Neurology of Allergic Inflammation and Rhinitis

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Afferent nerves, derived from the trigeminal ganglion, and postganglionic autonomic nerves, derived from sympathetic and parasympathetic ganglia expressing many different neurotransmitters, innervate the nose. Reflexes that serve to optimize the air-conditioning function of the nose by altering sinus blood flow, or serve to protect the nasal mucosal surface by mucus secretion, vasodilatation, and sneezing, can be initiated by a variety of stimuli, including allergen, cold air, and chemical irritation. Activation of nasal afferent nerves can also have profound effects on respiration, heart rate, blood pressure, and airway caliber (the diving response). Dysregulation of the nerves in the nose plays an integral role in the pathogenesis of allergic rhinitis. Axon reflexes can precipitate inflammatory responses in the nose, resulting in plasma extravasation and inflammatory cell recruitment, while allergic inflammation can produce neuronal hyper-responsivenesss. Targeting the neuronal dysregulation in the nose may be beneficial in treating upper airway disease.

Introduction

Nerve fibers innervating the mucosa and capacitance vessels of the nose are loaded with an arsenal of neurotransmitters that can induce multiple effects on nasal function [1]. Alterations in neuronal action, induced either reflexively or by therapeutic interventions that counteract or dampen the effects of these nerves in the nose, reveal the essential role played by the nervous system in regulating all of the major symptoms of rhinitis, including mucus secretion, sneezing, and congestion [1–3,4••,5]. It follows logically that dysfunction or dysregulation of upper airway nerves might contribute to the pathogenesis of rhinitis.

The symptoms of allergen-induced rhinitis, the most common cause, are produced secondary to the interactions of specific aeroallergens with IgE bound to cell surface receptors on immune cells such as mast cells, basophils, and perhaps eosinophils and monocytes [4••,5–7]. Pharmacologic evidence in support of this hypothesis is apparent from the efficacy of antihistamines and leukotriene antagonists in the treatment of allergic rhinitis [8,9]. Neuronal reflexes play a prominent role in the pathogenesis of allergic rhinitis, and the response to mast cell- and basophil-derived mediators [1,3,7]. The inflammation associated with allergen exposure produces profound hyper-reflexia in the nose [10,11•,12]. Recent studies indicate that neuronal activation can precipitate inflammation of the human nasal mucosa through axonal reflexes [13,14•]. These and other observations highlight the integral role played by the nervous system in rhinitis.

Afferent Innervation of the Nasal Mucosa

Afferent innervation of the nose not associated with olfaction is derived primarily from the trigeminal ganglion [15••,16,17]. Unlike the airways where multiple afferent nerve subtypes have been defined based on their morphologic properties and responsiveness to specific chemical and mechanical stimuli [18], similar subtypes have not been described in the nose. It is likely that the difficulty with which these nerves are accessed contributes to this gap in our knowledge.

Afferent nerve fibers innervate the nasal mucosa branch extensively, innervating the epithelium, vessels, and glands of nasal mucosa [16,17]. Studies in animals suggest that the majority of afferent fibers innervating the nasal mucosa are unmyelinated C-fibers [16,17]. The extensive branching and innervation of multiple effectors in the mucosa, along with synthesis and peripheral transport of neuropeptides with many potential actions in the nose and nasal mucosa, provides the anatomic substrate necessary for producing axonal reflexes.

Reflexes can be initiated in the nose by a variety of stimuli, including mechanical probing, hypertonic saline, cold and/or dry air, histamine, allergen, nicotine, bradykinin, and capsaicin [1,3,5,10,12,19] (Fig. 1). In the lower airways, bradykinin, capsaicin, and hypertonic saline are relatively selective stimulants of nociceptor-like C-fibers, while histamine and allergens activate airway mechanoreceptors indirectly, secondary to their effects on lung mechanics (more specifically, dynamic lung compliance [18]). Whether stimuli such as histamine and bradykinin activate afferent nerve subtypes in the nose is unknown. It is interesting, however, that while both histamine and

