

Neural Abnormalities in Nonallergic Rhinitis

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Abstract Sensory nerve endings within the airway epithelial cells and the solitary chemoreceptor cells, synapsing with sensory nerves, respond to airborne irritants. Transient receptor potential (TRP) channels (A1 and V1 subtypes, specifically) on these nerve endings initiate local antidromic reflexes resulting in the release of neuropeptides such as substance P and calcitonin G-related peptides. These neuropeptides dilate epithelial submucosal blood vessels and may therefore increase transudation across these vessels resulting in submucosal edema, congestion, and rhinitis. Altered expression or activity of these TRP channels can therefore influence responsiveness to irritants. Besides these pathogenic mechanisms, additional mechanisms such as dysautonomia resulting in diminished sympathetic activity and comparative parasympathetic overactivity have also been suggested as a probable mechanism. Therapeutic effectiveness for this condition has been demonstrated through desensitization of TRPV1 channels with typical agonists such as capsaicin. Other agents effective in treating nonallergic rhinitis (NAR) such as azelastine have been demonstrated to exhibit TRPV1 channel activity through the modulation of Ca^{2+} signaling on sensory neurons and in nasal epithelial cells. Roles of antimuscarinic agents such as tiotropium in NAR have been suggested by associations of muscarinic cholinergic receptors with TRPV1. The associations between these channels have also been suggested as mechanisms of airway hyperreactivity in asthma. The concept of the united airway disease hypothesis suggests a significant association between rhinitis and asthma. This concept is supported by the development of late-onset asthma

in about 10–40 % of NAR patients who also exhibit a greater severity in their asthma. The factors and mechanisms associating NAR with nonallergic asthma are currently unknown. Nonetheless, free immunoglobulin light chains and microRNA alteration as mediators of these inflammatory conditions may play key roles in this association.

Keywords Neural · Nonallergic rhinitis · Capsaicin · Trigeminal · Irritants · Irritant-induced triggers · Allergic rhinitis · Inflammation · Tiotropium · Neurogenic · TRPA1 · TRPV1 · Sensory · Muscarinic · Dysautonomia · Asthma · Free immunoglobulin light chain

Introduction

Nonallergic rhinitis (NAR) is considered a diagnosis of exclusion [1] made typically when symptoms of nasal sinus congestion and anterior/posterior rhinorrhea are precipitated and worsened by exposure to non-immunologic stimuli e.g., irritants or changes in environmental humidity or temperature, without evidence of specific IgE responses by skin or serologic testing and without localized specific IgE production in the nose. Nasal cytology has been used to sub-characterize NAR conditions. For example, NAR with nasal eosinophils has been referred to as nonallergic rhinitis with eosinophilia (NARES) and NAR without nasal eosinophils has been termed vasomotor rhinitis (VMR) [2]. As a specific therapeutic agent, intranasal capsaicin has consistently been shown to improve nasal symptoms associated with NAR yet its mechanism of action in this condition has been poorly elucidated aside from its probable desensitization of transient receptor potential ion channels (TRPV1). However, symptomatic improvement of NAR with capsaicin suggests possible involvement of neurogenic pathways in the pathogenesis of this condition. A systematic review of the published

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scientific literature related to neurogenic mechanisms of NAR is therefore warranted. This review will attempt to highlight specific involvement of the sensory and sympathetic nervous systems in the probable neurogenic inflammatory mechanism of NAR. The probable innovative roles of transient receptor potential (TRP) channels and neuropeptides will also be reviewed.

Among patients with chronic rhinitis, it is estimated that 23 % have NAR, 34 % mixed rhinitis, and 43 % allergic rhinitis [3]. However, the prevalence of NAR has varied from 17 to 52 % in different studies which translates to an estimated 17 to 19 million Americans being affected by this condition [4, 3]. Demographic characteristics pertaining to NAR relate to age, gender, and perennial occurrence. About 70 % of patients diagnosed with NAR develop this condition in their adult life (age >20 years), in contrast to allergic rhinitis which typically develops before age 20 [3]. Moreover, there is very high probability that a patient with chronic rhinitis will have NAR (~96 %) if they have a history of late onset of symptoms (>35 years), symptoms triggered by irritant exposures, no seasonality or symptoms around furry pets and no family history of allergies [5]. Even though nonspecific irritant triggers have become an integral part of the diagnosis of NAR, a significant percentage of patients with NAR cannot determine triggers eliciting their symptoms and therefore the distinct response mechanism(s) to these various triggers other than nonspecific nasal hyperreactivity are unknown.

Localized IgE production to a specific aeroallergen in the nasal mucosa in conjunction with a positive nasal provocation test to that allergen in nonatopic rhinitis is defined as entopic rhinitis. This condition has been reported to exist in about 40 % of idiopathic rhinitis; however, this prevalence has not been confirmed by other investigators [6]. This cohort of allergic rhinitis (AR) may clinically be differentiated from NAR as it tends to have a better response to allergy-targeted therapies such as second-generation antihistamines and corticosteroids [6]. However, further investigation is still required to demonstrate mechanistically how localized IgE isotype class switching takes place in this AR subtype.

