

## **Nasal Reflexes**

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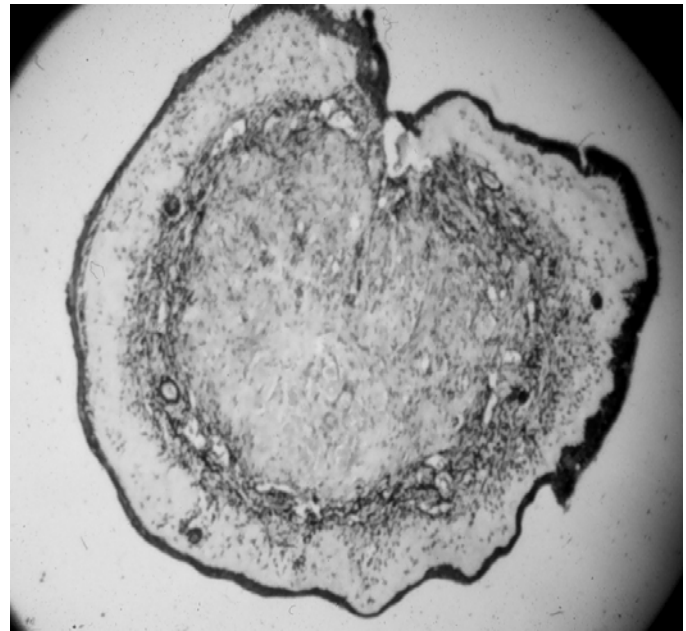
Nasal reflexes offer an opportunity to delineate the distinct subjective and objective factors that contribute to patient symptoms and local mucosal, systemic, and central nervous system afferent and efferent mechanisms. However, a major issue continues to be the surprising lack of consensus on the definition of specific nonallergic syndromes and nasal symptoms [1,2]. There is a need to reconcile subjective nasal and psychometric symptoms, objective measures, and the many potential mucosal and neural mechanisms. Many lines of investigation on the multiplicity of afferent neuron subtypes, the factors that lead to depolarization of specific sets of nerves, and their central and systemic efferent responses are leading to new insights into nasal reflexes and pathophysiology.

**Itch.** For example, itch is conveyed by histamine stimulation of H-1 receptors on a subset of very slow conducting Type C neurons that release calcitonin gene-related peptide (CGRP) and cause axon – response mediated vasodilation (flare) responses [3]. These neurons activate the systemic sneeze reflex. Methods as simple as counting sneezes and as complex as measuring systemic inhalation / exhalation events and turbulent / laminar airflow can now be applied to better evaluate and understand the pathways of this reflex and the modulating effects of antihistamines and novel therapies.

**Drip.** An high subjective score for the sensation of nasal “drip” is not always synonymous with changes in the mass of nasal discharge or changes in either glandular or plasma proteins in nasal lavage fluids. Gland exocytosis, and plasma extravasation followed by transepithelial exudation are independent processes with different mechanisms arising from different regions of the nasal mucosa.

**Histology and Physiology.** The histology of the inferior turbinate demonstrates the compartmentalization of these functions (FIGURE 1). The anterior inferior turbinate is covered by an outer layer of respiratory epithelium that forms the interface between the conditions of inhaled air, epithelial lining fluid, sensory neurons, inflammatory, epithelial and other cells. The superficial arterioles, fenestrated capillaries, and high endothelium post – capillary venules are placed below the basement membrane. The arterioles may regulate superficial blood flow that is measured by laser Doppler methods. Fenestrated capillaries permit free exchange of plasma and interstitial fluid. Differences in hydrostatic

**FIGURE 1.** Histological Compartmentalization of the Human Nasal Turbinate Mucosa. Concentric layers of epithelium, superficial permeable vessels, glands and deep venous sinusoids are shown.



pressure will determine the next exit of plasma. The post – capillary venules are vital for mediator – induced diapedesis of inflammatory cells and endothelial cell contraction with plasma extravasation. These vessels have a relative paucity of innervation. The submucosal glands form the next concentric ring. Both acid mucin – secreting mucous cells and antimicrobial protein – secreting serous cells are present. Myoepithelial cells ring the acini. When they contract, they squeeze the exocytosed mucus out of the gland ducts and onto the mucosal surface. The innermost functional unit is the nasal erectile tissue. Arteriovenous anastomoses regulate the flow of blood into the deep venous sinusoids. Dilation of the anastomoses combined with closure of the venous exit “cushion veins” leads to blood engorgement of the venous sinusoids and increased nasal mucosal thickness. This change can be detected by acoustic rhinometry. Sympathetic mediators vasoconstrict the anastomoses and sinusoid walls to squeeze the blood out of the sinusoids so they collapse and the mucosa decreases in thickness. This accounts for the increase in nasal patency brought on by  $\alpha$ -adrenergic agonist drugs. Below the erectile tissue is the periostium and turbinate bone. The bones strategically position the three turbinates to alter the flow of inspired air; induce turbulence to enhance the deposition of particulate materials such as diesel fuel agglomerations, pollen grains and fungal spores; and to function as an heat and water exchanger to cool / warm and humidify / dehumidify inhaled and exhaled air. The separate functions of each of these histological components can be assessed using a reductionist approach. This facilitates understanding of how these functional units

are independently regulated by different sets of nerves and inflammatory mediators, and how they may interact in both normal nasal homeostasis and defense, and in disease.

