

What are the Primary Clinical Symptoms of Rhinitis and What Causes Them?

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KEYWORDS

• Rhinitis • Symptoms • Neuropeptides

The nose has a limited repertoire of responses regardless of the triggers. These responses primarily serve as a protective mechanism for the lower respiratory tract.¹ Although the nasal reactions to pollens, particles, and pollution may have a beneficial effect for the lower airway, they create symptoms in some individuals that lead to significant morbidity. In large surveys of patients, the typical nasal symptoms include nasal congestion, nasal drainage (including postnasal drainage), sneezing, and itching.^{2–4} Ocular symptoms include itchy/red eyes and watery eyes. Other symptoms that may be secondary include cough (often related to postnasal drainage or to stimulation of nasal sensory nerves⁵) and headache and sinus pressure (related to congestion).⁶ Rhinitis has been associated with sleep-disordered breathing, which could be the basis for the fatigue, irritability, and difficulty concentrating.^{7–9} The symptoms of allergic rhinitis extend far beyond the nose, and the morbidity associated with rhinitis is significant. The nasal symptoms of rhinitis and their causes are the focus of this review.

Patients may have immunologic sensitivities to specific allergens, or they may have a heightened response to what would be benign exposures (irritants) in others. The many different permutations of triggers and responses have made it difficult to determine the exact mechanisms in the groups of patients studied. Some studies have focused on isolated triggers and mediators, whereas a real-life clinical situation often involves multiple triggers and many mediators. The inflammatory mechanism in allergic rhinitis involves immunoglobulin (Ig)E-activating mast cells and the consequent early and then late-phase reactions that have been well described previously.

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Mediators, such as histamine, leukotrienes, prostaglandins, bradykinin, and platelet-activating factor, are released. Lymphocytes are activated and release cytokines that enhance the cellular inflammatory response and lead to the late-phase reaction.^{10,11} Neuropeptides and nasal secretions have been extensively reviewed.¹² Recent investigations have studied the neuropeptides substance P and secretoneurin, which are increased in nasal mucosa and nasal lavage fluid in patients with allergic rhinitis. In vitro studies indicate these neuropeptides are potent chemoattractants for basophils, providing yet another interaction of the nervous system and inflammatory cells.¹³ These inflammatory mediators and neuropeptides have a high degree of interconnectedness.

Furthermore, the various types of rhinitis are determined mainly by clinical descriptions and definitions, and, therefore, study populations may exhibit overlap, further confounding the data. For instance, in one study of idiopathic rhinitis, patients with vasomotor rhinitis were excluded.¹⁴ Other reports use the two terms, idiopathic and vasomotor, synonymously. The literature varies as to the initiating features of these diseases, partly because of the differences in the definitions. Idiopathic rhinitis has been suggested to have an inflammatory basis by some investigators,¹⁴ whereas others think hyperactive neuronal pathways are more likely responsible.^{15,16} The understanding of causal factors in the symptoms of rhinitis depends, in part, on the clear definition of the population being studied. Efforts to clarify these various clinical entities may lead to a better understanding of both possible causes and a potential therapy.¹⁷

The inflammatory response in rhinitis triggered by allergens, whether systemic or local, is the initiating feature of symptoms. Recent studies have demonstrated that some patients who previously would have been classified as having idiopathic rhinitis may instead have a local allergic rhinitis.^{18–20} Nasal challenge studies have attempted to elucidate the mediators and mechanisms responsible for symptoms of rhinitis.^{21,22} These mediators have been studied in various models to better understand the cause of rhinitis symptoms. Nasal-allergen challenge studies have evaluated both symptoms and mediators in an attempt to attribute certain symptoms to specific mediators.^{23,24} Wang and colleagues²⁴ found that itch and sneeze started within 20 to 30 seconds and abated about 5 minutes after the antigen challenge. Rhinorrhea and nasal congestion started a few minutes after the challenge and lasted more than 1 hour. When evaluating histamine, tryptase, and leukotriene C4, the investigators were unable to find any significant correlation between the concentration and dynamics of the mediators in nasal secretions and the specific nasal symptoms. This lack of correlation to specific symptoms is reflective of the complex nature of the underlying pathophysiology. The two unique aspects of nasal anatomy and physiology that interact to produce the typical symptoms of rhinitis are the vascular (**Fig. 1**) and the neurologic (**Fig. 2**) systems.