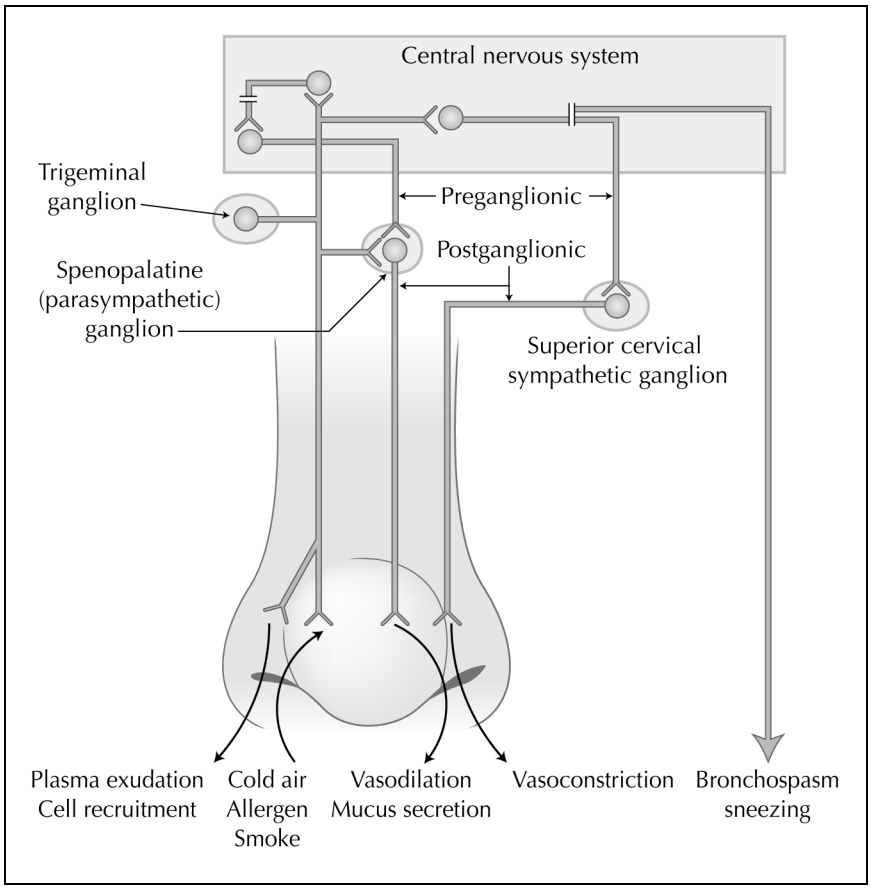

Figure 1. Schematic representation of the innervation of the nose. The trigeminal ganglion provides afferent innervation to the nose (depicted on the left side of the schematic nose). Afferent nerves innervating the nose branch extensively, innervating the epithelium, glands, and the vasculature. When stimulated, nasal afferents can release neuropeptides such as substance P during axon reflexes, resulting in vasodilatation, plasma exudation, mucus secretion and inflammatory cell recruitment. The autonomic (sympathetic and parasympathetic) innervation of the nose is depicted on the right side view of the schematic. Postganglionic sympathetic and parasympathetic nerves innervating the nose arise from the superior cervical ganglia and the sphenopalatine ganglion, respectively. Autonomic nerves synthesize and release a variety of neurotransmitters, including the vasodilators and/or mucus secretagogues VIP, nitric oxide and acetylcholine, and the vasoconstrictors noradrenaline and NPY (see Table 1). Parasympathetic nerve stimulation induces mucus secretion and vasodilatation. Sympathetic nerves have little direct influence on mucus secretion but mediate vasococonstriction. Preganglionic nerves regulating autonomic outflow to the nose arise from the facial nerve nuclei (parasympathetic) and thoracic spinal cord (sympathetic). Synaptic transmission in the sphenopalatine ganglion might be modulated by peripheral reflex regulation from collaterals of trigeminal afferent nerves.

bradykinin, when applied selectively and locally to the nasal mucosa, initiate reflex-mediated, atropine-sensitive mucus secretion in the contralateral nasal passage, only histamine readily initiates sneezing in normal patients [4••,5,10,11•]. Whether this distinction is due to effects on afferent nerve subtypes or to the intensity of activation of one afferent nerve subtype evoked by the autacoids is not clear. Circumstantial evidence based on c-fos expression in the brain indicates that afferent nerve subtypes innervating the nasal mucosa may exist [20].