Limitations in Determining Neurogenic Mechanisms of NAR

In the USA, the prevalence ratio of allergic (pure and mixed combined) rhinitis to nonallergic rhinitis is approximately 3:1. However, the classification of NAR has been indistinct and therefore often overlaps with other rhinitis phenotypes. A logical pathogenic mechanism of NAR has not been described because most of the descriptive, pathophysiologic, and intervention studies have focused more on AR rather than on NAR [7]. Nonetheless, in patients with NAR, an increase in mucosal sensitivity and reactivity has been confirmed by

various studies conducting nasal provocation testing using various stimulants such as methacholine, histamine, cold dry air, and capsaicin. Nasal symptoms induced by these irritants or stimulants have been greater in rhinitis groups than in controls. However, comparison of allergic and nonallergic rhinitis patients has revealed an overlap in symptom responses. Comparison between such studies is not justified since differences in results observed between these studies may reflect differences in their study methodologies. In addition, more than one type of reaction can be elicited simultaneously with provocation, e.g., inflammatory mediator release and an exaggerated autonomic response. Therefore, several aspects need to be considered when studying the pathophysiology of NAR before a specific model can be established for this condition [3].

Pathophysiology of Nonallergic Rhinitis

Air quality affects olfaction and sensory irritant responses within nasal mucous membranes. Nasal airway reacts acutely or chronically to various airborne irritants through sensory or physiologic mechanisms. Ciliated cells dominate the normal nasal epithelium. Narrowing of the osteomeatal complex in some NAR subtypes is accompanied by replacement of ciliated cells by goblet cells. These pathological conditions result in epithelial mucin hypersecretion with decreased mucociliary activity [8]. Mean goblet cell density in the inferior turbinate as well their mucus secretory ratio have been observed to be higher in NAR compared to controls, but this difference was not statistically significant possibly due to the small sample size in these studies [9, 10]. Consequently, the pathological responses induced by irritant exposures can cause hypersecretion with or without associated inflammation and alteration in mucociliary clearance (Fig. 1) [7]. Other studies have reported that reduced mucociliary transport rate is associated with irritant-induced occupational exposures [11]. Secretions from anterior nasal glands, seromucous submucosal glands, serous/mucinous epithelial secretory cells, lacrimal glands, and transudation from blood vessels all contribute to nasal secretions. Furthermore, inflammatory mediators in pathologic rhinitis conditions increase transudation due to increase in vascular permeability [12].

A comprehensive understanding of nasal function is necessary to achieve a basic understanding of the possible pathophysiology of NAR. The pseudostratified ciliated columnar epithelium lines upper and lower respiratory tracts. Goblet cells, ciliated cells, and basal cells form this epithelial lining. These cells regulate olfaction and other conditioning functions of the nose including filtration with humidification of inspired air and temperature regulation. The nasal mucosa has a rich vascular supply and also secretes mucus. Lysozyme,

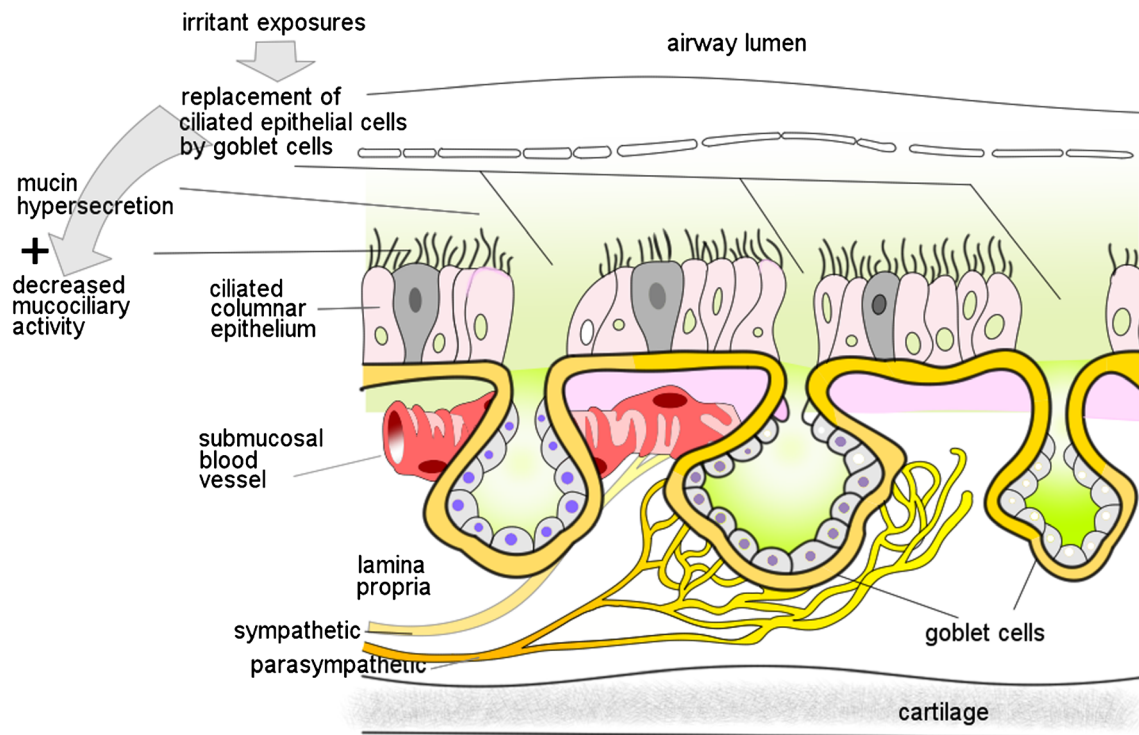


Fig. 1 Irritant-induced nasal airway metaplasia is manifested by replacement of ciliated columnar epithelial cells by goblet cells resulting in mucin hypersecretion by goblet cells and decreased mucociliary activity due to loss of ciliated cells

glycoproteins, lactoferrin, and secretory immunoglobulin A secreted in the mucus protect the airway. The cilia projecting into the epithelial surface force the mucous layer contents toward the natural sinus ostia and further down into the nasopharynx [13, 14••].

