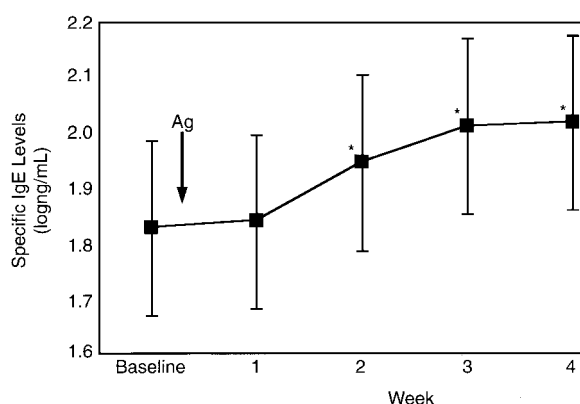


FIG. 1. Nasal challenge with ragweed leads to a rise in the level of serum anti-ragweed IgE antibodies. Ag represents nasal challenge with antigen. * $p < 0.05$ versus baseline. Adapted with permission from Naclerio RM, et al. Nasal provocation with allergen induces a secondary serum IgE antibody response. *J Allergy Clin Immunol* 1997;100:505-10.

stances (Fig. 2). In the lower airway, segmental bronchial antigenic challenge causes the release of many of the same mediators.

Microenvironment

Particles larger than 5 μm are filtered almost 100% by the nose; thus few intact pollen grains would be expected to reach the lower airway when the nose functions properly.^{9,10} On the other hand, gases affect primarily the lower airway, except for the amount partially cleared by impaction of inspired air into the extracellular fluid over the nasal mucosa.¹¹ The differential filtration of air by the nose probably accounts for some of the differences in the baseline composition of the extracellular lining fluid in the lung and the nose.

In a series of studies,^{12,13} preconditioning of individuals with allergies to different environmental conditions (i.e., temperature, humidity) affected the response to nasal antigenic challenge. Whereas little difference could be detected in the early response to allergen during challenges in room air (22°C, 30% relative humidity [RH]) and cold, dry (4°C, < 10% RH) environments, challenge during exposure to a warm, humid (37°C, > 90% RH) environment resulted in a significant reduction in antigen-induced nasal congestion, nasal airway resistance, and vascular permeability.¹² It also significantly reduced histamine release, sneezing, and pruritus. There was no effect on the glandular response, as assessed by the volume of secretions and the amount of lactoferrin recovered. The effect did not persist when the subjects were challenged with antigen 22 hours after leaving the warm, humid environment.¹² These studies point to potential differences in the responses of the upper and lower airways to antigen because of different microenvironmental conditions.

The mechanism underlying the beneficial effects of hot, humid conditions on the nasal mucosa is unknown.

Conditioning of inspired room air by the nose requires both heating and humidification. Humidification requires the addition of water through evaporation, which increases the osmolality of nasal secretions.¹⁴ In the 37°C, > 90% RH environment, the osmolality of secretions may have been reduced. Existing evidence supports the fact that changes in both osmolality and temperature can reduce mast cell degranulation.^{15,16} It is conceivable that in the hot, humid chamber, osmolality decreased sufficiently to alter a potential synergistic effect of osmolality and antigen on the mast cells. Increased temperature can also decrease histamine release from mast cells. Because the temperature of the nasal mucosa under normal ambient conditions is between 30.4°C at inspiration and 32.0°C at expiration,¹⁷ we propose that the optimal functioning temperature of mast cells of the nasal mucosa is probably in this range and that increasing the nasal mucosal temperature above 32°C may inhibit histamine release. It is possible that modifications of both temperature and osmolality act synergistically in decreasing the release of mast cell mediators. Alternatively, hot, humid air could directly affect the nerves, blood vessels, and glands within the nose.