These systems have recently been reviewed.^{25,26} The allergic response and mast cell activation produces mediators, such as histamine, tryptase, leukotrienes, and prostaglandins. Although histamine nasal challenge can produce all the symptoms of allergic rhinitis, it is clear that other mediators are also responsible for the clinical symptoms in patients.²⁷ Investigators have used specific mediators, such as histamine or serotonin, applied to the nasal mucosa to identify the subsequent symptoms these substances produce.²⁸ These investigators found that in normal volunteers serotonin produced itch, sneeze, and drainage similar to histamine, but produced less congestion than histamine. Histamine-related symptoms may be mediated directly via the histamine receptors on vessels or through activation of neuronal H1 receptors. Other histamine receptors, H2 and H3, may play a role in nasal

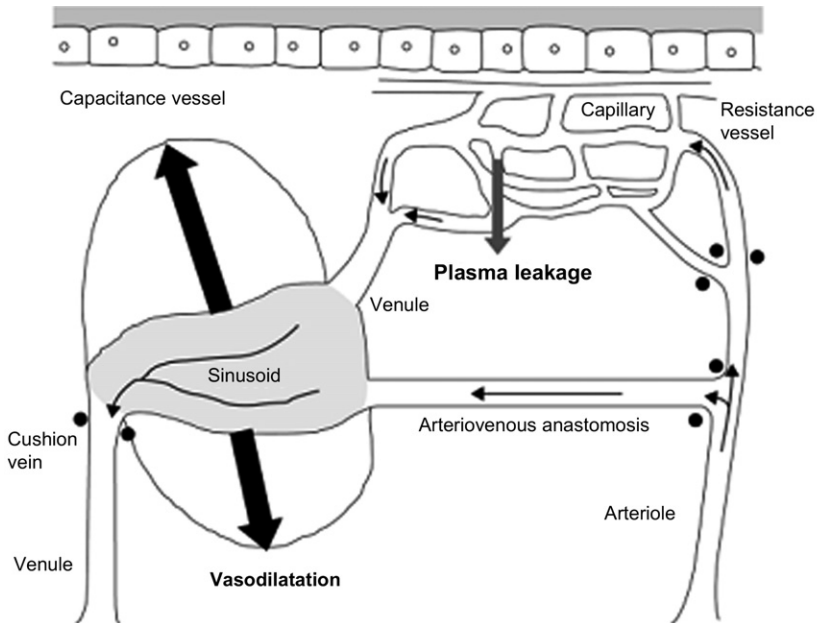


Fig. 1. Vascular mechanism of nasal congestion. (From Ichimura K. Mechanism of nasal obstruction in patients with allergic rhinitis. Clin Exp Allergy Rev 2010;10:21; with permission.)

congestion.²⁹ Such studies help differentiate the direct effect on neuronal reflex initiation of symptoms from those effects of mediators on the vascular bed in causing rhinitis symptoms.

Other investigators have attempted to differentiate between the cause of symptoms in nonallergic and allergic rhinitis by using nasal challenge models. Capsaicin selectively stimulates a subpopulation of sensory fibers. These fibers (unmyelinated C fibers and some A δ fibers) provide stimulus to the central nervous system through their sensory function and also have an efferent arch through antidromic release of neuropeptides.³⁰ The capsaicin challenge has been used to further differentiate the mechanisms causing symptoms in allergic and nonallergic rhinitis. In a study of nonallergic rhinitis (defined by negative skin tests) compared with allergic subjects (with both rhinitis groups having perennial symptoms of nasal congestion or rhinorrhea), capsaicin challenge was used to compare nasal responses.³¹ These investigators found that all subjects developed burning, lacrimation, and rhinorrhea after the capsaicin challenge. Although rhinorrhea was present in all groups, the composition of nasal lavage fluids was different between the groups. Lactoferrin (a marker of submucosal gland secretion), albumin (a marker of vascular effect through plasma extravasation), and total protein were measured. Only the patients with allergic rhinitis had a significant increase in albumin secretion compared with nonallergic and nonrhinitic subjects, suggesting that in allergic rhinitis there is a hyperresponsiveness to neuronal stimulation. Increased neuronal responsiveness in patients with symptomatic allergic rhinitis has been shown in other studies. Nasal challenge with bradykinin produced greater symptom scores in patients with symptomatic allergy than in those challenged out of their season or in nonallergic control subjects.³² There were significantly greater symptoms of rhinorrhea and congestion in allergic subjects tested in season versus