Autonomic and Sensory Innervation of the Nasal Mucosa

Alternate spontaneous engorgement and decongestion of nasal mucosa from one side to the other is referred to as the “nasal cycle.” These physiological events are regulated by the autonomic nervous system which alters the vasculature and glandular secretory responses [13, 15]. Nasal cycles between 30 min to 4 h have been conspicuously detected in humans [16, 17]. The functional significance of the nasal cycle is currently unknown. However, despite the reciprocal physiological changes between two sides of the nasal cavity, the total nasal airway resistance remains constant [17, 18]. Thus, the nasal cycle likely plays an important role in the respiratory function of the nose. It may also be involved in defense function of the nose by protecting against airborne irritants or in response to changes induced by autonomic stimuli [19]. Chronic exposures to airborne oxidant pollutant (e.g., ozone) can increase susceptibility to respiratory illness and infections. This susceptibility may be related to pollutant-induced nasal epithelial alterations resulting in impairment of

normal physiological functions such as filtration and mucociliary clearance important for protecting the distal airways from inhaled pollutants [20].

The trigeminal nerve relays sensory information from the nasal mucous membrane. Axons in the ethmoid and nasopalatine branches of the trigeminal nerve transmit afferent sensory input from the nasal epithelium, blood vessels, and secretory glands. These nerve endings extend close to the nasal epithelial surface and between tight junctions of epithelial cells. A subset of these nerves fibers, known as C-fibers, store neuropeptides such as substance P (SP) and calcitonin G-related peptides (CGRP). These nerve fibers respond to environmental irritants, pain, and variations in temperature and osmolarity. Irritants are believed to stimulate free nerve endings in the nasal epithelium, and therefore, these nerves may have relevance in the pathogenesis of NAR. Stimulation of C-fibers innervating nasal mucosal endothelial and epithelial cells increases vascular permeability and secretions from glands resulting in the production of mucoïd rhinorrhea [15]. A single ethmoid nerve axon may relay its branches to the nasal mucosa, olfactory bulb, as well as to the spinal trigeminal complex. In addition, other relevant sensory cells referred to as the solitary chemoreceptor cells (SCCs) are scattered throughout the nasal cavity. The SCCs synapse with trigeminal nerve fibers and may also react in response to chemical stimuli and sensory nasal irritants.

Role of Autonomic Nervous System in Hyperreactivity of Nasal Mucous Membrane

Clinical factors that may differentiate allergic rhinitis from NAR are seasonality, age of onset, family history, triggers (i.e., cats, dogs vs. irritant/chemical exposures), and better symptomatic response to H1-antihistamines [21]. In general, symptoms are not useful for differentiating allergic from nonallergic rhinitis [22]. The nonspecific and varied symptoms of NAR make it frequently difficult to differentiate from perennial AR. Therefore, investigating the specific pathophysiology of NAR is of utmost importance for identifying a discrete clinical phenotype for NAR. Currently, the suggested etiologies for NAR have been limited to chronic inflammation of the nasal mucosa, possibly associated with hypersensitivity of sensory C-fibers. A balance between sympathetic and parasympathetic systems regulates the vascular supply to the nasal mucosal membrane. The sympathetic and parasympathetic components of the autonomic nervous system form the efferent nasal reflex arc. Equal contributions from both components maintain a balance between the vasoconstriction and vasodilation of nasal vasculature and stimulation of serous glands [13, 15, 23]. This phenomenon maintains nasal patency by adjusting vascular engorgement that affects mucosal thickness. An imbalance of these components (dysautonomia) is believed to contribute to the sequence of events that lead to glandular hypersecretion [24]. Stimulation of the sympathetic nerve constricts resistance vessels and more prominently the capacitance vessels through alpha-adrenergic receptors and partially through a non-adrenergic and non-cholinergic mechanism. Parasympathetic non-cholinergic activity dilates both resistance and capacitance vessels which is more evident in the posterior venous system. Concurrent stimulation of the autonomic nerves constricts the capacitance vessels, which signifies that reduced sympathetic activity rather than parasympathetic overactivity may be more important in contributing to nasal congestion. Nonallergic rhinopathies may, therefore, result from loss of sympathetic tone that would normally cause arterial vasoconstriction and decrease in mucosal blood flow [25].

Role of Specific Neuropeptides Released from Sensory Nerve Endings in NAR

Aside from autonomic dysregulation, distinct immunologic or non-immunologic mechanisms of NAR are not yet established. No differences in olfaction have been found between chronic rhinitis subtypes (e.g., allergic, nonallergic, or mixed). Therefore, aberrant reactivity of patients to irritants and odorants constitutes other possible mechanisms in NAR [26]. Chronic inflammation due to irritant triggers may be a common mechanism for both, AR and nonallergic rhinitis (NAR) [27••, 28•, 29]. For NAR, however, none of the etiologies are systemically modulated by IgE as in AR.

