Nonallergic Rhinitis
Mechanism of Action

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KEYWORDS

• Nonallergic rhinitis • Neurogenic • Reactivity • Histamine • Cold-dry air

KEY POINTS

- Cellular inflammation is not a consistent finding in patients with nonallergic rhinitis.
- Neuropeptides play an important role in the pathophysiology of nonallergic rhinitis.
- Transient receptor potential ion channels have an important role in mediating the response of patients with nonallergic rhinitis to environmental stimuli.
- Patients with nonallergic rhinitis exhibit various degrees of nasal reactivity to certain nonspecific stimuli, such as histamine, cold-dry air, and capsaicin.

INTRODUCTION

Nonallergic rhinitis (NAR) is a chronic condition of the nasal mucosa that predominantly involves symptoms of nasal congestion and rhinorrhea with no evidence of allergic sensitization (ie, negative skin testing and/or serum-specific immunoglobulin E [IgE] testing). Although the primary and most common symptoms are congestion and anterior and posterior rhinorrhea, other associated symptoms include throat clearing, cough, eustachian tube dysfunction, sneezing, decreased sense of smell, and facial pain/pressure.[1] Itching of the eyes, throat, and ears is not a common symptom. The timing of symptoms may be perennial/persistent, intermittent, and/or precipitated by recognized triggers. Some of these include cold air, changes in environmental temperature and humidity, changes in barometric pressure, strong smells (perfumes, food, chemical odors), environmental tobacco smoke, pollutants and chemicals, ingestion of certain foods (gustatory rhinitis), and alcohol.

Unlike allergic rhinitis (AR), which is the most common chronic condition in children, NAR presents predominantly with adult onset; the female to male incidence varies

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between 2:1 and 3:1. Data from rhinitis epidemiologic studies suggest that the prevalence of AR is around 3 times more than that of NAR (AR:NAR = 3:1).[2] Thus, based on our knowledge of the prevalence of AR in the United States and the aforementioned ratios, one can estimate the number of Americans with NAR as 20 million or 7% of the population.

The classification of NAR has been unsolidified over the years and its pathophysiology relatively unexplored. Although *vasomotor rhinitis* was a common term used to describe such an entity, this term is no longer favored and is mostly replaced by NAR. It is important to realize that there are other types of rhinitis that are nonallergic but have specific and identifiable precipitating factors and triggers. These types include chronic rhinosinusitis with and without nasal polyps; NAR with eosinophilia syndrome (NARES); aspirin-exacerbated rhinosinusitis; infectious rhinitis/rhinosinusitis such as triggered by viral, bacterial, or fungal infections; rhinitis of pregnancy; and drug-induced rhinitis. Furthermore, the presence of inflammation in the nasal mucosa of patients with NAR is not ubiquitous leading some investigators to consider the term *rhinopathy* instead of rhinitis to refer to this entity. In the following pages, the author attempts to discuss available information that pertains to the pathophysiology of this disease and mostly centers around a description of inflammation in the nasal mucosa in NAR as well as neurogenic mechanisms thought to be important for this disease process. The author also details various methods of nasal provocation the results of which might shed some light on pathophysiologic processes involved in NAR.

INFLAMMATION

Van Rijswijk and colleagues[3] performed nasal biopsies in patients with chronic rhinitis symptoms but negative evidence of allergic cause and compared those with the results of biopsies obtained from a normal control group with no nasal symptoms and negative skin test results. They evaluated various markers of lymphocytic cells, mast cells, Langerhans cells, macrophages, IgE+ cells, and eosinophils using immunohistochemistry. Most biopsies had a negligible number of eosinophils, which suggests that local AR and NARES were probably not a large contributor to this group. There were essentially no significant differences in the number of inflammatory cells between the rhinitis and control groups suggesting that cellular inflammation was not a prominent factor in this group of patients with NAR. The investigators also failed to show any relation between the number of immunocompetent cells in the nasal mucosa and nasal complaints in those patients when treated with either an intranasal corticosteroid or capsaicin.[4–6] In those studies, the intranasal corticosteroids resulted in a reduction of inflammatory cells but no improvement in symptoms and capsaicin reduced nasal symptoms without affecting the number of nasal inflammatory cells or mediators.