Efferent Innervation of the Nasal Vasculature and Glands

Retrograde neuronal tracing studies, immunohistochemistry, selective denervation, and electrical stimulation of specific autonomic pathways have been used to define the origin and chemical neuroanatomy of the autonomic nerves innervating the nose of animals (Fig. 1, Table 1). Both sympathetic and parasympathetic nerves innervate the vasculature and glands of the nasal mucosa in animals. Postganglionic sympathetic nerves arise from the superior cervical ganglia. Postganglionic parasympathetic nerves arise from the sphenopalatine ganglion. Neurotransmitters associated with parasympathetic nerves innervating the nose include acetylcholine, vasoactive intestinal peptide (VIP and related peptides), neuropeptide Y, nitric oxide (NO, synthesized from arginine by the neuronal isoform of NO synthase), enkephalin, and somatostatin. Neurotransmitters associated with sympathetic nerves innervating the nasal mucosa include norepinephrine, neuropeptide Y and somatostatin [21–25].

Many experimental approaches used to define the innervation of the nasal mucosa in animals are not feasible in human subjects, and thus there is no definitive evidence for the origin and nature (sympathetic, parasympathetic, afferent) of specific nerve fiber subtypes innervating the nasal glands and vessels. The available evidence would suggest, however, that the innervation of the human nasal mucosa is comparable to that found in animals. Thus, the chemically defined nerve fiber subtypes described in animals are present in the human nasal mucosa. Moreover, NPY and norepinephrine mediate vasoconstriction, while VIP, NO, and acetylcholine mediate vasodilatation and/or mucus secretion in the nose in all species studied, including humans [1,21–30].

Studies conducted in animals using selective stimulation of autonomic nerve pathways, and pharmacologic studies in human subjects suggest that the sympathetic and parasympathetic nerves have opposing actions on structures in the nasal mucosa (Fig. 1, Table 1). The parasympathetic nerves and the neurotransmitters primarily associated with parasympathetic nerves mediate mucus secretion and/or vasodilatation. Conversely, the sympathetic nerves and neurotransmitters primarily associated with sympathetic

Table 1. Neurotransmitters found in nerve fibers innervating the nasal mucosa: origin and effects on nasal function

Neurotransmitters*	Origin†	Effects in the nose
Acetylcholine	Parasympathetic	Vasodilatation, mucus secretion
VIP‡	Parasympathetic	Vasodilatation, mucus secretion
Nitric Oxide§	Parasympathetic	Vasodilatation
Norepinephrine	Sympathetic	Vasoconstriction
Neuropeptide Y	Sympathetic	Vasoconstriction
CGRP¶	Afferent	Vasodilatation
Tachykinins	Afferent	vasodilatation, Plasma exudation, inflammation, mucus secretion

*Other putative neurotransmitters have been localized to nerve fibers in the nose (*eg*, gastrin releasing peptide, galanin, enkephalin). Their function, however, is poorly characterized.
†Several neurotransmitters (*eg*, neuropeptide Y, VIP) localized to nerve fibers innervating the nasal mucosa are found in both sympathetic and parasympathetic nerves. Their primary origin is listed.
‡Vasoactive intestinal peptide and related peptides (peptide histidine isoleucine (PHI), peptide histidine methionine (PHM), pituitary adenylate cyclase activating peptide (PACAP).
§Synthesized from arginine by nitric oxide synthase.
¶Calcitonin gene-related peptide

nerves have little or no effect on mucus secretion but constrict the blood vessels of the nasal mucosa and the capacitance vessels of the sinuses. The opposing actions of these systems likely determine levels of end organ function in the nose [1,21–30]. Postganglionic nerves might also interact prejunctionally on adjacent autonomic nerve endings to modulate neurotransmitter release [1,23].