Primary afferent neurons from the dorsal root ganglia form a perivascular web of fibers around the arterial systems. Exposures to nonallergic triggers, such as chemical, thermal, or mechanical irritation can precipitate rhinitis by activating TRPA1 and TRPV1 channels on nasal mucosal perivascular nerve fibers that initiate the release of neuropeptides such as CGRP from sensory nerve endings [30–34]. Irritant-induced release of peptides from peptidergic nerves through a local axonal reflex, referred to as antidromic reflex, facilitates vasodilation and plasma extravasation causing neurogenic edema and glandular hypersecretion [35]. CGRP-mediated vasodilatation occurs by nitric oxide (NO)-dependent and NO-independent mechanisms in a tissue-specific manner. Release of CGRP after TRPA1 and TRPV1 stimulation mediates vasodilation via NO-independent mechanisms (Fig. 2) [36]. Besides aggravating symptoms in NAR patients, this phenomenon may worsen symptoms in AR patients who also experience symptoms due to perennial allergens, a condition referred to as “mixed” rhinitis. Thus, *hyperresponsiveness* of the afferent sensory limb leads to an overwhelming efferent response. Similar symptoms may occur with normal afferent input along with a *hyperreactive* efferent arc. An intrinsic epithelial problem or an abnormality with the central nervous system regulation is a less common source of disordered responsiveness in NAR.

Substance P (SP) is a neuropeptide localized in afferent nerve fibers that are abundant along arteries and to some extent along veins and nasal glands [37]. SP mediates inflammatory effects through NK1 receptors localized in nasal and airway epithelium. Although SP levels are elevated in nasal secretions of patients with AR, various evidences support involvement of this neuropeptide in causing NAR. Capsaicin, an agent that depletes SP from sensory nerve endings, provides significant and long-lasting relief of symptoms in NAR [38••]. Sensory neuropeptides and inflammatory mediators cause gaping between the endothelial cells of postcapillary venules. Plasma then extravasates into the interstitium of mucosal membranes through these gaps. Minor increases in interstitial pressure further widen intercellular spaces between the epithelial cells and increases exudation of plasma into the airway lumen. These mechanisms may explain the possible etiology for the pathogenesis of NAR due to cold air, hyperosmolar solutions, and inflammatory mediators [39].

Osmotic challenge induces SP release into nasal secretions while worsening symptom scores in NAR patients [27••]. In response to odorants, NAR patients have also been demonstrated to have increased blood flow to several regions of brain relevant to olfactory sensation or sensory processing of irritant stimuli [40••]. In these studies, azelastine treatment significantly reduces SP release and improved vasomotor rhinitis symptom scores. This is consistent with significant attenuation of blood flow to regions of the brain associated with processing of olfactory or irritant stimuli. These mechanisms of action may account for clinical efficacy of topical azelastine in patients with perennial NAR symptoms which has been demonstrated in clinical studies.