**Perceived Sensations.** The sensations of “congestion”, “fullness”, “obstructed nasal airflow”, and “mid facial discomfort / pain” are more difficult to address. They may be different cortical interpretations of afferent stimuli from individual or combinations of nerves that sense mechanical stretch of deep venous sinusoids as a measure of their engorgement and so mucosal thickness, nasal epithelial cooling, trigeminal chemosensory system input, or the work of breathing. It is likely that these diverse stimuli become extensively integrated through trigeminal afferent signaling at the trigeminospinal primary synapses, brainstem and thalamic nuclei, and interpretation in primary and secondary parietal and insular cortex regions in the context of memory and emotion (amygdala, hippocampus, anterior cingulate gyrus, and other frontal “executive function” regions). The semantic differences between these symptoms and patient – defined syndromes such as “sinus” and “allergies” are important to define especially given the overlap of allergic and nonallergic mechanisms in rhinitis, sinusitis and rhinosinusitis syndromes. Education of patients about these complaints is an important part of our jobs as clinicians since some symptoms may not be amenable to therapy (e.g. “congestion”) or may require extensive evaluations (e.g. chronic nonproductive cough related to post-nasal drip, gastroesophageal reflux syndromes, or overactive nasopharyngeal and glottic afferent sensitivity).

**Congestion.** An additional complication has been the laissez-faire inference that measures of nasal function such as acoustic rhinometry, laser Doppler measures of superficial blood flow, anterior and posterior rhinomanometry, and plasma exudation are equivalent “objective” measures of vascular congestion, and that vascular congestion is the same as the subjective sensations of “congestion”, “fullness”, “blockage”, and related complaints. For example, do changes in acoustic rhinometry nasal volume measurements of nasal patency “define” the sensation of “nasal congestion” (TABLE 1) [4]? Nasal polyps obstruct airflow, but patients may be relatively free of pain, congestion, or any sensation of obstructed airflow until the polyps are large enough to interfere with the ability of turbinate vasoconstriction to maintain an optimally patent bilateral nasal airway. Slow progression of the polyp may lead to progressive cortical accommodation to the obstructed nasal airflow suppress and consciously perceptible sensation such as “congestion”.

Clear definitions are critical, since that is a wide interindividual variation in the thresholds of afferent visceral (i.e. nasal mucosa) that nociceptive input must achieved in order to activate cerebrocortical

**TABLE 1. What is “congestion”? Comparison of Subjective and Objective Assessment of “Congestion”.**

<b>SUBJECTIVE CRITERIA</b>	
<ul style="list-style-type: none"> <li>- Visceral, mucosal sensation(s)</li> <li>- Poor localization in cerebral cortex</li> <li>- Perceptions subject to personal interpretation</li> <li>- Degree of perceived sensation depends on prior experience (cingulate gyrus, amygdala, limbic system)</li> <li>- Verbal descriptors have not been cross – validated:               <ul style="list-style-type: none"> <li>Fullness</li> <li>Congestion or discomfort in the nose, face, nasopharynx, middle ear, pharynx, supraglottic region</li> <li>Chemosensory irritation</li> <li>Obstruction to airflow</li> <li>Thick mucus prevents efficient airflow or sniffing</li> <li>“Swelling” of the mucosa</li> </ul> </li> </ul>	
<b>OBJECTIVE ANALYSIS</b>	
<ul style="list-style-type: none"> <li>- Acoustic Rhinometry               <ul style="list-style-type: none"> <li>Minimum cross – sectional area of the anterior nasal valve</li> <li>Volume of the nasal cavity</li> </ul> </li> <li>- Nasal Airflow Resistance               <ul style="list-style-type: none"> <li>Anterior and Posterior Rhinomanometry</li> <li><math>NAR = \Delta \text{ Pressure} / \Delta \text{ Flow}</math></li> </ul> </li> <li>- Mucosal swelling</li> <li>- Microstereoscopy</li> <li>- Superficial blood flow</li> <li>- Laser doppler</li> </ul> <p>Subjective complaints may be greater than Objective deficits Provocation tests may be needed to test differences between subject groups Subjective and Objective measures may not evaluate the same symptom</p>	
<b>Discrete definitions are essential to show relevance to rhinitis.</b>	

appreciation of the symptom and supratentorial planning to reduce the impact of the visceral stimulus [5]. One view of this concept is that some subjects and populations are more stoic than others. This will be discussed elsewhere in this book. Appreciation of these concepts is critical for making progress in symptomatic treatment and assigning mechanisms to selected symptoms. Consensus conferences focused on defining specific, sensitive, highly correlated and congruent symptom complexes, the mechanisms responsible for their generation, and the optimal objective methods for linking the effects of these mechanisms with the severity of the subjective sensations may be one approach to address these issues.

Comparisons of subjective and objective measures with definitions of their correlates are feasible. For example, three objective monitoring parameters were compared in an allergen provocation model [6]. The endpoints were the minimum cross-sectional area by acoustic rhinometry, nasal resistance by active anterior

rhinomanometry, and the amount of nasal secretion measured at 15 min intervals for 60 min. The secretion parameter was slightly superior to the acoustic rhinometry and rhinomanometry endpoints. The contralateral secretion amount was 1/3 of the ipsilateral secretion, indicating the magnitude of the contralateral nasonasal secretory reflex. The coefficient of variation was significantly lower for the acoustic rhinometry than for the rhinomanometry ( $P=0.0001$ ). The optimal threshold values for a positive test after 30 min were a secretion amount of 100 mg, 15% decrease in the minimum cross-sectional area and 50% increase in the resistance. After 60 min, the thresholds for positive tests were 210 mg, 30% and 100%, respectively.

Newer radiological methods that can image and perform volumetric analysis of nasal airways may provide an additional objective method for examining mucosal thickening and reflex effects [7]. Other methods, such as nonnociceptive mucosal stimulation with controlled puffs of air have been validated by assessing the activation of the immediate early gene *fos* [8]. This method is generally used to immunohistochemically assess the activation specific central nervous system pathways, but has also been used to assess the anti-inflammatory effect of glucocorticoids in nasal polyps *in vivo* [9].

