Nasonasal Reflexes, the Nasal Cycle, and Sneeze

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The nasal mucosa is a complex tissue that interacts with its environment and effects local and systemic changes. Receptors in the nose receive signals from stimuli, and respond locally through afferent, nociceptive, type C neurons to elicit nasonasal reflex responses mediated via cholinergic neurons. This efferent limb leads to responses in the nose (eg, rhinorrhea, glandular hyperplasia, hypersecretion with mucosal swelling). Anticholinergic agents appear useful against this limb for symptomatic relief of a "runny nose." Chronic exposure to allergens can lead to hyperresponsiveness of the nasal mucosa. As a result, receptors upregulate specific ion channels to increase the sensitivity and potency of their reflex response. Nasal stimuli also affect distant parts of the body. Nerves in the sinus mucosa cause vasodilation; the lacrimal glands can be stimulated by nasal afferent triggers. Even the cardiopulmonary system can be affected via the trigeminal chemosensory system, where sensed irritants can lead to changes in tidal volume, respiratory rate, and blink frequency. The sneeze is an airway defense mechanism that removes irritants from the nasal epithelial surface. It is generally benign, but can lead to problems in certain circumstances. The afferent pathway involves histamine-mediated depolarization of H1 receptor-bearing type C trigeminal neurons and a complex coordination of reactions to effect a response.

Introduction

The nose participates both as the afferent and efferent organ for many nasonasal, airway, and systemic reflexes [1]. These regulate processes ranging from acute effects of exposure to nociceptive stimuli, to the autonomic nasal cycle. In the peripheral mucosal tissue, stimulation of some populations of nociceptive nerves can lead to neurogenic axon responses [2]. These responses probably function as a very rapidly acting defense mechanism to mobilize a thick mucus coat that can adsorb irritant chemicals and particulate material. These local mucosal responses are likely to contribute to some extent in all types of rhinitis that have an irritating sensory component. For example, nasal allergen provocation leads to the release of the afferent nociceptive neurotransmitters substance P and calcitonin gene-related peptide (CGRP) and the parasympathetic vasoactive intestinal peptide (VIP) in the nose [3]. This supports the presence of both afferent nociceptive axon responses and parasympathetic reflexes in allergic rhinitis. These results are evidence for nasonasal reflexes.

Nasonasal Reflexes

Nasonasal reflexes generally refer to unilateral afferent stimulation that leads to bilateral efferent reflexes that can be identified by their effects in the contralateral nostril. Unilateral histamine provocations lead to contralateral secretion that is about 60% of the mass of the challenged side. The afferent limb of the reflex arc is broken by cocaine anesthesia to the ipsilateral trigeminal nerves, while the efferent parasympathetic limb is blocked by contralateral topical anticholinergics or Vidian neurectomy [4].

Afferent Sensitivity

Nociceptive afferent-cholinergic efferent reflexes (Table 1) account for the nasal discharge that follows consumption of hot, spicy foods (gustatory rhinitis) [5]. Nasal capsaicin treatment can block the afferent limb of this reflex [6]. Anticholinergic drugs blocked the discharge, indicating that parasympathetic reflexes were involved. Trigeminal afferent nerves sensitive to capsaicin and other spices may be activated in the soft palate and induce salivary, nasal, and lacrimal cholinergic glandular secretion. This indicates extensive "cross-talk" between the irritant sensitive trigeminal chemosensory system from all three divisions of the fifth nerve with the seventh nerve and other parasympathetic motor nuclei. The

Table 1. Afferent stimuli of nasal reflexes

Nasal afferents	Systemic afferents
Nociceptive nerve axon responses	Postural reflex
Nasal cycle	Crutch reflex
Nasonasal reflexes	Exercise reflex
Nasopharyngeal reflex	Hot and cold cutaneous temperature reflexes
Nasolaryngeal reflex	Visible and infrared light reflexes
Nasolacrimal reflex	Bronchonasal reflex
Nasosalivary reflex	Ovulatory rhinitis
Gustatory rhinitis ("salsa sniffles")	Sexual reflexes
Cold dry air-induced rhinitis ("skier's nose," "ski bunny rhinitis")	Alcohol reflex
	Psychogenic syndromes

role of this efferent pathway is supported by the benefits of Vidian neurectomy on nasal discharge [4].