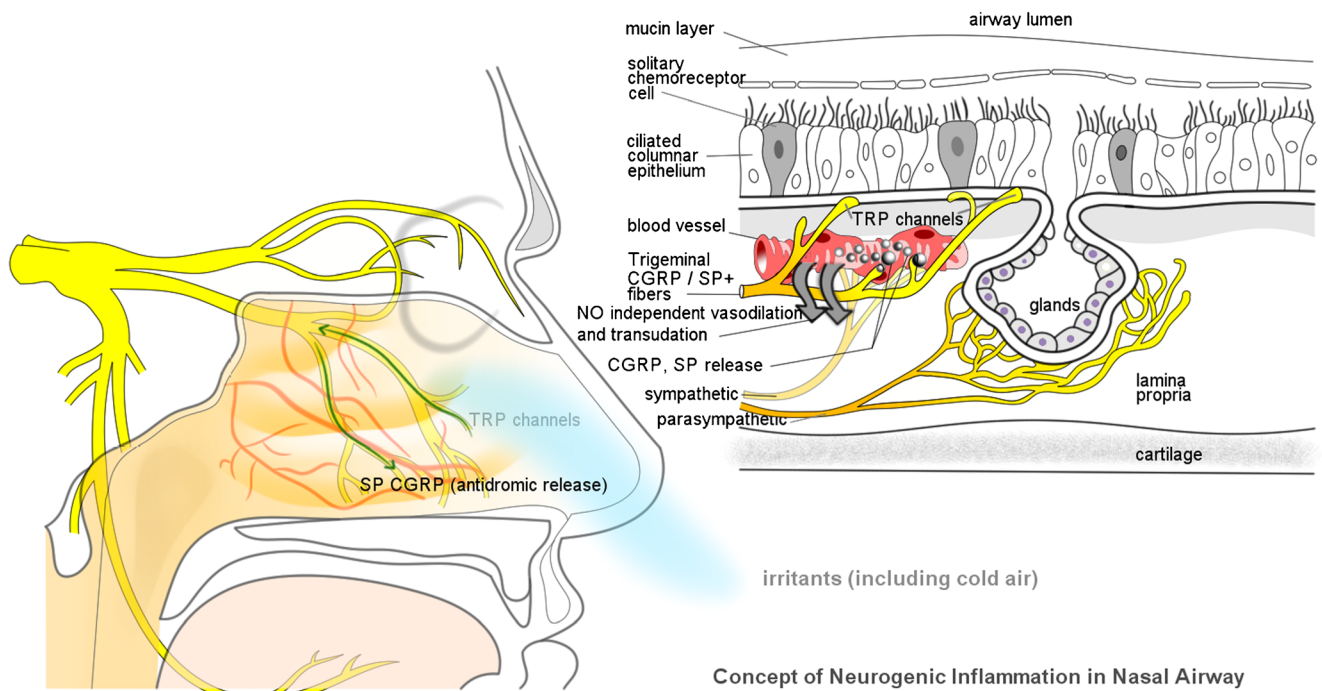


Fig. 2 TRP agonists promote the release of CGRP by activating peptidergic trigeminal sensory neurons resulting in relaxation of blood vessel smooth muscle causing vasodilation. Prostaglandins and bradykinins working through activation of their specific G protein-coupled receptors or indirectly through TRP channel activation can also

release neuropeptides. Neurogenic vasodilation in these conditions may therefore lead to neuronal sensitization. Exposures to environmental irritants can precipitate rhinitis by activating TRPA1 and TRPV1 channels on nasal mucosal perivascular nerve fibers that initiate the antidromic release of CGRP

Pro-algesic agents such as prostaglandins and bradykinin working through activation of their specific G protein-coupled receptors or indirectly through TRP channel activation can also contribute to neuropeptide release. Neurogenic vasodilation in these conditions may therefore lead to neuronal sensitization [41].

A decrease in tissue neutral endopeptidase (NEP) activity may amplify neurogenic vasodilation in the mucous membranes [42]. It has been demonstrated that a significant component of neurogenic vasodilation in rodent nasal mucosa is due to the stimulation of NK1 tachykinin receptors [43]. TRP channel stimulation releases tachykinins from sensory nerves which act on NK1 receptors to increase nasal blood flow via nitric oxide-dependent mechanisms. Therefore, NK1 receptor antagonists may be useful for investigating the role of NK1 receptors in neurogenic inflammation associated with NAR.

Nasal Cellular Infiltrate and MicroRNA as Determinants of Neurogenic Inflammation in NAR

In view of the above discussions, a detailed case history is currently the most important approach for establishing a diagnosis of NAR [44•, 45••]. Confirmation of a NAR diagnosis requires exclusion of specific sensitivities through skin prick

and/or serum-specific IgE testing and exclusion of structural problems using CAT scan imaging and/or nasal endoscopy to assess for chronic sinusitis and osteomeatal complex disease. Other adjunctive diagnostic testing may include nasal peak flow, anterior rhinomanometry or acoustic rhinometry to assess for nasal airway resistance; nasal provocation testing to assess specific triggers known to induce NAR symptoms such as cold dry air, cold to warm air changes, various odorants and chemicals; and nasal cytology which has been demonstrated to be potentially useful for subcategorizing NAR subtypes [46••]. Clinical symptoms vary between NAR with inflammation (NAR+) and NAR without inflammation (NAR-) and between different NAR+ subtypes. Nasal cell infiltrates influence symptom severity in NAR and therefore nasal cytology may differentiate these different phenotypes of NAR. For example, NAR with eosinophils and mast cells (singularly or mixed) has been reported to be associated with significantly higher symptom scores compared to NAR- or NAR with neutrophils [47]. Evidence of inflammation in more than half of NAR patients has been determined predominantly by cellular infiltrates in nasal cytology [47]. Despite these exclusionary approaches, there are no specific diagnostic tests or biomarkers that are useful for diagnosing NAR [47].

MicroRNAs regulate RNA expression including expression profiles in nasal mucosal inflammation induced by exposures to irritants as determined in experimental animal models and therefore could serve as a novel

approach for identifying biomarkers associated with NAR [48•]. Recently, human studies have determined significant expression of specific microRNAs (such as miR-155, miR-205, miR-498, and let-7e) in allergic nasal mucosal inflammation. However, none of these microRNAs (miRNAs) were significantly associated with nasal mucosal inflammation of NAR that was otherwise evident through nasal cytology [49•]. Therefore, the possible roles of other miRNAs in the pathogenesis of neurogenic inflammation in NAR remain to be established.

Roles of TRP Channels in Neurogenic Inflammation Mediating Pathogenesis of NAR

Cloning and functional characterization of channels activated by physical and chemical stimuli has led to better appreciation of the cellular and molecular mechanisms of chemosensation in the trigeminal system [50]. The following sections will outline a functional description of various sensory channels, especially TRP channels, involved in trigeminal chemosensitivity that likely play a significant role in the pathobiology of NAR.