### **Stimulation of Nasal Nociceptive Afferent Nerves**

Activation of trigeminal chemosensory neurons has been difficult to understand without information about the subpopulations of nociceptive nerves and activating ion channels (e.g. TRP). Challenge studies with multiple chemical using cross – desensitization paradigms in anosmic subjects have proposed that there may be 6, 12 or higher numbers of distinct chemosensory trigeminal neuron subtypes [10]. For example, repeated inhalation of acetic acid vapors led to a loss of sensation (self-desensitization) and a loss of reactivity to mustard oil (allyl isothiocyanate) following acetic acid (cross-desensitization) [11]. In contrast, pretreatment with mustard oil did not alter the burning sensation and psychophysiological (skin conductance response) measurements induced by subsequent acetic acid. This suggested that acetate or protons desensitized Type C or A $\delta$  neurons bearing both TRPV1 and TRPA1 ion channels by inducing depolarization or hyperpolarization via TRPV1 – mediated neural activation. As a result, these nerves could not respond to mustard oil stimulation of TRPA1 channels. In the opposite sequence, TRPA1 neurons would be desensitized to mustard oil, but have no effect on H<sup>+</sup> mediated activation of other Type C nerves bearing TRPV1 or other acid sensing channels. Seemingly innocuous chemicals may be rapidly metabolized within epithelial and other airway cells and lead to toxic irritants that activate afferent reflex effects [12]

About half of spinal dorsal root ganglion cells in guinea pigs are immunoreactive for CGRP [13]. Single neuron

measurements localized CGRP to Type C polymodal and high threshold mechanosensitive neurons. No CGRP was found in cool temperature or low threshold mechanosensitive neurons. Analogous mapping studies have not been performed in the upper airway or humans. CGRP is also colocalized with acetylcholine in large diameter primary motor neurons. CGRP has an important myotrophic effect and helps maintain neuromuscular junction integrity [14]. Similar trophic effects for airway mucosal cells have not been examined.

### **Trigeminal Axon Responses**

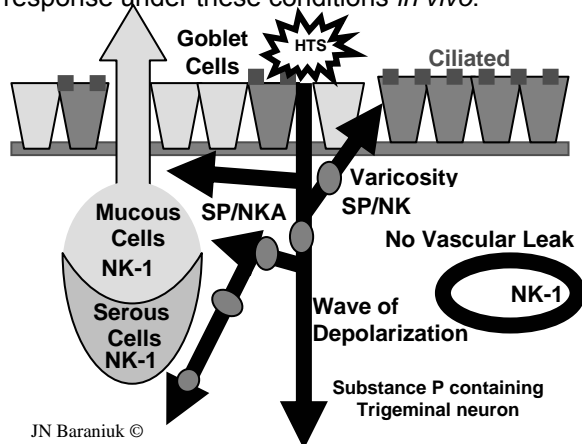
Unilateral hypertonic saline nasal provocations that cause modest pain (e.g. 4 cm on a 10 cm visual analog scale), are associated with unilateral sensations of congestion and nasal discharge, and unilateral glandular exocytosis [15]. No changes in plasma exudation were found using either albumin or IgG assays. Although subjects felt that they had nasal congestion or fullness, volume changes detected by acoustic rhinometry were accounted for by the volume of glandular secretions [16]. Substance P was detected only on the challenged side, while substance P preferring neurokinin 1 (NK1) receptors were localized to glands [15]. This suggests that the human nasal airway axon response following hypertonic saline released substance P and produced glandular secretions (FIGURE 2). Vascular processes, including plasma exudation, filling of venous sinusoids, and mucosal edema were not detected in normal subjects. However, when higher levels of pain were induced in allergic rhinitis subjects with untreated disease in season, they did have an increase in contralateral secretions suggesting development of nasonasal reflexes in severe allergic disease [17].

### **Nasonasal Reflexes**

Nociceptive nerve neurogenic axon responses may act as a rapidly acting defense mechanism to mobilize a thick mucous coat to adsorb irritant chemicals or 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 [18]. 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 generally refer to unilateral afferent stimulation that leads to bilateral efferent reflexes that can be identified by effect 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

**FIGURE 2. Neurogenic Axon Response to Hypertonic Saline (HTS) Nasal Provocation.** HTS lead to depolarization of a subset of substance P (SP) – containing trigeminal neurons. The wave of depolarization spreads throughout the highly branched, dendritic neuronal processes in the mucosa. Varicosities that contain SP and probably other neurotransmitters are activated and release these near glands. SP and/or neurokinin A (NKA) act on neurokinin – 1 receptors (NK1) that are most dense on glands to induce glandular exocytosis. Unlike animal models or much higher doses of HTS, the superficial vessels do not appear to be significantly activated. There is no plasma extravasation as part of the nociceptive nerve axon response under these conditions *in vivo*.



broken by cocaine anesthesia to the ipsilateral trigeminal nerves, while the efferent parasympathetic limb is blocked by contralateral topical anticholinergics or Vidian neurectomy [19].

**Afferent Sensitivity.** Nociceptive afferent – cholinergic efferent reflexes account for the nasal discharge that follows eating hot, spicy foods (gustatory rhinitis) [20]. Nasal capsaicin treatment can block the afferent limb of this reflex [21]. 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 3 divisions of this nerve with VIlth nerve and other parasympathetic motor nuclei. The role of this efferent pathway is supported by the benefits of Vidian neurectomy on nasal discharge [19,22].