Late response

The late response to antigens, which occurs hours after the immediate response, has been demonstrated in both the upper and the lower airways. It does not occur in every subject, but it appears to be dose dependent (i.e., the greater the dose of antigen, the more likely one is to observe a late response).¹⁸ Physiologically, the late response is manifested primarily as airflow obstruction. The physiologic changes are accompanied by mediator release; the pattern, however, differs from that of the early response (Fig. 3).¹⁹ In contrast to the early response to nasal challenge with antigen, the late response is reduced by oral glucocorticosteroids. This preferential steroid effect on the late reaction caused investigators to focus their studies on this response in attempting to understand the pathophysiology of allergic inflammation. Whether repetitive, low-dose antigen exposure rather than a single challenge with observation of a late response would be a better model of natural disease remains to be established.²⁰

Cellular infiltration

Eosinophilia has long been associated with allergic diseases. Eosinophils can affect the allergic response by releasing cytotoxic proteins (e.g., major basic protein), lipid mediators (e.g., leukotriene C4), oxygen radicals, and cytokines (e.g., IL-3).²¹ Investigators have studied the movement of eosinophils and other cells to the site of antigen provocation.

Hours after challenge, the number of eosinophils and basophils increase in nasal secretions.²² The recruited cells release mediators that affect the local environment. In the submucosa, eosinophils also increase in number, but the greater increase is in the number of lymphocytes, particularly T-helper cells. These cells provide a source

of cytokines, proteins released and secreted by stimulated cells that amplify and regulate local immune responses.²³ The pattern of cytokine secretion of T-helper cells allows their further subdivision into T_{H1} and T_{H2} cells. T_{H1} cells elaborate cytokines involved in effector functions of cell-mediated immunity (ie, IL-1, interferon), whereas T_{H2} cells elaborate cytokines that control and regulate antibody responses (ie, IL-4, granulocyte-macrophage colony-stimulating factor, IL-13).²⁴

T_{H2} cells, the predominant lymphocytes in allergic mucosal inflammation, help to perpetuate the allergic response. For example, IL-4, released mainly by T_{H2} lymphocytes, supports B-cell growth and differentiation, increases expression of vascular cell adhesion molecules (VCAMs) on endothelial cells, induces uncommitted T cells toward the T_{H2} phenotype, and promotes switching to IgE antibody formation. Other cytokines support eosinophil growth and prevent apoptosis, or programmed cell death. The importance of individual cytokines is speculative at this date because cytokines have overlapping functions and multiple activities.

Chemokines, or chemotactic cytokines, attract and activate lymphocytes, granulocytes, and monocytes.²⁵ They are 7 to 16 kd proteins with four conserved cysteine residues. Based on the position of the first two conserved cysteines, they are divided into two subfamilies, which differ in the cells they primarily attract and in the chromosome location for their encoding genes. The C-C chemokines, located on chromosome segment 7q11-q21, selectively attract eosinophils.²⁶ These include RANTES, MCP-1, MCP-3, and eotaxin. Although they are classified as chemokines, some have other activities, such as affecting immunoglobulin production. Despite the fact that the number of chemokines is great, many activate eosinophils through a shared receptor, CKR-3. Thus a strategy to lessen their effect on eosinophil migration may be the use of receptor blockade rather than inhibition of their synthesis. When planning a strategy to stop cellular migration to the site of allergic inflammation, one should consider that different chemokines may be expressed sequentially; whereas one chemokine may be important during recruitment early in the inflammatory response, another may be more important during the chronic stages of inflammation. Another important consideration is a possible synergism between chemokines.

Accumulating evidence supports the importance of leukocyte and vascular endothelial cell adhesion molecules in the migration of inflammatory cells, including eosinophils, into tissue sites during allergic reactions. This involves a sequence of events that includes margination of leukocytes along the walls of the microvasculature, adhesion to the endothelium, transmigration through the vessel walls, and migration along a chemotactic gradient within the extravascular compartment that contains extracellular matrix proteins such as fibronectin. These events are mediated by adhesion molecules such as integrins, selectins, and members of the Ig gene superfamily.²⁷