Powe and colleagues[7] performed similar investigations with different results. They evaluated nasal turbinate tissue obtained at the time of turbinectomies from patients with perennial allergic rhinitis, idiopathic rhinitis, and normal controls (undergoing surgery for mechanical, posttraumatic nasal obstruction) with no evidence of rhinitis. Using immunohistochemistry, they evaluated mast cells, IgE+ cells, eosinophils, and plasma cells and showed that both disease groups had essentially equivalent inflammatory cellular content, which was higher than that of the control, nonrhinitic subjects. The allergic group had a higher number of IgE+ cells and plasma cells compared with the group of patients with NAR. As mentioned earlier, the nonallergic group probably included subjects with local AR or NARES, as the number of

eosinophils was equivalent in both rhinitis groups and was higher than the number of eosinophils found in the nonrhinitis control subjects. Another difference between this study and the previous one quoted, whereby there was no significant inflammation in the NAR group, is that the tissue was collected at the time of turbinectomies, which would indicate more severe disease that was mandating surgical intervention. A similar study by the same group evaluated the T-lymphocyte differences between similar subgroups and showed significant overlap in lymphocytic inflammation between the patients with allergic and NAR.[8] However, there were differences in some cells between the 2 groups with fewer antigen-presenting cells and more CD8+ cells in the NAR group compared with the subjects with perennial AR. Furthermore, in both groups with rhinitis, there was an association between lymphocytes and mast cells suggesting a common pathway in persistent nasal inflammation.

More recently, De Corso and colleagues[9] evaluated nasal inflammation in a large, well-characterized group of subjects presenting to their rhinology clinics over a 6-year time interval. NAR was diagnosed by history of symptoms of rhinitis for at least 12 weeks along with negative skin and/or serum allergy testing, negative response to allergen provocation, and negative nasal endoscopy and computed tomography scans to rule out paranasal sinus involvement. A nasal sample was obtained by scraping the inferior turbinates, and the cellular profile was used to subtype the subjects with NAR into NAR without inflammation (231 of 519 subjects, 44.5%) and NAR with inflammation (288 of 519 subjects, 55.49%). The group with inflammation was further subtyped into 4 different subgroups based on the predominant type of inflammatory cells: NAR with neutrophilia (32.95%), NAR with eosinophilia (15.61%), NAR with mast cells (3.66%), and NAR with mast cells and eosinophils (3.28%). The main finding from the study was that the groups of NAR without inflammation and NAR with neutrophils were fairly similar in that they had milder inflammation with fewer and milder symptoms compared with the groups of NAR with inflammation who reported more moderate or severe nasal symptoms. Also, the groups of NAR with eosinophils and mast cells were significantly more likely to have comorbidities than the NAR without inflammation and NAR with neutrophilia groups. This work suggests that a large portion of patients presenting with NAR have a significant inflammatory infiltrate and that the type of inflammatory infiltrate has a direct bearing on disease severity. The only issue that is not clarified in the study design was the number of allergens that were used in nasal challenges to confirm that these subjects had no local response to allergen.

As can be seen from the aforementioned information, studies on nasal cellular inflammation in patients with NAR do not yield uniform results probably related to the variations in clinical characterization of the subjects enrolled. Most investigators refer to the disease entity as idiopathic rhinitis and characterize the subjects by chronic nasal symptoms, such as nasal congestion and rhinorrhea, but carefully exclude infectious causes of such symptoms. Furthermore, all subjects enrolled in these studies had negative skin tests and/or specific IgE testing results.

Unfortunately, nasal challenge was not performed as part of the characterization of the subjects in all the studies, thus, potentially including a subset of subjects with what is now referred to as local or entopic AR.[10] In this entity, patients have an IgE-mediated, eosinophilic, nasal cellular infiltrate in the absence of evidence of positive skin or immunocap testing but do have a positive response to nasal provocation with relevant allergens and evidence of local IgE production. In contrast to NAR, these patients respond better to conventional therapies used to treat AR. This entity will be

discussed in detail in a subsequent article (See Campo P, Salas M, Blanca-López N, et al: Local Allergic Rhinitis, in this issue).