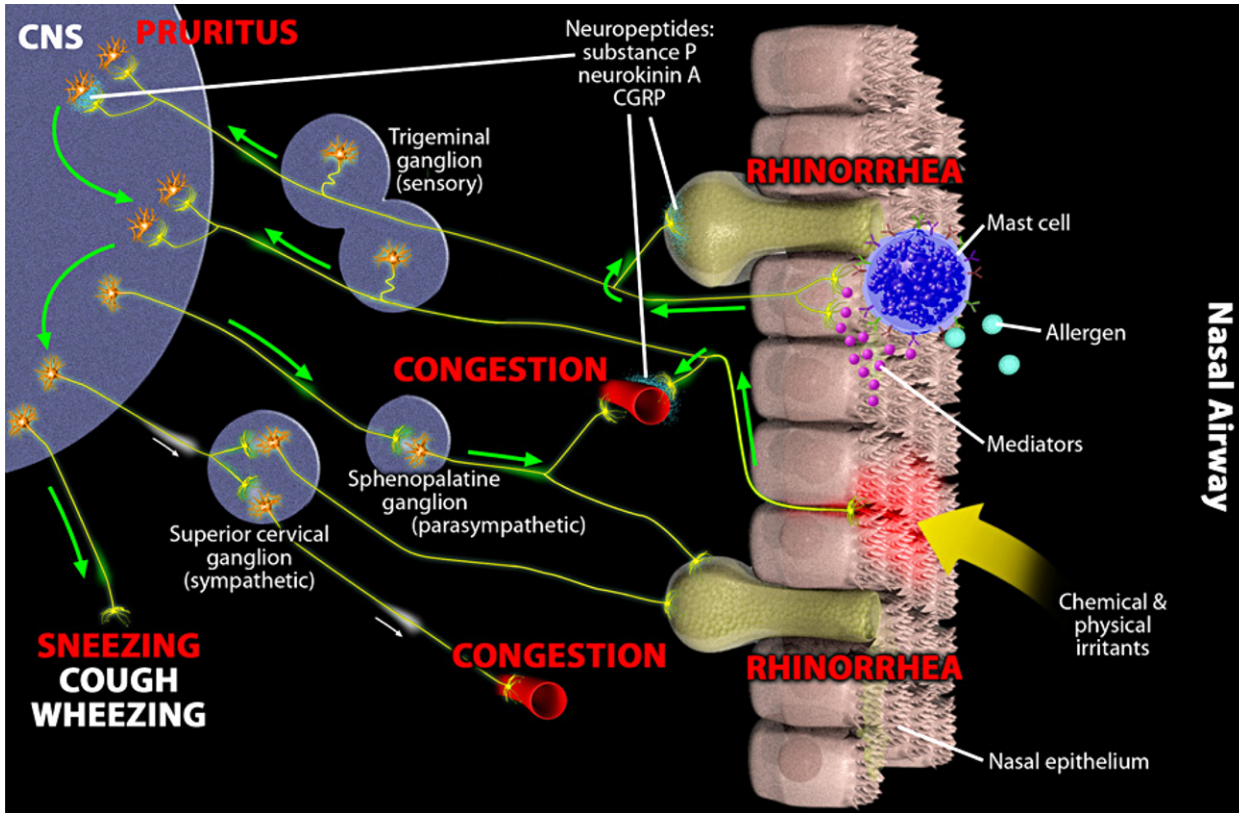


Fig. 2. Neuronal mechanisms of rhinitis symptoms. CNS, central nervous system. (From Sarim S, Undem B, Sanico A, et al. The role of the nervous system in rhinitis. *J Allergy Clin Immunol* 2006;118:1001; with permission.)

out of season, and there were a greater number of sneezes noted (although not statistically significant). This enhanced responsiveness in patients during their allergy season has been attributed to the increased sensitivity of the inflamed nasal mucosa in allergic rhinitis. Recent studies have demonstrated significant increases of neuropeptides (substance P, vasoactive intestinal peptide, and neuropeptide Y) in the mucosal nerve fibers of patients with seasonal allergic rhinitis compared with controls.³³