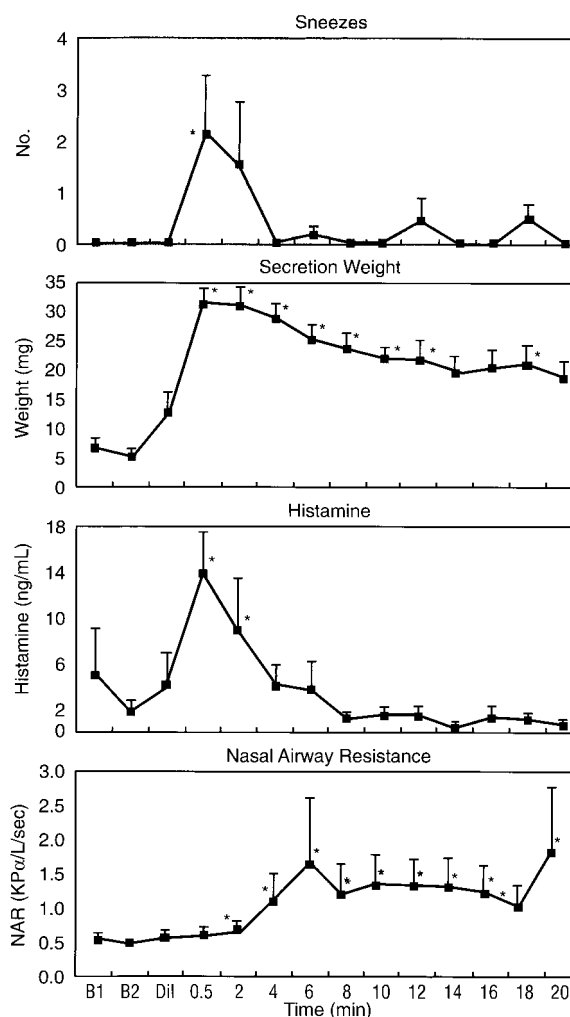


FIG. 2. Kinetics of the early response to nasal challenge with antigen. Histamine was released within 1 to 2 minutes and rapidly disappeared. Sneezing occurred at the same time as histamine release. Secretion weights, an objective measure of the secretory response, increased immediately and remained elevated over the entire 20-minute period. Nasal airway resistance (NAR) slowly increased, reaching a plateau within 6 minutes. B, Baseline; Dil, diluent for the antigen extract; 0.5, 2, etc., minutes after antigen challenge. * $p < 0.05$ compared with the response after diluent challenge.

Intercellular adhesion molecule-1 (ICAM-1), VCAM-1, and E-selectin are three representative endothelial adhesion molecules. They can be upregulated on endothelial cells by IL-1, tumor necrosis factor (TNF)- α , and lipopolysaccharide. ICAM-1, a ligand for the B₂-integrin molecules LFA-1 and Mac-1, which are present on the surface of leukocytes, mediates the attachment of all classes of leukocytes to endothelial cells. ICAM-1 is known to be constitutively expressed on vascular endothelial cells and can be induced by inflammatory mediators on other extravascular cells. E-selectin binds to sialyl Le^x, which is expressed on the surface of leukocytes.²⁸⁻³⁰