Breathing cold air leads to rhinorrhea in many individuals. Some are much more sensitive and have a greater mass of nasal secretions than others. The degree of variability in this response between subjects with allergic rhinitis, and those with different subtypes of nonallergic rhinitis, has not been well studied. The afferent activation may be cooling of the mucosa, evaporation of water (leading to hyperosmolar epithelial lining fluid), activation of cold-sensitive trigeminal neurons, or release of mediators from mucosal epithelial and inflammatory cells. The rhinorrhea is blocked by pretreatment with anticholinergic agents, as elegantly shown in "skier's rhinitis" [7] ("ski bunny rhinitis").

Afferent-cholinergic efferent reflexes contribute to the glandular secretion that differentiates the rhinorrhea subset of idiopathic rhinitis ("runners") from those with predominantly obstruction ("blockers") and normal subjects. Afferent nerve populations sensitive to capsaicin (transient receptor potential vanilloid 1 ion channels, TRPV1) and nicotine recruit cholinergic reflex-mediated glandular hypersecretion only in the "runners" [8]. Anticholinergic agents are a successful treatment for this subset of subjects with nonallergic rhinitis. "Runners" also have greater glandular secretory responses to methacholine than the other groups, indicating that glandular hyperplasia may also contribute to this syndrome. This is consistent with a subset of subjects with chronic rhinosinusitis who have glandular hyperplasia without eosinophilia or polyposis [9].

Nebulization of 22°C solutions of saline, histamine, N-acetylcysteine (NAC) and lidocaine decrease superficial nasal blood flow (14% ± 4% decrease in laser Doppler signal; $P < 0.05$) in nonallergic chronic rhinosinusitis subjects [10]. The effect began after 30 seconds and lasted 60 to 90 seconds. Nasal nitric oxide (NO) was decreased 8.03% ± 0.59% after 60 seconds ($P < 0.001$). These data suggest that activation of nasal "cold" receptors (eg, transient receptor potential ion channels TRPM4, TRPM8, TRPA1) on afferent nerves recruited transient sympathetic vasoconstriction that reduced the delivery of arginine to the mucosa and thus decreased nasal NO production. These temperature effects were more potent than histamine H1-receptor–mediated itch, NAC antioxidant, or local anesthetic effects. Activation of cold receptors may play a major role in the symptomatic relief of chronic rhinitis complaints.

Mechanosensitive receptors also stimulate nasonasal reflexes. Rubbing a cotton-tipped swab soaked with saline in the middle meatus caused an increase in nasal airflow resistance. Application of the vasoconstrictor and local anesthetic drug cocaine to the middle meatus and rubbing the inferior turbinate with a saline swab did not alter nasal airflow resistance. This indicates that different types of nociceptive stimuli that may activate different subpopulations of nasal type C neurons may induce protective, obstructive responses in vivo.

Animal studies suggest that inhibitory autoreceptors may prevent or reduce the depolarization of afferent nerves. However, agonists for individual autoreceptors, such as the muscarinic M2 receptor, do not appear to modulate human nasonasal reflexes. Opioid agonists can reduce axon-response–mediated glandular secretion from bronchial explants in vitro [11]. Combinations of inhibitor autoreceptor agonists may be required to obtain significant clinical benefits.