It now appears that the nerve hypersensitivity and growth may change in patients with allergic rhinitis. Studying inferior turbinate biopsy specimens from subjects with allergic rhinitis, nonallergic rhinitis, and controls, Keh and colleagues³⁴ showed differences in voltage-gated sodium channels. These sodium channels (Nav1.7, Nav1.8, and Nav1.9) were increased in tissues of allergic and nonallergic rhinitis subjects compared with controls. The channels are thought to play a role in the neuronal hypersensitivity seen in patients with rhinitis. Neurotrophins also contribute to hyperresponsiveness seen in patients with allergic rhinitis. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have been demonstrated in nasal mucosa.³⁵ Increased BDNF expression positively correlates with the maximum increase in total nasal symptom scores.³⁶ These neurotrophins are released from activated eosinophils. The increased symptoms and hyperresponsiveness to nonspecific stimuli may be partly caused by these neurotrophins released during the allergic response. The fact that there are also neurotrophin receptors on eosinophils in patients who have allergic rhinitis suggests a possible positive feedback loop amplifying this hyperresponsiveness.

Symptoms of vasomotor rhinitis may be primarily neurogenic, although inflammation and mast cell mediator release can occur secondary to this neurogenic activation.³⁷ The similarity between the causal factors in allergic and nonallergic rhinitis symptoms may account for some of the shared therapeutic effectiveness of the same drugs for both clinical entities.

THE CARDINAL SYMPTOMS OF RHINITIS

Nasal congestion is recognized in most patient surveys as the most bothersome symptom identified by sufferers of allergic rhinitis. Nasal obstruction is defined as discomfort manifested as a feeling of insufficient airflow through the nose.³⁸ Because nasal congestion is a subjective symptom, it is not always recognized in patients, especially those who have had the disease for many years and accept a degree of obstruction as normal. Observations of obstruction recognized on examination or by airflow measurement do not always correlate with a patient's perception of symptoms.³⁹ When severe nasal obstruction exists, patients may be bothered by their lack of sense of smell or taste but may not recognize the obstruction.

Nasal congestion in allergic rhinitis results mainly from tissue edema and vasodilatation in the nasal mucosa. The microvascular anatomy of the nose has been recently reviewed and consists of precapillary resistance vessels, capillaries, veins and venous erectile tissue, and capacitance vessels, as well as numerous arteriovenous anastomoses.²⁵ This vascular system (with arteriovenous anastomosis and with capacitance vessels in the nasal turbinates) differs from other areas of the respiratory tract. As these vessels become engorged and distended, the turbinates may block the airway lumen. This swelling may have a teleologic purpose and occur alternately from side to side in a normal state to enhance filtration and respiratory defense.⁴⁰ The enlarged turbinate in a confined space also produces symptoms of nasal congestion and obstruction. Ichimura⁴¹ recently reviewed the mechanisms of nasal obstruction. The autonomic nervous system is primarily responsible for the control of blood flow in

the nose, with sympathetic tone maintaining contraction of the cavernous sinusoids. If the sympathetic tone is reduced by inhibition of noradrenaline release, then direct vasodilatation occurs. This inhibition is thought to be mediated partly on presynaptic nerve endings by the H₃ histamine receptor and prostaglandin E₂ receptor.

Histamine plays an essential role in causing nasal congestion. Histamine challenge, as well as specific H₂ and H₃ agonist challenge, can cause nasal congestion.²⁹ Using H₁ and H₂ antagonists, these investigators were not able to totally block the congestion after the histamine challenge, thus suggesting that the H₃ receptor might play a role in reducing vascular sympathetic tone by inhibiting norepinephrine release.

Nasal challenge studies have demonstrated the presence of several mediators in addition to histamine that may contribute to nasal congestion. These mediators include bradykinin, platelet-activating factor, prostaglandin D₂ (PGD₂), leukotrienes C₄ and D₄, substance P, and calcitonin-gene related protein (CGRP).⁴² These mediators will be explored more thoroughly regarding their roles in nasal congestion. Bradykinin and platelet-activating factor may cause vasodilatation by direct action on vessel walls or through vasodilatory substances, such as nitric oxide (NO).⁴³ Maniscalco and colleagues⁴³ used platelet-activating factor and bradykinin nasal challenges to produce nasal congestion measured by anterior rhinomanometry. They confirmed that NO was important in the nasal response to bradykinin, but was not involved in the increased nasal resistance after the platelet-activating factor challenge. Nasal congestion may thus be mediated through NO or caused directly depending on the mediator involved. Substance P can be released from sensory neurons by a variety of stimuli, including allergens and other mediators. Substance P has been shown to increase nasal blood flow and microvascular leakage.⁴⁴ Hanf and colleagues⁴⁵ studied nasal tissue from subjects with allergic rhinitis and nonallergic controls who had surgery for nasal obstruction. Although substance P stimulated histamine release from tissue of both allergic and nonallergic subjects, there was increased histamine release in nasal tissues from subjects with allergic rhinitis. The amplification of the vascular response in rhinitis by this interplay of a neurotransmitter having a positive feedback on mast cell histamine release further illustrates the complex nature of the congestion seen in rhinitis.