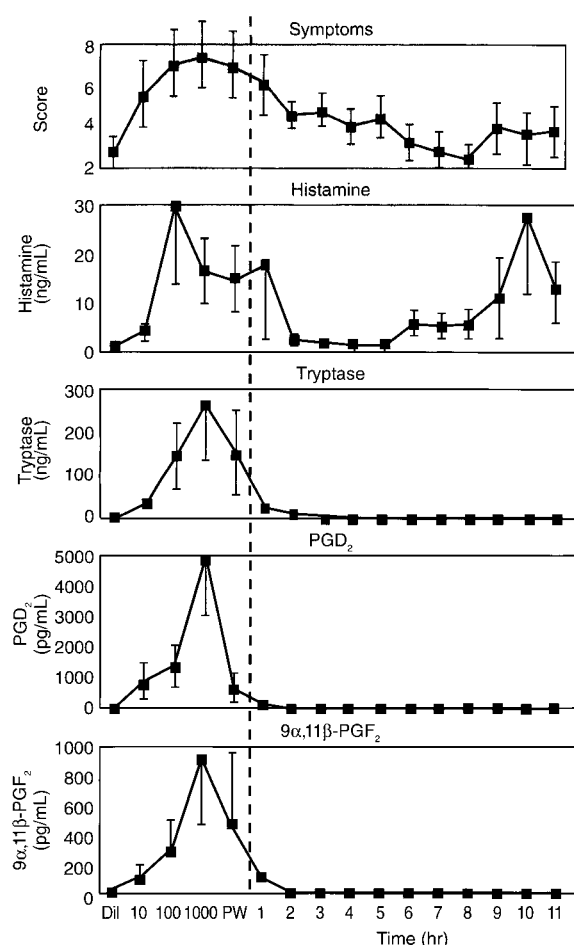


FIG. 3. Early and late responses to nasal challenge with antigen. The protocol for the challenge is marked on the abscissa. *Dil*, Nasal lavage performed 10 minutes after diluent; *10, 100, 1000*, nasal lavage performed 10 minutes after antigen challenge with 10, 100, and 1000 protein nitrogen units (PNU), respectively, of grass or ragweed extract; *PW*, nasal lavage performed 20 minutes after 1000 PNU challenge; *1, 2, 3, etc.*, nasal lavages performed hourly after the last nasal challenge; *Vertical dashed line* represents a separation of time units: times to the left are measured in minutes, those to the right in hours. Before the diluent challenge, six nasal lavages were performed and oxymetazoline was applied ($n = 6$). Data are presented as mean $\pm$ SEM. Panels represent measurement of parameters indicated above the graphs. PGD_2 , Prostaglandin D_2 ; $9\alpha,11\beta-PGF_2$, $9\alpha,11\beta$ -prostaglandin F_2 . Adapted with permission from Naclerio RM, Hubbard W, Lichtenstein L, Kagey-Sobotke A, Proud D. *J Allergy Clin Immunol* 1996;98:721-3.

VCAM-1, like ICAM-1, is a member of the Ig gene superfamily and supports the adhesion of leukocytes to endothelial cells through interactions with the integrin molecule VLA-4 ($\alpha_4\beta_1$), which is present on the surface of lymphocytes, monocytes, eosinophils, and basophils, but not neutrophils. VCAM-1 expression can be selectively induced on the endothelium by treatment with IL-4.³¹

Montefort and colleagues³² observed increased expression of ICAM-1 and VCAM-1 in nasal mucosal biopsy specimens from subjects with perennial allergic

rhinitis compared with that in normal control subjects. Georas et al³³ reported increased levels of a soluble form of E-selectin 19 hours after bronchoscopic allergen provocation in subjects with allergies. Subsequently, Lee and associates³⁴ confirmed the previously reported constitutive expression of ICAM-1 on the vascular endothelium in nasal biopsy specimens. They also showed that the percentage of vessels expressing VCAM-1 is upregulated 24 hours after allergen challenge and that E-selectin is modestly upregulated but ICAM-1 is not. This is consistent with a role for IL-4 in the induction of these changes and suggests that these events are mediated by an IgE-dependent mechanism, as they were observed in subjects with allergies but not in subjects without allergies after antigen challenge. Because the counterligand for VCAM-1, VLA-4, is present on eosinophils but not on neutrophils, we speculate that the upregulated VCAM-1 contributes, at least in part, to the selective recruitment of eosinophils into the nasal mucosa after antigen provocation and may therefore play an important role in the pathogenesis of allergic inflammation.

Changes in responsiveness

One result of the cellular influx after antigen stimulation and the release of proinflammatory mediators is a change in responsiveness of the upper and lower airways to a second stimulus.³⁵ The change can be specific (i.e., increased responsiveness to the same antigen) or non-specific (i.e., increased reactivity to irritants). The change in nonspecific reactivity is usually shown by challenge with histamine or methacholine.

Increased responsiveness to antigen (i.e., priming) occurs after provocation as well as during seasonal exposure.³⁶ The increased sensitivity to antigen that follows a prior antigen challenge is related to inflammation but is not obligatorily linked to it. Inflammation can occur in the absence of priming. Systemic steroids can effectively suppress the clinical, biochemical, and cellular manifestations of antigen-induced hyperresponsiveness. Topical steroids have a similar effect but are also capable of suppressing the early reaction to antigen.³⁷

Bronchial hyperactivity, increased responsiveness of the lower airways to histamine or methacholine, is a hallmark of asthma. Hyperactivity correlates with the number of eosinophils in sputum and is reduced by topical steroids.³⁸

In individuals with allergies who have both rhinitis and asthma, seasonal exposure to pollen can increase methacholine responsiveness in the lower airway. Treatment of the upper airway with topical steroids prevents this shift in reactivity.³⁹ The mechanisms for these observations are unknown, but they point to an interaction of the upper and lower airways when the response to antigen stimulation is assessed.