Reflexes Regulating Nasal Function

The nose filters and conditions inspired air. Reflexes initiated by activation of upper airway afferent nerves serve to preserve this conditioning function of the nose. Nasal reflexes also play an important defensive role for the exposed nasal mucosa, hindering infection and clearing inhaled pathogens and irritants either by sneezing or with mucus secretion. As mentioned above, such reflexes are initiated by a variety of physical and chemical stimuli.

Trigeminal afferent nerves terminate bilaterally and centrally in lateral regions of the pons, medulla and cervical spinal cord, either rostrally in the principal sensory nuclei of the trigeminal nerve, and/or caudally in the spinal trigeminal nuclei [20,31,32]. The spinal trigeminal nuclei occupy extensive portions of the midbrain and cranial spinal cord and lie lateral but adjacent to many key structures in the brainstem relevant to the airways. The proximity of trigeminal afferent nerve terminations to brainstem structures involved in regulation of airway function and respiration may facilitate coordination of respiratory reflexes. This arrangement also provides the anatomic substrate for reflex effects on the lower airways initiated by upper airway afferent activation.

When activated, nociceptor-like afferent nerves can release their neurotransmitters in the periphery via axon reflex. Axon reflexes are well characterized in the lower airways of rodents and guinea pigs and have also been described in the skin of several species including humans [18]. Studies conducted in human subjects indicate that axonal reflexes might also play an important role in the nose as well. Thus, capsaicin, hypertonic saline or bradykinin challenge evokes mucus secretion, plasma extravasation, substance P release and inflammatory cell recruitment [10,11•,12,13,14•]. The neurotransmitters mediating these effects have not been identified. Neurokinins such as substance P do, however, initiate comparable effects when applied selectively to the human nasal mucosa, and substance P-containing nerve fibers innervate the human nasal mucosa [16,27,29,30].

Collaterals of neuropeptide-containing trigeminal afferent nerves may also project axons to the sphenopalatine ganglion [33]. This suggests that trigeminal afferent nerves might regulate parasympathetic nerve activity independent of the central nervous system via peripheral reflexes.

Neuronal Hyper-responsiveness of the Upper Airways in Rhinitis

Symptomatic allergic rhinitics have heightened responsiveness to stimuli that activate nasal mucosal afferent nerves [10,11•,12]. Seasonal-allergic rhinitic patients in season have exaggerated secretory responses in contralateral nasal mucosa following unilateral challenge with the inflammatory peptide bradykinin [10,11•]. These exaggerated responses are markedly reduced or abolished by atropine pretreatment, confirming the reflexive nature of the responses. Importantly, whereas seasonal allergic patients do not sneeze when challenged with bradykinin out of season, most of these patients sneeze following nasal bradykinin challenge when studied in season and having symptoms of allergic inflammation and rhinitis [11•].

The mechanisms for the heightened neuronal responsiveness associated with allergic inflammation are

unknown. Since the effects of allergic inflammation are not specific for bradykinin (heightened neural responsiveness to endothelin-1 and capsaicin has also been noted [12,34]), it would seem that the allergic inflammation has direct effects on neuronal excitability. The enhanced sneezing and secretion reflexes would indicate that the afferent nerves become hyperexcitable during allergic inflammation. Interestingly, there may be hyperinnervation of the nasal mucosa in rhinitis [35•]. Inflammation may thus initiate changes in neuronal function and pattern of innervation [36]. It is unclear what, if any, effect inflammation has on the autonomic nerves innervating the nose.