NEUROGENIC MECHANISMS

Innervation of the Nasal Mucosa

The nasal neural supply is overwhelmingly sensory and autonomic (sympathetic, parasympathetic, and nonadrenergic noncholinergic). The sensory nasal innervation comes via both the ophthalmic and maxillary divisions of the trigeminal nerve and supplies the septum, the lateral walls, the anterior part of the nasal floor, and the inferior meatus.[11] The parasympathetic nasal fibers travel from their origin in the superior salivary nucleus of the midbrain via the nervus intermedius of the facial nerve to the geniculate ganglion where they join the greater superficial petrosal nerve that, in turn, joins the deep petrosal nerve to form the vidian nerve.[11] This nerve travels to the sphenopalatine ganglion where the preganglionic parasympathetic fibers synapse and postganglionic fibers supply the nasal mucosa. The sympathetic input originates as preganglionic fibers in the thoracolumbar region of the spinal cord, which pass into the vagosympathetic trunk and relay in the superior cervical ganglion. The postganglionic fibers end as the deep petrosal nerve, which joins the greater superficial nerve to form the vidian nerve. They traverse the sphenopalatine ganglion without synapsing and are distributed to the nasal mucosa.[11] Nasal glands receive direct parasympathetic nerve supply, and electrical stimulation of parasympathetic nerves in animals induces glandular secretions that are blocked by atropine. Furthermore, stimulation of the human nasal mucosa with methacholine, a cholinomimetic, produces an atropine-sensitive increase in nasal secretions.[12]

Parasympathetic nerves also provide innervation to the nasal vasculature, and stimulation of these fibers causes vasodilatation. Sympathetic fibers supply the nasal vasculature but do not establish a close relationship with nasal glands, and their exact role in the control of nasal secretions is not clear. Stimulation of these fibers in animals causes vasoconstriction and a decrease in nasal airway resistance. Adrenergic agonists are commonly used in man, both topically and orally, to decrease nasal congestion.

The presence of sympathetic and parasympathetic nerves and their transmitters in the nasal mucosa has been known for decades, but recent immunohistochemical studies have established the presence of additional neuropeptides. These neuropeptides are secreted by unmyelinated nociceptive C fibers (tachykinins, calcitonin gene-related peptide [CGRP], neurokinin A [NKA], gastrin-releasing peptide), parasympathetic nerve endings (vasoactive intestinal peptide [VIP], peptide histidine methionine), and sympathetic nerve endings (neuropeptide Y). Substance P (SP), a member of the tachykinin family, is often found as a cotransmitter with NKA and CGRP and has been found in high density in arterial vessels and to some extent in veins, gland acini, and epithelium of the nasal mucosa.[13] SP receptors (NK1 receptors) are located in epithelium, glands, and vessels.[13] CGRP receptors are found in high concentration on small muscular arteries and arterioles in the nasal mucosa.[14] The distribution of VIP fibers in human airways corresponds closely to that of cholinergic nerves.[15] In the human nasal mucosa, VIP is abundant and its receptors are located on arterial vessels, submucosal glands, and epithelial cells.[16] In addition to the identification of neuropeptides in the nasal mucosa, several studies support their potential contribution in the creation of nasal symptoms. VIP stimulates serous cell secretion,[16] dilates nasal vessels[17] and may regulate mucociliary clearance in dogs.[18] Nasal challenge with SP induces few changes in normal subjects but leads to a modest increase in vascular permeability, nasal airway resistance, and eosinophil and neutrophil chemotaxis in rhinitic subjects.[19]

Transient receptor potential (TRP) is one of a family of calcium ion channels involved in transducing external stimuli to sensory neurons.[20] Among those channels, TRP vanilloid-1 (TRPV1) is capsaicin sensitive and mediates the pungency of capsaicin and TRP ankyrin 1 (TRPA1) mediates the effects of noxious stimuli, such as cold temperatures, pungent natural compounds, and environmental irritants.[21] These channels are being recognized as increasingly important in mediating the nasal response to noxious chemical, mechanical, and osmotic stimuli and probably do so by mediating the release of neuropeptides from sensory nerve endings.[22] Therefore, their role in the pathophysiology of NAR is being investigated.