A nonallergic form of inflammation can be induced by inhalation of cold, dry air (CDA). Studies on the mechanism of CDA-induced rhinitis have shown elevations in the osmolality of nasal secretions after CDA challenge.⁴⁰ Elevated osmolality correlates with mediator release,

suggesting a role of nasal fluid tonicity in the initiation of the reaction. Studies of the lower airway do not consistently result in the same conclusion. Antigen challenge of the upper airway causes an increased responsiveness to CDA. This demonstrates the additive effect of two naturally occurring triggers of symptoms.

Epithelium

The epithelium, like the skin, has long been considered a barrier between the external environment and the inside of the body. For example, the epithelium covering the conducting airways contains cilia. The nasal cilia clear surface secretions toward the pharynx, which are then swallowed, helping protect the body. In the lung, cilia clear secretions to the proximal trachea and then to the hypopharynx, at which point they are swallowed.

In addition to being a barrier, the epithelium can participate in inflammation by presenting antigen and producing cytokines such as granulocyte-macrophage colony-stimulating factor, IL-6, and IL-8. Some of these cytokines can recruit neutrophils and prolong eosinophil survival. Inducible nitric oxide synthase has been found in epithelial cells as well as in vascular endothelial cells, smooth muscle cells, and submucosal glands.⁴¹ Nitric oxide has vasodilating and bronchodilating effects and plays an important role in neurotransmission, immune defense, cytotoxicity, ciliary beat frequency, and mucus secretion.

Autopsies performed on patients who died of asthma have shown denuded epithelium. Although epithelial changes are seen in patients with perennial allergic rhinitis, denuded areas are not.²³ In seasonally allergic patients, the epithelium appears to proliferate after seasonal exposure; in subjects with perennial allergies, the epithelium increases in thickness after treatment with topical steroids. These observations are preliminary, but they support a role for the epithelium in allergic inflammation.

Nervous system

The neuronal pathways potentially involved in allergic rhinitis include the sympathetic, parasympathetic, and peripheral sensory nerves. The presence of sympathetic and parasympathetic nerves and their transmitters in the nasal cavities and lungs has been known for decades. Recent evidence has established the additional presence of neuropeptides in the nasal and pulmonary mucosa.

Neuropeptide Y, a 36-amino acid peptide colocalized with norepinephrine in sympathetic fibers, is a potent vasoconstrictor.⁴² Both neuropeptide Y and somatostatin contract smooth muscle around the nasal capacitance vessels by nonadrenergic mechanisms. Provocation of the human nose with neuropeptide Y not only induces vasoconstriction but also increases the expression of intercellular adhesion molecules.⁴³ Nasal challenge with substance P, a neuropeptide found in sensory nerves, induces few changes in normal patients but in rhinitic patients causes a modest increase in vascular permeability, nasal airway