Of the mediators released by mast cells in response to allergens, prostaglandin D₂ is regarded as the most potent inducer of nasal congestion. Nasal challenge with PGD₂ produces nasal congestion in both normal subjects and in those with rhinitis.^{46,47} A specific PGD₂ receptor antagonist has recently been shown to reduce such congestion in PGD₂ nasal challenge studies.⁴⁸ These studies suggest that PGD₂ is a primary mediator enhancing congestion in patients with rhinitis.

The role of leukotrienes in rhinitis has been the subject of recent reviews.^{49,50} Early studies delineated the effect of leukotriene D₄ in producing nasal congestion. Several studies have looked at the clinical benefit of blocking this pathway either with 5-lipoxygenase inhibitors or with leukotriene receptor blockers.^{51,52} These studies and reviews have shown efficacy of these two classes of leukotriene modifiers compared with placebo treatments, indicating that leukotrienes are partially responsible for some of the symptoms in allergic rhinitis.⁵³

The rhinorrhea associated with rhinitis may be associated with a variety of stimulants, including the ingestion of food and the exposure to cold air.^{54,55} The mechanisms causing symptoms in rhinitis were the subject of investigation over several years at the National Institutes of Health (NIH), and these results regarding rhinitis were reviewed several years ago.⁵⁶ Since that time, other investigations of rhinorrhea have evaluated the differences in idiopathic (nonallergic) and allergic rhinitis, as well as differences between patients with active, symptomatic, and asymptomatic allergic

rhinitis. Comparing the effects of bradykinin stimulation in normal, nonallergic subjects to patients with either perennial or seasonal allergic rhinitis, investigators have shown increased secretions containing increased lactoferrin levels in patients with perennial allergic rhinitis.³² They also demonstrated that in seasonal allergic rhinitis, bradykinin stimulation produced greater secretions with higher lactoferrin and albumin levels during the pollen season. The increases in lactoferrin suggest there is enhanced glandular secretion in patients with allergic rhinitis compared with normal control subjects. Increased lactoferrin and albumin secretions noted seasonally suggest that there is increase vascular leakage and glandular secretion during the pollen season. Further studies show that patients with idiopathic rhinitis compared with those with allergic rhinitis or no rhinitis have increased secretions following cold stimulation of the feet as well as cold, dry air nasal challenge.¹⁶ Aberrant neurologic responses appear to be the most likely cause of this nasal secretory response. Using natural environmental factor variations in a study of nonallergic and noninfectious patients with perennial allergic rhinitis, Braat and colleagues⁵⁷ showed a correlation between nasal secretions and environmental NO and ozone levels. Symptom scores also related to minimum daytime temperature. These investigators did not evaluate possible mechanisms for these findings. Using nasal mucosa tissue samples from allergic and nonallergic patients, Schierhorn and colleagues⁵⁸ demonstrated an increase in both neurokinin A and substance P following tissue exposure to ozone. The tissue from allergic patients released more of both neuropeptides than the tissue of the nonallergic patients. These experiments suggest that nasal mucosa may respond to increased ozone exposure in a manner similar to bronchial mucosa with an increased release of neuropeptides. In summary, neurogenic mechanisms stimulating cholinergic efferent pathways with enhancement from allergic inflammation seem to be the primary causes of rhinorrhea in rhinitis.

Nasal itch is considered one of the diagnostic symptoms of rhinitis, although it appears to be more common in seasonal allergic rhinitis than in other types of rhinitis. In one study, nasal itching and sneezing were the most common presenting symptoms in both seasonal allergic rhinitis and in perennial allergic rhinitis with seasonal exacerbations.⁵⁹ This finding is consistent with IgE-mediated rhinitis involving histamine release from mast cells. Nasal itch is produced by histamine nasal challenge and blocked by H1-receptor antagonists. The itch is thought to be completely mediated by nasal sensory nerves through the activation of neuronal H1 receptors.⁶⁰ These nasal sensory neurons are also capsaicin sensitive. The capsaicin receptor, transient receptor potential vanilloid-1 (TRPV1), has been identified on both nasal neuronal cells and nonneuronal cells in human nasal mucosa.⁶¹ This receptor is in a family of transient receptor potential (TRP) ion channel activators that have been identified. They may play a role in the nasal response to temperature as well as aroma (Fig. 3).³⁵