Breathing cold air leads to rhinorrhea in many subjects. Some are much more sensitive and have a greater mass of nasal secretions than others. The degree of variability in this response been allergic and different subtypes of nonallergic rhinitis subjects 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 have been elegantly shown in “skier’s rhinitis” [23] (“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 (TRPV1 ion channels) and nicotine recruit cholinergic reflex – mediated glandular hypersecretion only in the “runners” [24]. Anticholinergic agents are a successful treatment for this subset of nonallergic rhinitis subjects. “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 chronic rhinosinusitis subjects who have glandular hyperplasia without eosinophilia or polyposis [25].

Nebulization of 22°C solutions of saline, histamine, N-acetylcysteine (NAC) and lidocaine decrease superficial nasal blood flow ( $14 \pm 4\%$  decrease in laser Doppler signal;  $p < 0.05$ ) in non-allergic chronic rhinosinusitis subjects [26]. The effect began after 30 s and lasted 60 to 90 s. Nasal nitric oxide was decreased  $8.03 \pm 0.59\%$  after 60 s ( $P < 0.001$ ). These data suggest that activation of nasal “cold” receptors (e.g. TRPM4, TRPM8, TRPA1) on afferent nerves recruited transient sympathetic vasoconstriction that reduced the delivery of arginine to the mucosa and so 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 swabbed soaked in saline in the middle meatus caused an increase in nasal airflow resistance [27]. 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 [28]. Opioid agonists can reduce axon – response mediated glandular secretion from bronchial explants *in vitro* [29]. Combinations of inhibitor autoreceptor agonists may be required to obtain significant clinical benefits.

**Hyperresponsiveness.** Exposure to allergen for over 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 [30-33]. Nerve growth factor may play a critical role in upregulation of the afferent neuron sensitivity [34]. Efferent neural reflex responses are also increased with greater glandular exocytosis and potentially vasodilation [35-36]. Glandular responses may be increased in chronic rhinitis by either or both increased efferent reflex stimulation (e.g. increase neural release of PGD<sub>2</sub> [37,38]) and glandular hypertrophy with increased exocytosis [39,40]. Reflex vascular hypersensitivity was evident in half of subjects who had unilateral nasal allergen challenge [41]. The contralateral nasonasal reflexes were detected by increased mucosal blood flow and reduced nasal cavity volume (acoustic rhinometry). They lasted a maximum of 15 min 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 min 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 – to 8 - fold, compared to 50-fold changes in the tracheobronchial tree in asthma [42].

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 untreated severe allergic rhinitis subjects compared to a group of nonallergic rhinitis subjects [36]. Investigations of other provocations and in additional subtypes of nonallergic rhinitis subjects 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 [43]. 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 [44] 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 [45]. 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 [46,47].

### **Nasal Cycle**

The existence of a reciprocating cycle of congestion and decongestion has been observed for over a century [48], and has been confirmed using manometric [49] to magnetic resonance methods [50]. Its exact function and neurological pathways remain largely unknown [51]. Recent studies using acoustic rhinometry have demonstrated that the cycle is present in some form in the majority of adults, in children as young as 3 years, and that it persists after cessation of nasal airflow [52]. 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 hr observation period [53]. 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 [54].

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: (a) alternating the work of air conditioning between the two nasal passages, (b) generation of a plasma exudate which physically cleanses the epithelium and provides a source of antibodies and inflammatory mediators, and (c) maintaining the patency of the airway during the inflammatory response to infection [55]. 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 [56,57]. 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 [58]. This hypothetical “pump” mechanism would link the 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 [59]. Normal adult volunteers scored their subjective feeling of nasal congestion or patency (visual analog scale) just before bilateral acoustic rhinometry measurements every 15 minutes over a 4 hour period [60]. 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 relatively constant [61]. 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" [62].

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 [63]. Airflow resistance, hydraulic diameter, friction coefficient  $\lambda$  (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 of with the mucosa, become firmly adsorbed onto mucus, and swallowed.

Mucociliary clearance was 2.5 – fold faster in the patent nostril compared to the obstructed side [64]. Therefore, the more rapid and presumably efficient ciliary activity would have coincided with the turbulent airflow through the more patent nostril.

Nasal nitric oxide was highest in the obstructed nostril (highest airflow resistance), and reached concentrations of 1100 parts per billion (ppb) [65]. As nasal patency increased, NO concentrations dropped. A patent nostril with nasal resistance  $< 6 \text{ cm H}_2\text{O}$  per liter per second, had NO dropped below 80 ppb. There was a significantly negative correlation between nasal cavity volumes and nasal NO concentrations ( $r = -0.8$ ;  $p < 0.001$ ). Thereafter, 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 increased this obstruction. This scenario suggests that brainstem cycling of unilateral parasympathetic tone regulated the nasal cycle.

The  $\alpha_1$  – 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 [66]. This suggests that the sympathomimetic 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 [67]. This was evident in baseline measurements and with exercise provocations. This is consistent with persistent inflammatory changes in these 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 hr [68]. These were multiples of the mean length of one sleep cycle (1.5 hr). The switch in patency from one nostril to the other may occur during REM sleep.

The role of the nasal inspiratory and expiratory airflow on the nasal cycle was examined by a series of breathing practices [69]. There were no changes in airflow through the obstructed nostril. However, the patent nostril became obstructed. This led to the hypothesis that air flow stimulated afferent nerves, and contributed to central reflexes that regulated the reciprocal congestion and decongestion of the nostrils.

The nasal cycle may be regulated by a hypothalamic center. This was suggested by studies in subjects with Kallmann's syndrome [70]. 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 [71]. 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 [72]. 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 mmHg (25%) in intraocular pressure in 46 patients with open and closed angle glaucoma. However, it significantly increased the IOP in three patients 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.