Primary afferent nociceptors on trigeminal nerves innervating the nasal mucous membrane transduce adverse environmental stimuli into electrical impulses. Specific areas within the central nervous system interpret these transmitted signals [32]. Transient receptor potential (TRP) channels represent a group of peripheral nociceptors that are ubiquitous throughout the respiratory tract [33]. Here these channels mediate neurovascular reflexes and have significant physiological roles in detecting and reacting to multiple stimuli, e.g., changes in temperature, osmolarity, and oxidant stress. Expression or activity of TRP channels are altered in various diseases. As suggested by indirect evidences, NAR patients may have altered TRP channel function that are affected by exogenous and endogenous factors such as environmental irritants and oxidative and mechanical stresses [51••]. Modulators of TRP channel

function are therefore under investigation for a range of diseases including upper and lower respiratory tract disorders [52••]. Regulation of TRP channel function can modify common and unique features of respiratory diseases, such as mucus hypersecretion, airway inflammation, and hyperresponsiveness as well as airway remodeling. There are specific TRP channels that are more likely involved in NAR pathogenesis and therefore may have important mechanistic roles in NAR.

Transient receptor potential ankyrin 1 (TRPA1) channels expressed on sensory neurons, specifically C-fibers, innervating nasal mucous membrane are oxidant sensors in sensory nerve terminals. These channels initiate neuronal excitation and subsequent physiological responses mediated through neuropeptide release following activation-induced elevations of intracellular calcium and redox factors [53]. Deleterious stimuli including noxious cold temperatures, reactive electrophilic molecules produced by oxidant stress and inflammation, nicotine, and mustard oil activate these channels through covalent protein modification [32, 54•, 41, 55]. Protective physiological responses to these stimuli in healthy individuals include rhinorrhea and increased mucin (MUC5B) production; however, disease states such as NAR with significant overexpression and activity of TRPA1 in small diameter nociceptive neurons would likely have exaggerated sensations to these noxious stimuli leading to neurogenic inflammation [56]. These channels are co-expressed with TRP channels belonging to the vanilloid subfamily (TRPV1) in nasal mucous membranes. Co-expression modulates agonist-induced TRPA1 desensitization and thereby prevents TRPA1 internalization [57, 30]. Activation-induced calcium signaling through these channels activates phospholipase C in sensory neurons and therefore increases TRPA1 sensitivity by releasing these channels from inhibition by plasma membrane phosphatidylinositol 4,5-bisphosphate (PIP₂) (Fig. 3). Through poorly understood mechanisms, the chronic changes in PIP₂ (the substrate for PLC) levels regulate TRPA1 and TRPV1 agonist responses and can produce TRPA1 tachyphylaxis to their typical agonists [54•]. Activation of co-expressed TRPA1 and

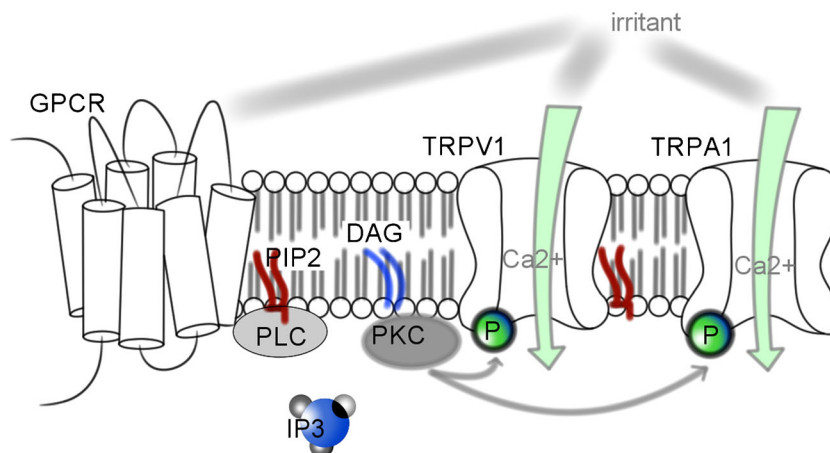


Fig. 3 Co-localization of TRPA1 and TRPV1 modulates desensitization of TRPA1 by preventing internalization of TRPA1

TRPV1 by components of environmental pollutants, such as acrolein (a surrogate marker for tobacco smoke), may be good models for studying their mechanistic roles in NAR [31]. N-terminal ankyrin repeat domains of these channels are the regions that functionally integrate diverse physiological signals and could have an important functional role for regulating sensory neuronal activity in response to chemical irritants.

TRPV4 channels respond to osmotic stress, mechanical stimuli, and changes in temperature. These channels regulate cell volume as well as other physiologic responses to osmotic stress and mucus homeostasis [58, 59]. Therefore, the neurogenic mechanism for NAR may also be mediated by TRPV4 overexpression [59]. Significant overexpression of these channels has been demonstrated in mucosal secretory cells of patients with chronic rhinosinusitis (CRS). TRPV4 channels are co-expressed with protease activated receptor 2 (PAR2) and neuropeptides, such as SP and CGRP, on dorsal root ganglia or on airway epithelial cells. Inflammatory processes generate proteases that cleave PAR2 and activate second messengers. This process promotes TRPV4-dependent release of nociceptive neuropeptides [60]. Thus, TRPV4 channel-sustained activity in neurogenic inflammation is dependent on inflammatory proteases that cleave and activate PAR2 receptors. Solitary chemoreceptor cells (SCCs) that include TRP-melastatin-5 (TRPM5)-enriched sensory cells are present throughout the upper and lower respiratory tracts and respond to irritants [61, 62]. Experimental evidence in animal models suggests that SCCs are linked to the neurogenic inflammatory mechanisms through cholinergic neurotransmission that trigger peptidergic trigeminal nociceptors [62]. In these experiments, ablating the peptidergic nerve fibers or blocking nicotinic acetylcholine receptors prevented SCC-mediated nasal inflammation.