In studying patients with seasonal allergic rhinitis, Alenmyr⁶² demonstrated a significant sensation of itch following the capsaicin challenge during the pollen season but not before the season. Another TRPV1 stimulant, olvanil, also produced the itch sensation during, but not before, the pollen season. Activation of other TRP receptors (TRPA1 and TRPM8) did not produce the itch sensation either before or during the pollen season in these 10 patients with seasonal allergic rhinitis. This study and others showing increased neuronal markers in patients with allergic rhinitis may help explain the enhanced ability for nonspecific stimuli to produce symptoms in patients with allergic rhinitis.⁶³

Sternutation (sneezing) is also induced by the application of capsaicin to the nasal mucosa.⁶⁴ Although the sneeze reflex is a common symptom of allergic and nonallergic rhinitis, it can also occur after such nonspecific events as exposure to bright

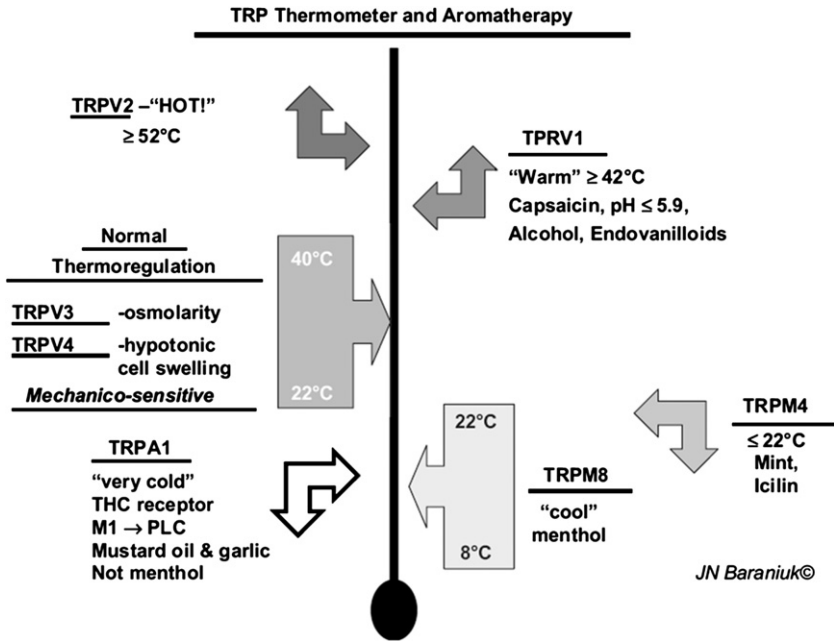


Fig. 3. Ion channel regulation of neuronal function in rhinitis. M1, Muscarinic M1 receptor; PLC, phospholipase C; THC, tetrahydrocannabinol. (From Baraniuk JN. Neural regulation of mucosal function. *Pulm Pharmacol Ther* 2008;21:447; with permission.)

light.⁶⁵ Baraniuk and Kim⁶⁶ recently described the complex constellation of consequences that occurs when the sneeze reflex is invoked. These investigators review multiple states of sneeze induction in addition to the classical pathway of histamine-induced activation of type C trigeminal neurons. Complications of the sneeze reflex may also occur, adding further morbidity to the symptoms of allergic rhinitis.⁶⁷ The sneezing reflex was evaluated in patients with allergic rhinitis and in healthy volunteers using histamine to induce the sneeze.⁶⁸ The investigators found a significantly greater percentage of responders in patients with allergic rhinitis at all dosing levels of histamine provocation. They also showed that nerve growth factor levels in nasal lavage fluids from patients with allergic rhinitis were significantly increased compared with the healthy controls, suggesting a possible role of this factor in the hyperresponsiveness of patients who are allergic.

As more is learned about the complex neurologic inflammation and vascular responsiveness associated with rhinitis and the induction of neurons and increased neuronal sensitivity in rhinitis, more effective interventions to control the symptoms of allergic and idiopathic rhinitis should emerge. The similarities in the mechanisms causing the symptoms in allergic and idiopathic rhinitis provide a rationale for the current treatment of the two clinical entities.

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