Potential mechanisms whereby allergic inflammation could enhance afferent neuronal excitability are numerous. Mediators of the immediate hypersensitivity allergic response such as histamine, prostaglandin D2, and the cysteinyl-leukotrienes are known to enhance neuronal excitability and obviously play a prominent role in the pathogenesis of rhinitis [8,9,37]. Other potential mediators of nasal afferent nerve hyper-responsiveness are tumor necrosis factor α (TNFα) and interleukin-1β (IL-1β). TNFα and IL-1β may be produced by mast cells or by resident cells activated by mast cell-derived mediators [38]. TNFα and IL-1β enhance afferent nerve excitability [39]. Chemokines, which may be released from epithelial cells during allergic inflammation, might also enhance afferent nerve excitability [40]. Eosinophil cationic protein (ECP) might also mediate the enhanced responsiveness of nasal afferent nerves. Eosinophils are recruited to the nasal mucosa during allergen challenge [41]. Activated eosinophils release ECP that can in turn activate airways C-fibers and might enhance their excitability to subsequent stimulation [42]. It is likely that many additional mediators could precipitate neuronal hyper-responsiveness in the nose. These issues await careful pharmacologic analyses, using selective antagonists of mediators associated with the allergic response.

The role of neurotrophins in allergen-induced neuronal hyper-responsiveness in the nose may also be worthy of further investigation [43•]. Neurotrophins, typified by nerve growth factor (NGF), are found in the airways and serum of allergic patients [44–46]. Allergen challenge markedly enhances neurotrophin release in the airways, while allergic asthmatics have exceedingly high NGF levels in serum relative to nonasthmatic patients [44–46]. NGF induces hyperalgesia in somatic tissues [39]. In transgenic animals, NGF overexpression produces hyperinnervation (both afferent and efferent nerves) in multiple tissues including the lungs [47]. Selective overexpression of NGF in mouse airways induces airways hyper-responsiveness [47]. Interestingly, NGF induces preprotachykinin gene expression in airway afferent nerves, mimicking exactly the effects of allergen on airway afferent nerves [48,49]. Potential sources of neurotrophins include the epithelium, T-cells, and mast cells [43•]. Other mediators associated with the airway mucosa that have neurotrophic effects include leukemia inhibitory factor, IL-6, IL-11, and endothelin-3 [50–52].

Effects of Rhinitis on Lower Airway Function: Potential Role of Nerves

It is well established that stimulation of the nasal mucosa in animals precipitates reflex bronchospasm [53]. Circumstantial evidence supports the hypothesis that similar reflexes initiated in the nose of allergic rhinitics might exacerbate lower airways disease [54]. The severity of asthma symptoms correlates with the symptoms of allergic rhinitis. Moreover, treating the symptoms of allergic rhinitis reduces symptoms of asthma, whereas inducing allergic inflammation in the nose worsens it. Attempts to associate these consequences of allergic rhinitis on the lower airways with altered neural reflexes have yielded conflicting results. Given that the necessary anatomical substrate for producing such reflexes exists, and that there is clear evidence for reflex bronchospasm initiated from the nose, it is reasonable to assume that afferent hyperexcitability in the nose will worsen the symptoms and physiology of asthma through neuronal mechanisms. This effect of rhinitis in asthma is analogous to the effects of gastroesophageal reflux disease in asthma [55]. Reflux disease, like rhinitis, is one of the most common causes of chronic cough [56]. Patients with reflux disease develop asthma-like symptoms that can be reversed or abolished entirely by treating the reflux. It is likely that the pulmonary symptoms are neurally mediated and initiated from the esophagus, as refluxate rarely, if ever, reaches the upper esophagus, much less the pharynx or airways, and reflux-induced bronchospasm is abolished by anticholinergics.

Conclusions

The nervous system plays an essential role in regulating nasal function. Dysfunction of the nerves innervating the nose likely contributes to the pathogenesis of rhinitis. Allergic inflammation initiates hyper-reflexia in the nose by mechanisms that have not been clearly elucidated. This hyper-reflexia might exacerbate pre-existing conditions such as asthma.

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