Hyperresponsiveness

Exposure to allergen for more than 4 weeks in persistent seasonal and perennial allergic rhinitis increases the potency of nasonasal reflexes. The sensitivity of nociceptive sensory afferent neurons is increased, and sensitivity to mediators such as bradykinin and endothelin 1 are induced [12,13]. Nerve growth factor may play a critical role in upregulation of the afferent neuron sensitivity. Efferent neural reflex responses are also increased, with greater glandular exocytosis and potentially vasodilation [14]. Glandular responses

may be increased in chronic rhinitis by either or both increased efferent reflex stimulation (eg, increased neural release of prostaglandin D2 by brain/neural prostaglandin D2 synthase [15,16]) and glandular hypertrophy with increased exocytosis [17,18]. Reflex vascular hypersensitivity was evident in half of subjects who had unilateral nasal allergen challenge [19]. The contralateral nasonasal reflexes were detected by increased mucosal blood flow and reduced nasal cavity volume (acoustic rhinometry). They lasted a maximum of 15 minutes and had 45% of the magnitude of the ipsilateral vascular changes. These effects were blocked by atropine sulfate, suggesting that bilateral cholinergic vasodilator responses were recruited. Ipsilateral vasodilation lasting longer than 20 minutes was likely due to local release of allergic mediators. These changes and their mechanisms have been difficult to assess in the nose because changes in hyperresponsiveness are on the order of 2-fold to 8-fold, compared to 50-fold changes in the tracheobronchial tree in asthma.

It remains to be seen if similar effects occur after chronic occupational, toxic inhalant, and other nasal stimuli in nonallergic rhinitis syndromes. Capsaicin, for example, had greater effects in subjects with untreated severe allergic rhinitis compared to a group of subjects with nonallergic rhinitis [20]. Investigations of other provocations and in additional subjects with subtypes of nonallergic rhinitis may reveal differences in pathological mechanisms, such as neural reflex modulation.

Nasosinal Reflexes?

Interactions between the nasal and sinus mucosa and nasosinus reflexes have been proposed to be active in chronic rhinosinusitis. However, the instillation of histamine into the maxillary sinuses of normal, nonrhinitic subjects did not produce any ipsilateral or contralateral nasal effects [21]. The magnitude of the secretory response to histamine in the sinus was less than half that of the inferior turbinate. This was expected based on the large histological differences between the thin sinus and thick turbinate mucosae. Sinus mucosa nerves are probably more important in stimulating vasodilation, given the relative paucity of submucosal glands. Vasodilation may increase the thickness of the mucosa and hydrostatic pressure-driven plasma exudation in both rhinitis and sinusitis. For example, swimmer's sinusitis does not seem to be related to inhaled water, but could result from stimulation of anterior nasal sensory nerves with recruitment of bilateral vasodilatory parasympathetic reflexes that lead to swelling of the osteomeatal mucosa [22]. In addition, swimmers can develop an occupational, toxic, nonatopic eosinophilic rhinitis due to chlorinated water (Personal observation). Eosinophil products, such as halogenated free radicals and alkaline proteins, are toxic to the nasal and sinus mucosa.

Nasal Cycle

The existence of a reciprocating cycle of congestion and decongestion has been observed for over a century [23], and has been confirmed by methods ranging from manometry [24] to magnetic resonance imaging [25]. Its exact function and neurological pathways remain largely unknown. Recent studies using acoustic rhinometry have demonstrated that the cycle is present in some form in the majority of adults and in children as young as 3 years, and that it persists after cessation of nasal airflow. For example, 36 of 50 (72%) subjects (12 of 18 males and 24 of 32 females) had at least one reciprocal reversal of nasal airflow that indicated a nasal cycle during a 7-hour observation period [26]. Normal individuals are not usually aware of this phenomenon because the total nasal resistance usually remains fairly constant and is less than the resistance of either one of the individual nasal passages. Nasal cycles can be overridden or modulated in many environmental and pathological situations. It is important to recognize the cycle as a normal phenomenon and to differentiate it from pathologic causes of nasal obstruction.

The normal nasal cycle consists of periodic congestion and decongestion of the nasal venous sinuses that lead to obstruction and patency, respectively, of each nostril. The alteration between sides occurs over a period of several hours. Eccles has proposed that the nasal cycle may have a role in respiratory defense by: 1) alternating the work of air conditioning between the two nasal passages; 2) generation of a plasma exudate, which physically cleanses the epithelium and provides a source of antibodies and inflammatory mediators; and 3) maintaining the patency of the airway during the inflammatory response to infection [27]. The period of vascular congestion and nasal obstruction may permit the accumulation of increased amounts of interstitial fluid derived from plasma extravasation. Parasympathetic discharge during this phase may replenish surface mucus through cholinergic glandular secretion. Sympathetic constriction of the nasal venous sinusoids during decongestion and the airway patency phase "wring out" the interstitial fluid and promote its exudation onto the epithelial surface. This hypothetical "pump" mechanism would link vasodilation, plasma extravasation, and nasal obstruction, while vasoconstriction, plasma exudation, and nasal patency would be temporally connected.