Contribution of Neurogenic Mechanisms to the Pathophysiology of Nonallergic Rhinitis

The sympathetic and parasympathetic components of the autonomic nervous system equally contribute input to the nasal efferent organs to maintain a delicate homeostasis between vasoconstriction and vasodilation of nasal vasculature and the secretion of nasal glands. An imbalance of these components is likely to contribute to glandular hypersecretion and increased nasal congestion, often seen in patients with NAR.[23–25]

Exposure to nonallergic triggers can precipitate rhinitis by activating TRPA1 and TRPV1 channels on nasal mucosal nerve fibers, which would lead to the release of neuropeptides, such as CGRP and SP, from sensory nerve endings.[26,27] These neuropeptides, in turn, will facilitate vasodilation and plasma extravasation causing edema and glandular hypersecretion. Evidence for the involvement of SP in the pathophysiology of NAR is indirect and relates to the beneficial effects on symptoms of the disease obtained by treatment with capsaicin, a substance known to deplete SP from sensory nerve endings and considered a TRPV1 agonist.[28,29] Another piece of supporting evidence was generated when symptoms and levels of SP in nasal lavage fluid were shown to increase significantly in subjects with NAR after hypertonic saline challenge.[30] In the same study, pretreatment with azelastine led to a reduction in SP levels as well as a significant improvement of nasal symptoms in the same subjects.

Van Gerven and colleagues[31] further investigated the role of TRP channels and SP in idiopathic rhinitis. They enrolled 14 subjects with idiopathic rhinitis and 12 controls and treated them with capsaicin for 12 weeks. There were significant reductions in symptoms of nasal obstruction, sneezing, and rhinorrhea after 4- and 12-week treatment with intranasal capsaicin coupled with a decrease in the nasal responsiveness to cold-dry air (CDA) provocation. More importantly, from a mechanistic standpoint, mRNA expression of TRPV1 and levels of SP were significantly higher in the nasal mucosa of subjects with idiopathic rhinitis at baseline compared with that from normal controls and were significantly reduced by capsaicin treatment. Levels of CGRP were not detectable and those of NKA showed no significant differences between subjects and controls. This study provides elegant support for the role of TRPV1 as well as SP in the pathophysiology of NAR and at least partially explains the mechanism by which capsaicin exerts its beneficial actions in patients with NAR.

RESPONSE TO NASAL PROVOCATION

Another way to try to elucidate some facets of the pathophysiology of rhinitic conditions is to evaluate the responsiveness of the nasal mucosa to different challenges. Nasal challenge with allergen has been very useful in elucidating cellular events that are associated with the generation of symptoms of patients with allergic rhinitis and has also been very useful in evaluating response to different therapeutic agents and the elucidation of their mechanisms of action. In the context of NAR, challenge

with allergen has identified a group of subjects with local AR as mentioned earlier.[10] There are more limited data about other nasal provocation tests in NAR.

Histamine Challenge

Van De Heyning and colleagues[32] performed histamine nasal challenges in 53 subjects with chronic nasal symptoms and negative allergy testing and compared them to 11 subjects with no nasal complaints and negative allergy testing. The response to histamine provocation was measured by anterior rhinomanometry. Compared with normal controls, subjects with NAR had a higher nasal resistance at baseline and more reactivity to histamine as monitored by increase in the objective measure of nasal congestion. The dose of histamine that produced a 25% increase in nasal airway resistance was the best differentiator between subjects with NAR and controls and was significantly lower in the NAR group. A couple of other studies with smaller numbers and less rigorous characterization of study subjects suggested similar results.[33,34]

Cold-Dry Air Challenge

Many patients have significant history of nasal symptoms on exposure to CDA. This condition has been studied in the laboratory, and such patients will respond to a nasal challenge with CDA by generating nasal symptoms and releasing inflammatory mediators in nasal secretions, which include histamine, kinins, prostaglandins, and a marker of increased vascular permeability, suggesting a role for mast cell involvement.[35] Many responders to CDA do not have evidence of allergic disease and, thus, would qualify as having NAR in response to a specific trigger, CDA. In addition to investigating the pathophysiology of the CDA response in symptomatic individuals, CDA provocation has been used as a marker of nasal reactivity.