### **Nasobronchial Reflexes**

The classic nasobronchial reflex is a component of the diving reflex. Immersion of the head into cold water leads to immediate suppression of respiration (apnea), laryngospasm, and bronchoconstriction. The nasocardiac component of the diving reflex includes bradycardia, decreased cardiac output, vasoconstriction in the skin, muscles, gastrointestinal and renal circulation systems [51,73,74]. The reflex keeps water out of the lungs, decreases oxygen consumption while maintaining cerebral perfusion. In aquatic mammals, this reflex permits prolonged underwater diving [75]. Nasal inhalation of dust, smoke, ammonia, phenylethylacetate (perfume), sulfur dioxide, and other water soluble chemicals can induce immediate bronchoconstriction with cessation of respiration in the expiratory phase due to relaxation of inspiratory muscles.

The afferent pathway was established by studying these reflexes in tic douloureux subjects who had undergone unilateral transection of the 2<sup>nd</sup> branch of the trigeminal nerve for symptomatic pain relief [76]. Intranasal crystalline silica dust to the innervated nostril produced nasal mucosal burning, nasolacrimal reflexes, and significantly increased pulmonary airways resistance. Provocation of the nostril on the surgically transected side failed to produce either local nasonasal or nasobronchial responses. Further study localized the afferent pathway to the maxillary nerve (V2) since neither the ethmoid nor olfactory nerve could induce these effects [77].

Interactions between the nose and lung, including neurogenic and nasobronchial reflexes and neural plasticity have been investigated in allergic and nonallergic rhinitis and asthma [78,79]. Activation of

nasal afferent receptors can lead to significant bronchial obstruction [80] and cardiodepressor reflexes. Mechanosensitive nasal receptors can stimulate nasobronchial reflexes. Rubbing the middle meatus or inferior turbinate caused significant decreases in FEV1 in healthy nonsmoking subjects [27]. Nasal histamine provocation induced bronchoconstriction in 8/12 allergic rhinitis and asthma subjects in an early study [81].

Nasal inhalation of particulate material such as crystalline silica particles [82] or granulated charcoal [83] leads to bronchoconstriction that can be prevented by cooling the vagal nerve or inhaled atropine. This implicates the Xth nerve in the efferent limb of the reflex.

Chronic unilateral nasal obstruction in rabbits leads to ipsilateral hypoinflation and thoracic deformities [84]. This suggests that the bronchial obstruction does not attenuate over time. It is not known if prolonged unilateral nasal obstruction during the pediatric growth periods can lead to similar chest wall abnormalities or scoliosis.

Nasal stimulation with cold dry air significantly decreased proximal tracheal mucosal blood flow (Qaw) in nine healthy humans [85]. Topical nasal local anesthetic treatment mucosa prevented this reduction suggesting that a nasobronchial vasoconstrictor reflex was induced by nasal cold dry air. In contrast, airflow was not affected. Nasal cold dry air, nasal lidocaine application, and inhalation of an anticholinergic bronchodilator had no effects on either tracheobronchial specific airways conductance (SGaw) or nasal airways resistance. Nasal provocation with warm air may reverse bronchoconstriction in asthmatic, but not normal, subjects [86]. Nasal cold dry air can stimulate bronchoconstriction in asthmatics but not normal subjects [87].

**Work of Breathing and Nasal Reflexes.** Afferent nasal, tracheobronchial and inspiratory muscle mechanoreceptors participate in the coordination of inspiratory efforts [88]. Dynamic inspiratory load, a measure of the changing muscular effort during inhalation, is active in awake subjects, and is modified by changing from a seated to supine posture, mouth to nose breathing, and rest to mild exercise. Deep nasal breathing can induce bronchodilation in asthma attacks [89]. Sniff and gasp – like maneuvers may reverse central apnea. These stimuli may activate adrenergic sympathetic reflexes.

Patients who have had laryngectomies do not use their nose for inhalation, exhalation, or environmental sensing. However, the nasal mucosa remains reactive for both the sensory afferent and efferent limbs of nasal bronchial and other reflexes [90]. Air blown into one nostril of patients with laryngectomies produced ipsilateral hyperinflation [74,84]. Pretreatment of the

nose with local anesthetic prevented the hyperinflation, demonstrating the neural afferent origin. The hyperinflation was prevented by atropine, implicating cholinergic bronchial constriction followed by air trapping.

Nasal intermittent positive-pressure ventilation (nIPPV) has been used for the treatment of respiratory failure in patients with neuromuscular disease. Interruption of the positive nasal air pressure increased nasal airflow resistance [91]. Nasal anaesthesia or inhalation of a cholinergic antagonist blocked these effects, suggesting the presence of nasonasal and nasobronchoconstrictor reflexes. These reflex effects were suppressed by adding CO<sub>2</sub> to the inspired gas. This suggested that CO<sub>2</sub> activated chemosensitive nasal reflexes could override the obstructive reflexes.

**Extrathoracic and Intrathoracic Obstruction.** Sinusitis and posterior nasal and adenoid inflammation also stimulate airflow obstruction. Nasal provocations in relatively mild disease leads to glottic reflexes and extrathoracic obstruction [92]. Variable extrathoracic obstruction can be identified by the flattening of the inspiratory loop during a spirometric maneuver. This can be distinguished from laryngeal pathology with fixed airflow obstruction that shows flattening of both the inspiratory and expiratory loops. More severe sinusitis with nasopharyngeal epithelial sloughing and eosinophilia is associated intra – and extra – thoracic obstruction with bronchial hyperresponsiveness [93]. These changes can not be appreciated using spirometers that fail to measure inspiratory flows and volumes. The extrathoracic reflexes are of great clinical importance. Many subjects who are given diagnoses such as multiple chemical sensitivity, *globus hystericus*, and malingering develop glottic or supraglottic muscular contractions following exposures to “harmless” citrus, cleaning agents, glutaraldehyde, and other small, water soluble chemical agents. The fermentation products of fungi may also precipitate this syndrome in the absence of atopy and positive allergen skin tests or provocations to the fungal proteins. These observations generate the hypothesis that these chemicals activate neural ion channels and other receptors leading to local pharyngeal – laryngeal reflexes with hoarseness, a sensation of throat tightness, cough, and extrathoracic obstruction. Treatment of these subjects with abrupt dismissal from the clinic heightens their sense of paranoia and fears that the problem is all in their heads. These subjects respond to an understanding approach, related inspiratory – expiratory flow volume loops during exposures that demonstrate the dysfunctional reflex, attempts to reduce pharyngeal afferent activation with honey, menthol lozenge, hot tea and other stimuli that can modify TRP ion channel sensitivity, and avoidance of the offending agents. A search for underlying acid reflux and dysfunction of the upper or lower esophageal sphincters is often beneficial. Erythema and mild edema