The nasal cycle appears to be remarkably stable for individuals studied by rhinostereometry, peak nasal inspiratory flow (PNIF), and symptom scores over a period of several days [28]. Normal adult volunteers scored their subjective feeling of nasal congestion or patency (using a visual analog scale) just before bilateral acoustic rhinometry measurements every 15 minutes over a 4-hour period. The subjective feeling of patency was not correlated to the changing nostril volumes or cross-sectional areas during the nasal cycle. This was likely because the sum of the left and right nostril volumes and areas remained rela-

tively constant. This suggests that subjects may monitor the total nasal airflow by integrating inputs from both nostrils. Conscious awareness of nasal patency may be alerted when the total nasal airflow is suddenly changed, as occurs in the lateral recumbent position, in response to inhaled agents, or when systemic stimuli lead to reflexes that dilate or obstruct one or both nostrils. This discrepancy highlights the difference between the objective measurements of nasal dimensions and airflow to assess obstruction, and the subjective sensation of "congestion."

The nasal cycle was investigated in 10 healthy human subjects using endoscopic imaging, rhinoresistometry, and acoustic rhinometry of each nostril every 20 minutes for up to 15 hours [29]. Airflow resistance, hydraulic diameter, friction coefficient λ (an indicator of the wall configuration triggering turbulence), the transition from laminar to turbulent flow, and the minimum cross-sectional areas were measured. The cyclic changes in airflow resistance and nasal patency were associated with transitions from laminar to turbulent airflow. The obstructed nostril had predominantly laminar flow. The process leading to nasal patency began with an increase in the cross-sectional area for airflow in the anterior cavum between the anterior tip of the inferior turbinate and septal tuberculum. Even though flow velocities were low, the air motion became turbulent. Turbulent airflow is required for inspired particulate material to come into contact with the mucosa, become firmly adsorbed onto mucus, and be swallowed.

Mucociliary clearance was 2.5-fold faster in the patent nostril compared to the obstructed side [30]. Therefore, the more rapid, and presumably more efficient, ciliary activity would have coincided with the turbulent airflow through the more patent nostril.

Nasal nitric oxide (NO) was highest in the obstructed nostril (highest airflow resistance), and reached concentrations of 1100 parts per billion (ppb) [31]. As nasal patency increased, NO concentrations dropped. A patent nostril with nasal resistance less than 6 cm H_2O per liter per second, had NO that dropped below 80 ppb. There was a significantly negative correlation between nasal cavity volumes and nasal NO concentrations ($r = -0.8$; $P < 0.001$). Therefore, the higher the resistance, the greater the NO concentration. There are two potential explanations. First, anterior nasal obstruction with low airflow may have trapped a greater amount of the NO generated within the sinuses or potentially the nasal mucosa in the nostril. Increased airflow through the patent nostril may have significantly diluted the NO, resulting in low concentrations. This scenario suggests NO had no significant role in the regulation of vasodilation during the nasal cycle. Alternatively, higher NO levels may have caused greater vasodilation, mucosal thickening, and an obstructed nostril. If local NO production began to fall at the onset of the transition from nasal obstruction to nasal patency, then absence of this vasodilator may have permitted default sympathetic vasoconstriction and nasal patency. An extension of this scenario would suggest that cyclic regulation of parasympathetic NO/VIP neurons may have precipitated the onset of nasal obstruction. High mucosal NO production may progressively increase this obstruction. This scenario suggests that brainstem cycling of unilateral parasympathetic tone regulated the nasal cycle.