The cold and menthol receptor, TRPM8, regulates vascular tone and mediates neurovascular reflexes [33, 63]. These channels are expressed extensively on the sensory nerve fibers branching to the sub-epithelium of nasal mucosal membrane and around the microvasculature in these regions. Their expression in NAR patients do not appear to be significantly greater compared to healthy subjects.

TRP Channels as Therapeutic Targets in NAR

In addition to the roles proposed for TRPA1 inhibitors in suppressing unfavorable tissue remodeling, inflammation in asthma, or stroke, these agents may also be helpful in modulating or preventing pathogenic responses in NAR [41]. Functional approaches for therapeutic management of NAR should emphasize desensitization of TRP ion channels on sensory afferent nerves which are ubiquitous in the nasal mucosal membranes [64, 65]. Because of the overexpression of TRPV1 channels in the human airway epithelium of NAR and asthma patients, these channels might represent an innovative therapeutic target

for managing NAR and uncontrolled asthma [65, 66]. Pharmacologic agents effective in treating nonallergic rhinitis such as azelastine have recently been demonstrated in vitro to modulate Ca^{2+} signaling in neuronal and nasal epithelial cells and thus desensitize TRPV1 channels in neuronal cells and regulate cellular homeostasis in nasal epithelial cells. Further work on primary nasal cells from NAR patients is needed to verify the mechanism of action for this agent specifically through TRPV1. Interestingly, other agents currently used to treat NAR such as olopatadine and fluticasone do not demonstrate specific activity on TRPV1 [67].

Recent studies have determined inhibition of TRPV1 but not TRPA1 channels by the structurally similar muscarinic antagonists, tiotropium and ipratropium [68]. These agents inhibited TRPV1-specific responses in isolated guinea pig vaginal tissue, whereas atropine (antimuscarinic agent) did not. These studies suggest that symptoms mediated by neuronal TRPV1 are inhibited by tiotropium via mechanisms distinct from its anticholinergic action.

Alternatively, the vasodilatory effects of muscarinic agonists on muscarinic acetylcholine receptors may be mediated by TRPV1 channels downstream of the muscarinic acetylcholine receptors (Fig. 4).

Association between muscarinic receptors and TRPV1 channels has been demonstrated in the CNS. In these regions, the striatal inhibitory postsynaptic currents (IPSCs) are reduced by inhibiting acetylcholine degradation and by stimulation of muscarinic (M1) receptors. TRPV1 agonists such as capsaicin prevent the effects of M1 receptor activation on IPSC (i.e., M1 receptor-mediated reduction in IPSC is prevented by possible desensitization of TRPV1). Tiotropium is recognized as an antimuscarinic agent. It has bronchodilator, anti-inflammatory, and mucolytic properties. Because of the demonstrated associations between TRPV1 and M1 receptor activity, the antimuscarinic activity (antitussive responses) of tiotropium could be hypothesized to be secondary to the modulation of airway sensory nerves through its primary activity on TRPV1 [69]. Thus, it can be reasoned that the anticholinergic effects of ipratropium and tiotropium may be due to the modulation of TRPV1 channels and not directly on the muscarinic receptors as suggested in Figure 4. This proposed mechanism of action

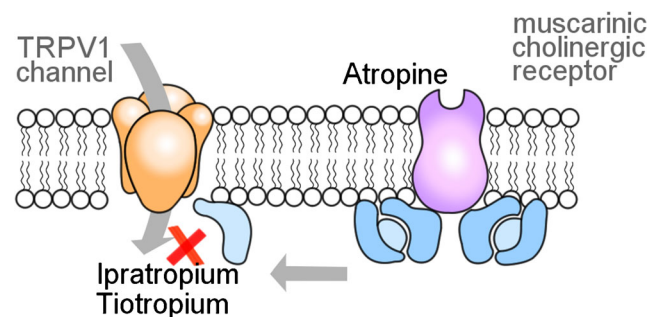


Fig. 4 Hypothetical mechanism of action of ipratropium and tiotropium on TRP channels downstream of muscarinic cholinergic receptors

of ipratropium and tiotropium may more aptly explain their usefulness in airway inflammation and hyperresponsiveness due to neuronal mechanisms initiated by various stimuli acting through TRP channels including capsaicin, environmental tobacco smoke, inflammatory mediators, and cold and dry air [70].

Association Between NAR and Nonallergic Asthma

Released Neuropeptides May Promote Neurogenic Inflammation in both NAR and Asthma

Patients with NAR have a high association with asthma with an estimated 10–40 % of NAR rhinitis patients developing late-onset asthma [71, 72••, 73•]. Moreover, asthma symptom severity is greater in patients with rhinitis [73•]. Studies investigating such associations have revealed that environmental irritants act as modulators of allergic or nonallergic inflammation in these contiguous airways [71, 72••]. NAR patients with a high irritant index trigger burden (34 %) have been found to be more likely to have a physician diagnosis of asthma compared to NAR patients with a low irritant index burden (~13 %) [72••]. Although atopy is a strong predictor of asthma, a significant percentage of individuals suffering from asthma and rhinitis do not produce specific IgE responses to allergens [74]. This implies that the pathophysiology of asthma could involve nonallergic inflammatory pathways [74]. In addition, the severity of asthma correlates with TRPV1 expression in bronchial epithelium [75••]. Therefore, it is implied that, as in rhinitis, the TRP channels located on airway sensory nerves may be important for the development of AHR in asthma through the release of neuropeptides upon activation by irritants [73•]. As in rhinitis, the role of neuropeptides in irritant-induced inflammation of lower airways have been supported by high levels of SP in the airway secretion irrespective of allergic status [76•].