may be seen in on rhinolaryngoscopy, especially if there is severe cough, hoarse, reflux, inflammatory post-nasal drip, asthma or chronic eosinophilic rhinosinusitis.

Bronchonasal reflexes have also been described. Inhalation of ultrasonically nebulized distilled water increased nasal airway resistance in 19/23 allergic rhinitis and 2/12 nonrhinitic subjects [94]. There was no sneezing or rhinorrhea, the latter suggesting that parasympathetic efferent reflexes were not recruited. The vagal afferent innervation from the lung falls into 3 categories: C-fibres, rapidly adapting stretch receptors (RARs), and slowly adapting stretch receptors (SARs) [95]. As noted above, the plasticity of nociceptive receptors, ion channels, and neurotransmitters that can be induced by neutrophins released during different types of inflammation may lead to severe perturbations of these nerves and generate neurons with novel afferent sensitivities and efferent axon response and central effects.

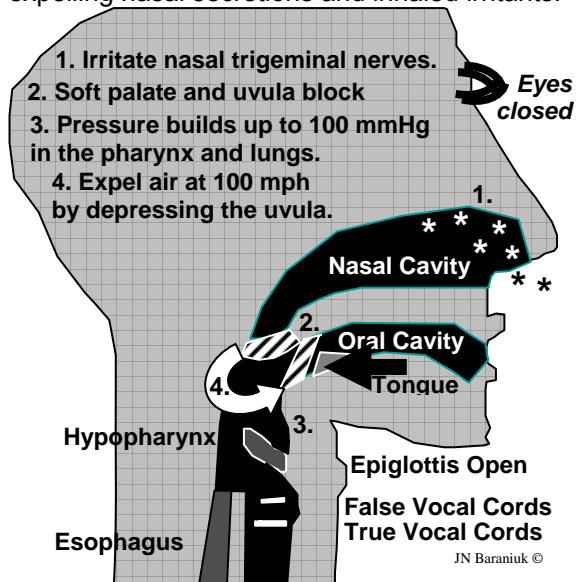
### **Systemic Reflexes Originating from Nasal Mucosal Stimulation**

The trigemino-cardiac reflex is a component of the diving reflex [96]. It is also a well-recognized surgical phenomenon consisting of bradycardia, arterial hypotension, apnea, and gastric hypermotility. It occurs during ocular surgery or other manipulations around the orbit and can also be elicited by stimulation of the central part of the trigeminal nerve during surgery for processes of the cerebellopontine angle. The nasocardiac reflex was examined in 80 healthy volunteers by stimulating their middle turbinate mucosa with 25% ammonia [97]. Almost all individuals had a significant decrease in the heart rate. Eleven had apnea before bradycardia. These responses were blocked by pretreatment of the nasal mucosa with 2% lidocaine.

Electrical stimulation of the trigeminal nerve can stimulate the trigemino-cardiac reflex [51]. Pretreatment with intravenous atropine or transection of the maxillary nerve prevented the bradycardia and hypotension. “Sudden sniffing death” can occur upon sniffing organic solvents such as glue, cleaning fluid and gasoline. Insertion of nasogastric tubes and inhalation of water into the nose have both been associated with bradycardia and cardiac arrest [98].

The trigemino-cardiac reflex is activated in 10% of subjects having transsphenoidal surgery for pituitary adenomas [99]. Heart rate and mean arterial blood pressure were decreased by 43 and 54%, respectively, in these subjects. The decreases were worse with more severe histological tumor grades. The molecular mechanisms of this reflex are not fully understood, but may involve activation of mechanosensitive trigeminal or sympathetic afferents with recruitment of brainstem cholinergic parasympathetic output.

**FIGURE 3.** The Sneeze Reflex. Nasal mucosal irritation (1) activates nociceptive afferent nerves. After a deep hyperinflation through the mouth, the soft palate, uvula, posterior tongue, and lips close to occlude the airway. A Valsalva maneuver increases the intrathoracic and glottic pressure to ~100 mm Hg. The uvula is suddenly pulled anteriorly. The pressurized air escapes through the nose at speeds of 100 to 200 miles per hour (mph) expelling nasal secretions and inhaled irritants.



**Sneeze.** The sneeze reflex has been experienced by everyone, and is an important airway defense response for expelling inhaled irritant materials [100] (FIGURE 3.). Normal subjects have an average of 4 sneezes with nose blowing per day [101]. Sneezing has been described as the nasal orgasm. While generally benign, paroxysm of sneezing induced an acute aortic dissection in one hypertensive patient [102]. Acute orbital emphysema occurred after sneezing in a chronic rhinosinusitis subject who had had multiple surgeries, and potential weakening for medial orbital wall [103]. Mild head trauma, such as jumping from a 1 meter rock and sneezing may precipitate cavernous sinus thrombosis [104]. This combined with other risk factors such as use of birth control pills and procoagulant states may help explain the 20% of unresolved causes of sinus thrombosis. Intractable psychogenic sneezing has been described and resolves after appropriate psychotherapy [105-107].