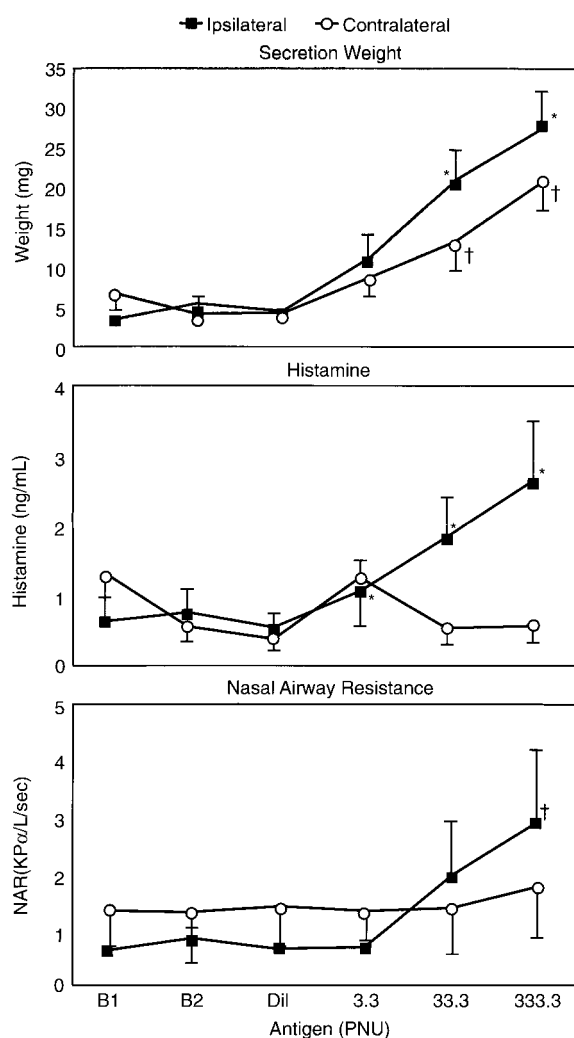


FIG. 4. Unilateral nasal challenge with antigen with assessment of response bilaterally. Antigen challenge caused a dose-dependent increase in histamine, secretion weight, and nasal airway resistance on the side of challenge (ipsilateral). Only secretion weights increased significantly on the contralateral side. The protocol is indicated at the bottom. B, Baseline; Dil, diluent for antigen extract; 3.3, 33.3, 333.3, antigen dose in protein nitrogen units (PNU); * $p \leq 0.001$, † $p < 0.05$ compared with the diluent challenge. Adapted with permission from Baroody FM, Ford S, Lichtenstein L, Kagey-Sobotka A, Naclerio RM. Physiologic responses and histamine release after nasal antigen challenge: effect of atropine. *Am J Respir Crit Care Med* 1994;149:1457-65.

resistance, and eosinophil and neutrophil chemotaxis.⁴⁴ Levels of substance P increase to a small but significant amount after antigen challenge. Cytokine expression of nasal mucosal explants is upregulated by substance P as well as by allergen stimulation. Calcitonin gene-related peptide, another neuropeptide found in sensory nerves, can induce changes in epithelial and fibroblast proliferation, two consistent findings in patients with chronic sinusitis and asthma.⁴⁵ Vasoactive intestinal peptide (VIP) exists primarily in peripheral nerves containing acetylcholine,

but it has also been identified in sensory nerves. In the upper respiratory tract, VIP fibers occur primarily around blood vessels, seromucinous glands, and surface epithelium, on all of which VIP receptors are found. Besides causing vasodilation, VIP affects water and ion transport in the gut through both cyclooxygenase and cyclic adenosine monophosphate pathways. Furthermore, VIP was reported to be absent from the lungs of patients dying of asthma and to be increased in patients with allergic diathesis and with nasal obstruction.⁴⁶ These represent only a sampling of studies that suggest a potential role for neuropeptides in modulating mucosal function.

Unlike that of neuropeptides, the function of central reflex responses involving the parasympathetic nervous system is firmly established (Fig. 4).⁴⁷ Konno and Togawa⁴⁸ unequivocally showed the existence of a reflex glandular response by abolishing it after vidian neurectomy. Birchall and colleagues⁴⁹ showed small but significant decreases in contralateral blood flow after a localized histamine challenge. Raphael et al⁵⁰ also investigated the contralateral response to histamine and showed increases in the glandular markers and in the levels of lysozyme and lactoferrin. With respect to unilateral antigen provocation, atropine-sensitive changes in secretions have been seen routinely, whereas changes in airway resistance and albumin have been reported inconsistently. In addition to these changes, we have made some interesting preliminary observations about early and late mediator release and lymphocytic activation in the nostril contralateral to that of antigen challenge.⁵¹ Histamine, which is released only at the site of nasal challenge during the early reaction, increases both at the site of challenge and in the opposite nostril hours after provocation. In addition, basophils, the source of histamine during the late response, increase at the site of challenge and in the opposite nostril during the late-phase response. If these contralateral responses can be proved to be mediated by neurogenic mechanisms, a new dimension will be added to our understanding of neurogenic inflammation.

Smooth muscle proliferation

Contraction of smooth muscle in the bronchi contributes to the early bronchoconstricting response to antigen. In patients with chronic asthma, smooth muscle proliferates and may contribute to some of the irreversible changes in the lower airway.³⁵ Some mediators, such as tryptase released from mast cells, can induce smooth muscle proliferation. Thus prolonged allergen stimulation may lead to chronic asthma. Because smooth muscle occurs only around vessels in the upper airway, its proliferation in upper airway disease is not a significant factor.

CONCLUSIONS

We have briefly reviewed some of the events that occur after antigen stimulation of the upper and lower

airways of individuals with allergies. Provoking either the upper or the lower airway leads to similar pathophysiologic responses. The responses cause different clinical manifestations. Studies of the pathophysiology of other forms of nonallergic asthma and rhinitis, such as those induced by pollution, will be our task in the future.

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