These observations, in addition to the united airways disease hypothesis, support the concept of neurogenic inflammation, induced by chronic exposures to irritants or harsh environments, as a predominant mechanism explaining the relationship between nonatopic asthma and NAR. Airway sensory neurons in this circumstance perceive the presence of irritants or adverse stimuli and activate TRPA1 or TRPV1 which as discussed for NAR may also perpetuate airway inflammation in asthma [77]. However, despite these observations, the exact pathogenic mechanism by which rhinitis progresses to asthma is currently unknown.

Free Immunoglobulin Light Chains as Mediators of Inflammatory Reactions in NAR and Asthma

In several chronic inflammatory diseases, mast cell activation and release of bioactive mediators play a critical role in allergic asthma pathogenesis. However, mast cells may also play an important role in the development of NAR and nonallergic

asthma. Nasal mucosa of some subjects with idiopathic NAR has significantly higher levels of mast cells compared with normal control subject mucosa [78]. Mast cells can be activated by a byproduct of B lymphocytes, the free immunoglobulin light chains (IgFLC) [79]. Although the roles of IgFLC are well known for cancers, their roles in noncancerous inflammatory disorders are only recently being investigated. IgFLC-induced mast cell activation releases pro-inflammatory mediators that subsequently contribute to inflammatory responses. Positive correlations between levels of IgFLC (kappa/lambda) and mast cell tryptase are seen in nasal secretions of NAR patients [80•]. Moreover, serum mRNA expression of IgFLC (lambda) also correlates positively with eosinophilic cationic proteins (ECP) in these patients. In addition, the serum concentration of free immunoglobulin light chains are increased in individuals with nonallergic as well as with allergic rhinitis compared to healthy controls. Irrespective of the atopic status, the patient with persistent rhinitis have more mast cell numbers expressing free immunoglobulin light chains in immunohistochemical analysis of nasal mucosal biopsies, compared to healthy controls [80•]. Therefore, the role of free light chain (FLC) in nonallergic chronic inflammation of the upper airway is suggested by the high association of FLCs with mast cells and plasma cells in the nasal mucosa of NAR patients [79].

RNA interference has been shown to significantly reduce free light chain synthesis [81]. Therefore, such findings provide a future basis to investigate the roles of microRNAs specifically regulating FLC mRNA expression. Accordingly, reduced levels of these microRNAs have prognostic indicators for the development of NAR. Although a few miRNA specific to allergic inflammation of nasal mucosa have been determined, they are presently not known to be associated with NAR or asthma. NAR-specific microRNAs as biomarkers of this non-allergic condition could therefore hold promise for determining the definitive molecular pathways in NAR as well as further elucidate the probable association of NAR with asthma.

Role of Long-Acting Antimuscarinic Agents as an Add-on Therapy in Asthma

Clinical trials and meta-analysis have demonstrated the effectiveness of tiotropium as an add-on therapy to standard asthma treatment with high-dose inhaled corticosteroids/long-acting β_2 -agonists (ICS/LABA) in patients with severe asthma. The addition of tiotropium improved asthma control and lung function as well as reduced emergency visits and hospital admissions for asthma [82••, 83•, 84••]. Animal models of asthma have demonstrated an increased expression of TRPV1 and $[Ca^{2+}]$ currents in airway smooth muscle cells [85•, 86]. Because of the possible modulation of TRPV1 channels in airway sensory nerves by long-acting antimuscarinic agents (LAMA) such as tiotropium, future therapies for severe asthma should also target TRPV1 channels [85•, 86].

Conclusion

1. Chronic rhinitis is difficult to differentiate clinically based on symptoms alone. Modified questionnaires incorporating irritant indices are necessary to classify rhinitis, i.e., allergic (AR) vs. nonallergic rhinitis (NAR) more accurately.
2. Transient receptor potential (TRP) ion channels on sensory nerve endings on nasal mucosa act as primary irritant sensors.
3. Following activation of TRP channels, the local antidromic reflexes mediated by neuropeptides released from nerve ending cause vasodilation and consequent increase in transudation.
4. Sympathetic dysautonomia reduces the vasoconstrictive effect on mucosal vasculature and therefore may be involved in the pathogenesis of NAR.
5. Epigenetic changes manifested by irritant-induced changes in microRNA profiles leading to differences in TRP channel expression or activity in addition to alterations in other signaling pathway may be useful as biomarkers of NAR.
6. In the future, therapeutic options for treating NAR could target desensitization of TRP channels or using antagomirs and miRNA mimickers to target defective miRNAs.
7. Occurrence of NAR appears to predispose patients to developing asthma but the pathogenesis of this interaction remains poorly defined.

Compliance with Ethics Guidelines

Conflict of Interest Jonathan Bernstein reports grants and personal fees from Meda and grants from BI. Umesh Singh declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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