Braat and colleagues[36] compared CDA with histamine nasal challenge in differentiating patients with nonallergic, noninfectious perennial rhinitis from control subjects. The response was monitored by the weight of generated nasal secretions and nasal obstruction as measured by anterior rhinometry. The results suggested that CDA challenge was more suitable than histamine challenge in differentiating between NAR and controls as it had a much higher specificity than the histamine challenge. Van Gerven and colleagues[37] modified the protocol of CDA challenge by making it shorter and measuring symptoms and nasal peak flow after CDA, thus, simplifying the challenge and making it to be of potential use in clinical practice. They also demonstrate an increase in nasal obstruction (subjective and objective) after CDA in both patients with AR and NAR but not in healthy controls. Rhinorrhea and sneezing were not induced by this shortened challenge protocol. In another CDA provocation study, Shusterman and Tilles[38] demonstrated more symptoms and objective increase in nasal airway resistance in subjects with NAR compared with controls after CDA challenge. CDA challenge was successful in differentiating between the 2 groups if the subjects with NAR reported 2 or more triggers for their clinical symptoms. Similar results were obtained by Kim and Jang[39] who demonstrated a stronger response to CDA challenge in patients with both AR and NAR and the ability of nasal obstruction scores after CDA to differentiate between patients with NAR and controls.

Challenge with Capsaicin

Capsaicin has been used both to treat patients with NAR and as a challenge agent. It is a TRPV1 receptor agonist and has been shown to deplete neuropeptides in sensory nerves. If used for a prolonged period of time, it will lead to desensitization of the TRPV1 ion channels and improvement of the symptoms of NAR. Indeed, a recent

Cochrane review of available evidence shows that capsaicin seems to have beneficial effects on overall nasal symptoms up to 36 weeks after treatment, based on few small studies.[40] On the other hand, if used for short challenges, capsaicin generates significant symptoms and has been used to test nasal hyperreactivity.

Sanico and colleagues[41] performed nasal challenges with capsaicin in subjects with AR and NAR as well as normal controls and measured symptoms and levels of the glandular marker lactoferrin and the vascular permeability marker albumin in nasal secretions. They showed an increase in symptoms and lactoferrin in all 3 groups in response to capsaicin challenge and an increase in vascular permeability only in the allergic group, suggesting that NAR was not characterized by increased responsiveness to capsaicin. In contrast, Lambert and colleagues[42] challenged healthy controls and subjects with nonallergic irritant rhinitis with capsaicin and measured changes in nasal blood flow by optical rhinometry. Their results showed significantly higher optical density measurements in subjects with rhinitis compared with the healthy controls after capsaicin suggesting that this challenge could prove a viable option in the diagnosis of nonallergic irritant rhinitis. The difference between the two studies could be related to the different end points evaluated in response to capsaicin challenge. The first looked at glandular secretion and increased vascular permeability, whereas the second evaluated blood flow changes in the nasal mucosa. More work in this area would shed further light on the utility of capsaicin challenges in elucidating the mechanisms involved in the pathophysiology of NAR.

In summary, it is clear from the aforementioned information that the pathophysiologic events that underlie NAR have not been extensively investigated. In some subtypes, such as NARES and local AR, cellular inflammation is important akin to what investigators have shown in AR. In other subtypes, neurogenic factors and increased nasal reactivity to certain stimuli seem to be more important and dominant. Clearly, a more systematic effort is needed to elucidate the pathophysiology of NAR. This method would start by a careful phenotyping of these patients on multiple fronts, which would include type of symptoms and their temporal pattern; the type of environmental stimuli that trigger the symptoms; reactivity of the nasal mucosa to specific stimuli, such as histamine, CDA, and capsaicin; nasal cellular inflammation; prevalence of neuropeptides; and the role of the various TRP channels. Gaining this information would then allow better targeted therapies that would help relieve the symptoms in affected patients.

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