The best defined afferent pathway involves histamine – mediated depolarization of H1 receptor – bearing Type C trigeminal neurons. Other stimuli include allergen, 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 [73,108]. 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. Intercoastal 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 >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 miles per hour (33 m/s). The shearing forces remove mucus strands and any particulate or other irritant 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 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 and subsequently inhaled irritants. The sneeze reflex may be coordinated by a latero – medullary sneeze center localized to near the spinal trigeminal tract and nucleus. This centre appears to be bilateral and functionally independent on both sides based on its unilateral loss in strokes affecting this region [109].

Sneeze, vascular permeability and epithelial cell cytokine production may also be stimulated by reactive oxidant species (ROS) generated by pollen grain NADPH oxidase [110]. This signal augments IgE – 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 proteases that activate epithelial protease-activated receptor 2 (PAR-2) [111]. *Der p 1*, *Der p 3* and *Der p 9* are cysteine proteases active on PAR-2 [112, 113]. Activation of protease-activated receptor (PAR)-1, PAR-2, and PAR-4 stimulates IL-6, IL-8, and prostaglandin E2 release from human respiratory epithelial cells. [114]. The activity of these enzymes may explain the high prevalence of cysteine proteases in submucosal gland serous cells secretions [115-117]. They may represent an important mucosal defense mechanism. These enzymes may explain the worsening of rhinitis symptoms in nonallergic rhinitis subjects that occurs at the peak of pollen seasons, 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 [118]. A novel peptide – based cysteine protease inhibitor may block this

activation [119]. When dry pollen grains are deposited on the wet epithelial lining fluid, they release proteins and low molecular solutes that create a locally high osmolarity environment [120-122]. This mechanisms may also contribute to particulate effects in nonallergic rhinitis syndromes, and even the potential syndrome of "seasonal non-allergic rhinitis" (SNAR) [123].

**Viral Rhinitis.** Viral rhinitis is associated with sneezing, rhinorrhea, nasal obstruction, mid – facial symptoms of "fullness" or "congestion", cough and mucosal hyperresponsiveness and hypersecretion [124,125]. First - generation antihistamines reduces sneezing, rhinorrhea, nasal mucus weight, and, in some instances, cough in subjects with experimental or natural colds [126]. Antagonism of histamine receptors on epithelium, vessels and nociceptive nerves has been proposed as the mechanism for reducing rhinorrhea and blocking the afferent limb of the sneeze reflex. However, 2<sup>nd</sup> generation antihistamines do not have these benefits. Instead, the antimuscarinic effects of 1<sup>st</sup> generation antihistamines may block cholinergic parasympathetic reflexes that cause glandular secretion [127]. The ability of these 1<sup>st</sup> generation drugs to cross the blood – brain barrier and block histamine and muscarinic receptors may allow them to modulate sneeze reflexes in the medulla, and be responsible for their sedative properties. Cholinergic reflex – induced glandular secretion accounts for ~60% of the nasal discharge in the first days of naturally acquired common colds [128].

**Other Stimuli.** The nasolacrimal reflex has nasal afferents that generate cholinergic lacrimal gland exocytosis [129]. It can be assessed using Schirmer test strips. Clinically, this method is of value for assessing the differential diagnosis of nasal mucosal damage, intracranial or lacrimal disease (e.g. Sjogren's syndrome), and afferent or efferent denervation.

Inhaled capsaicin induced more coughs in chronic coughers than normal subjects [130]. Substance P was elevated in the nasal lavage fluids from chronic coughers. This suggested that activation of TRPV1 – bearing, substance P secreting Type C neurons were activated as part of the afferent and axon responses leading to the nonproductive coughing.

Airborne chemical irritants from pollution and cigarette smoke modulate tidal volume, breathing frequency, and eye blink rates [131]. These reflexes are induced by trigeminal chemosensory afferent nerves since they are detected in both normal and anosmic subjects. The degree of irritation is worse in normal subjects indicating that there is also an afferent olfactory component. Chamber studies (unencumbered exposures) of nonsmoker responses to environmental tobacco smoke indicate an increase in tidal volume and decrease in breathing frequency with moderate irritation. Prolonged exposures to higher concentrations were required to increase eye blink rates. Very brief, nose only

exposures caused decreases in tidal volume that were inversely correlated to the perceived nasal irritation intensity. Higher exposures decreased the duration of inhalation. These responses were mediated by the trigeminal chemosensory afferent system.

### **Systemic Reflexes Originating from Perinasal Stimulation**

Cooling of the facial skin, rather than inhalation of cold air, is predominantly responsible for the bronchoconstriction during cold weather both in patients with COPD and in healthy subjects [132]. Placing bags of 23°C water on the face did not cause bronchoconstriction. However, bags of 4°C water placed over areas of trigeminal, but not cranial nerve innervation, produced a 14% drop in SGaw [133]. Results such as these have led to the suggestion that cold receptors may be more important in triggering the diving reflex than previously assumed [134]. Covering the face is effective at preventing this facio-bronchoconstrictor reflex.

In contrast, ice cold water sprayed on the trunk produced gasps followed by hyperventilation [135]. Water temperature was inversely related to the level of respiration. Both were independent of pain perception.

**Central Nervous System Triggers.** Cerebral injury can uncover primitive reflex activity [136]. Tapping the bridge of the nose activates trigeminal afferent – facial nerve efferent motor reflexes with cranial muscle spasms. Acoustic stimuli evoke patterned motor activity with a rostrocaudal progression of muscle spasms. Sternal tapping activates cervical cord H-reflexes with sternocleidomastoid and arm muscle spasms. Serotonin may participate in these central nervous system arcs [137].