The α1-adrenergic agonist pseudoephedrine had no effect on the decongestion, or patent, phase of the nasal cycle, but did significantly limit the degree of congestion during the nasal obstruction phase [32]. This suggests that the sympathomimetic effect augmented the sympathetic vasoconstrictor effect on the nasal blood vessels.

Allergic subjects out of the pollen season have more congested (obstructed) and more hyperreactive nasal mucosa than nonallergic subjects [33]. This was evident in baseline measurements and with exercise provocations. This is consistent with persistent inflammatory changes in the mucosa of these subjects.

The nasal cycle may become synchronized to the sleep cycle. The patency of each nostril cycled over periods of 1.5, 3.0, and 4.5 hours [34]. These were multiples of the mean length of one sleep cycle (1.5 hour). The switch in patency from one nostril to the other may occur during rapid eye movement sleep.

The role of the nasal inspiratory and expiratory airflow on the nasal cycle was examined in a series of East Indian traditional breathing practices and postures [35]. Changes in airflow could not be induced through the more obstructed nostril. However, the patent nostril could become obstructed by posture and other activities. This led to the hypothesis that tidal air flow stimulated afferent nasal nerves that activated central brainstem and other cerebral centers, and caused the coordinated reflexes that regulated the reciprocal congestion and decongestion of the each nostril.

The nasal cycle may be regulated by a hypothalamic center. This was suggested by studies in subjects with Kallmann's syndrome [36]. This disorder is characterized by coexisting hypothalamic hypogonadism and hyposmia or anosmia due to hypothalamic and olfactory center hypoplasia. All of the subjects with Kallmann's syndrome had abnormal nasal cycles. Electrical stimulation of hypothalamic nuclei leads to pronounced bilateral sympathetic activation and nasal vasoconstriction. These results have not been confirmed in other syndromes of hypothalamic dysfunction.

Another hypothesis contends that the nasal cycle reflects the dynamic lateralization of the autonomic nervous system. This lateralization may present with sympathetic activity induced by left brain hemisphere stimulation and parasympathetic activity induced by right hemisphere stimulation [37]. Twenty minutes of forced unilateral right nostril breathing (left nostril occluded) was proposed to have stimulated the left cerebral hemisphere. The maneuver led to a significant bilateral decrease of 4.6 mm Hg (25%) in intraocular pressure in 46 patients with

open and closed angle glaucoma. However, it significantly increased the intraocular pressure in three patients—one with neovascular, one with juvenile onset, and one with closed angle glaucoma. These changes were interpreted as an indication of reduced parasympathetic cholinergic tone (functional vagotomy) with increased sympathetic effects.

Sneeze

The sneeze reflex has been experienced by everyone, and is an important airway defense response for expelling inhaled irritant materials [38]. Normal subjects have an average of four sneezes with nose blowing per day. Sneezing has been described as the nasal orgasm. Although generally benign, a paroxysm of sneezing induced an acute aortic dissection in one hypertensive patient [39]. Acute orbital emphysema occurred after sneezing in a patient with chronic rhinosinusitis who had undergone multiple surgeries, and potential weakening of the medial orbital wall [40]. Sneezing and mild head trauma, such as that experienced when jumping from a 1-meter height, may precipitate cavernous sinus thrombosis [41]. Combined with other risk factors, such as use of birth control pills and the presence of procoagulant states, this may help explain the 20% of unresolved causes of sinus thrombosis. Intractable psychogenic sneezing has been described, and resolves after appropriate psychotherapy [42,43].

The best defined afferent pathway involves histamine-mediated depolarization of H1 receptor-bearing type C trigeminal neurons. Other stimuli include allergens, chemical irritants, electrical stimulation of nociceptive afferent neurons in the trigeminal ethmoid and maxillary nerves (and potentially sympathetic afferents associated with the Vidian and greater petrosal nerves), sudden exposure to bright lights, and cooling of the skin of various parts of the body [44,45]. These stimuli activate a stereotyped series of actions that are choreographed by activation of a complex array of central pathways and nuclei leading to systemic muscle coordination. Intercostal and accessory respiratory muscle contractions provide a rapid oral inspiration to hyperinflated volumes, followed by closure of the eustachian tubes, eyes, glottic, and nasopharyngeal structures when at the maximum lung volume. Abdominal, neck, and other muscles contract in a forceful Valsalva maneuver that compresses the thoracic air to pressures of greater than 100 mm Hg. Sudden anterior flexion of the soft palate opens the nasopharyngeal space so that the pressurized air column can rush through the nose at speeds of over 100 mph (33 m/s). The shearing force removes mucus strands and any particulates or other irritants from the epithelial surfaces and blows them out of the nostrils. The pressure differential may introduce high-pressure waves into sinus cavities, up the nasolacrimal area, and potentially into the middle ear if the maneuver is not properly coordinated. This process can be rapidly repeated in staccato fashion. Cholinergic nasal, lacrimal, salivary, and posterior pharyngeal gland exocytosis follows to resurface the expelled epithelial lining fluid and adsorb the subsequently inhaled irritants. The sneeze reflex may be coordinated by a latero-medulary sneeze center localized to near the spinal trigeminal tract and nucleus. This center appears to be bilateral and functionally independent on both sides based on its unilateral loss in strokes affecting this region [46].

Sneeze, vascular permeability, and epithelial cell cytokine production may also be stimulated by reactive oxidant species (ROS) generated by pollen grain nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [47]. This signal augments immunoglobulin (Ig)E-mediated allergic inflammation induced by this and other pollen allergens. Removal of pollen NADPH oxidase activity from the challenge material reduced antigen-induced allergic airway inflammation, the number of mucin-containing cells in airway epithelium, and antigen-specific IgE levels in sensitized mice. Similar synergistic effects are induced by dust mite fecal cysteine proteases such as *Der p1, Der p3,* and *Der p9* that activate epithelial protease-activated receptor (PAR)-2 [47]. Activation of PAR-1, PAR-2, and PAR-4 stimulates IL-6, IL-8, and prostaglandin E2 release from human respiratory epithelial cells [48]. The activity of these enzymes may explain the high prevalence of cysteine protease inhibitors in epithelial and submucosal gland serous cell secretions [49]. They may represent an important mucosal defense mechanism. These enzymes may explain the worsening of rhinitis symptoms in subjects with nonallergic rhinitis that occurs at the peak of pollen season, in house dust mite–laden environments, with high pollution exposure on days when airborne allergen levels are low, and with cigarette smoke exposure in chemically sensitive subjects [50]. A novel peptide-based cysteine protease inhibitor may block this activation [51]. When dry pollen grains are deposited on the wet epithelial lining fluid, they release proteins and low-molecular-weight solutes that create a locally hypertonic environment [52]. This mechanism may also contribute to particulate effects in nonallergic rhinitis syndromes, and even the potential syndrome of "seasonal nonallergic rhinitis" (SNAR) [53].

Conclusions

The nasal mucosal epithelium and nociceptive nerves are lined with receptors that initiate the afferent limbs of reflexes within the nose that may also influence other more distant organ systems (Table 1). A wide variety of triggers for these receptors can contribute to upregulation and hypersensitivity of receptors. Understanding the triggers, mediators, and regulators for these responses may allow the manipulation or blockade of the mechanisms that lead to clinical disorders such as sinusitis, rhinitis, and chronic cough.

This review has selected a few highlights of the reflex control of nasal and airway function. Reflexes originating

in the lower airway and systemic afferents have not been discussed, but are critical in regulating nasal functions. The teleological origins of some of the vestigial reflexes may become apparent by studying their more potent effects in newly born infants and other animal species (eg, diving mammals, Hering-Breuer reflex). The diverse nature of the sensory afferent receptors and neurons, their spinal cord and brainstem connections, and diversity of autonomic efferent responses have been alluded to, and the transient receptor potential family of ion channels are discussed elsewhere in this issue. Investigation of these mechanisms may provide insights into peculiar aspects of upper and lower airway function and hyperresponsiveness induced by neurotrophins, allergic and nonallergic inflammation, viral syndromes, and nonallergic syndromes of rhinitis.

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