Clues to the neurological and molecular mechanisms of some of these trigeminal reflexes can be derived from diseases such as hyperekplexia (startle disease). This is a rare non-epileptic disorder characterized by an exaggerated persistent startle reaction to unexpected auditory, somatosensory and visual stimuli, generalized muscular rigidity, and nocturnal myoclonus [138]. Hyperekplexia is usually familial, most often autosomal dominant with complete penetrance. Because of variable expression, the time of presentation may be as early as fetal life, with abnormal intrauterine movements, to adulthood. The genetic basis is a mutation, usually of the arginine<sup>271</sup> of the  $\alpha$ -1 subunit of the inhibitory glycine receptor. This changes the actions of the glycine receptor agonists  $\beta$ -alanine and taurine into competitive antagonists. As a result, activation of the mutant receptor does not lead to inhibition of neuronal hyperexcitability in regions such as the caudal pontine reticular formation. The clinical hallmark is the persistent generalized flexor spasm that occurs in response to tapping of the nasal bridge (no habituation). The tonic

spasms may mimic generalized tonic seizures, leading to apnea, bradycardia, cyanosis, and death. Sudden, forced flexion of the head and legs towards the trunk is known to be life saving when prolonged stiffness impedes respiration. Clonazepam, a  $\gamma$ -aminobutyric acid (GABA) receptor agonist, is the treatment of choice for the hypertonia and apnea, but may not influence stiffness. These characteristics suggest that many types of stimuli converge upon a central reflex that leads to tonic spasms, with inadequate inhibitory glycinergic receptor - mediated reflex suppression. Other genotypic polymorphisms may play roles in nasal reflexes limited to subsets of rhinitis subjects.

Women with spinal cord injuries above T7 have difficulty breast feeding because they do not receive sensory input of the infant suckling at their nipples. This can be overcome using oxytocin nasal spray, active mental imaging and relaxation techniques to facilitate the milk let-down reflex [139].

**TABLE 2.** Nasal Reflexes.

	Nasal Afferents	Systemic Afferents
Nasal and other Upper Airway Efferent	Nociceptive nerve axon responses Nasal cycle Nasonasal reflexes Nasopharyngeal reflex Nasolaryngeal reflex Nasolacrimal reflex Nasosalivary reflex Gustatory rhinitis ("salsa sniffles") Cold dry air – induced rhinitis ("skier's nose" "ski bunny rhinitis")	Postural reflex Crutch reflex Exercise reflex Hot and Cold cutaneous temperature reflexes Visible and Infrared Light reflexes Bronchonasal reflex Ovulatory rhinitis Sexual reflexes Alcohol reflex Psychogenic syndromes
Systemic Efferent	Diving reflex Naso-broncho-cardiac reflex Sneeze Nasotracheo-bronchial vaso-dilation reflex	Crutch reflex Exercise reflex

### **Peripheral Stimuli Leading to Nasal Reflexes**

**Exercise.** Sympathetic reflexes are active in the nasal mucosa. Exercise promotes a drop in total nasal airway resistance within 30 sec that is maximal at 5 min, and may persist for up to 30 min after completing the aerobic performance [140,141]. Nasal airway resistance drops in proportion to exertion, with a 39% reduction at a workload of 75 watts and 49% after 100 watts. Sympathetic vasoconstriction of nasal vessels is part of

a general sympathetic effect to maintain the flow of oxygenated blood to the muscles [142]. Isocapnic hyperventilation does not alter nasal airflow, indicating that the workload, and not nasal or oral airflow, is the trigger for the nasal and systemic vasoconstrictor response. Body position also does not affect the nasal changes of exercise.

Exercise [143], and  $\alpha$ -adrenergic agonists [144,145] decrease the thickness of the mucosa and increase nasal and sinus ostial patency. Sympathetic nerves innervate arterial and venous vessels including arteriovenous anastomoses, with only occasional nerves found around glands. Sympathetic nerves contain either norepinephrine, or norepinephrine plus neuropeptide Y (NPY) [146]. Norepinephrine and NPY are both vasoconstrictors, but NPY is slower in onset, and very long in duration [147]. The presence of both NPY-containing nerves and NPY binding sites on arteriovenous anastomoses suggests that NPY acts as a vasoconstrictor at this key location in vivo. NPY nasal provocation leads to decreased nasal airflow resistance and reduced plasma exudation [148]. NPY agonists may be excellent long-acting vasoconstrictors that may augment or replace  $\alpha$ -adrenergic agonists.

**Positional Nasal Obstruction and Patency.** Positional regulation of nasal airflow has been demonstrated by having subjects lay in the right and left lateral decubitus positions to maximize nasal patency in the superior nostril and decrease patency in the inferior nostril [149]. Nasal peak flow rates were measured after 30 min. Position had no effect on peak flow in the superior nostrils, or if nostrils were 100% obstructed (zero flow in some rhinitis subjects). However, the inferior, reflexly obstructed nostrils had a significant reduction in mean peak flow of -12.8 L/min (SD = 4.1 L/min). This obstruction may have clinical implications. Fluid dynamics demonstrate that the physical force (frictional stress) exerted on the walls of a tube increase as tube diameter is decreased (increased airflow resistance). Reduced tube diameter may be equated with the reduction in cross – sectional area for airflow through the nostrils during rhinitis. If so, breathing through obstructed nostrils could generate mechanical forces that activate mechanosensitive neurons and the sensation of nasal obstruction, or even promote epithelial cell damage and apoptosis which may worsen nasal inflammation. This full hypothesis remains to be tested.

**Peripheral Cutaneous Temperature Exposures.** Cold water immersion of one upper limb leads to unilateral nasal obstruction in normal nonrhinitic subjects. Both the afferent and efferent arms of the reflex were limited to the chilled side [150]. Chilling one foot in water also increases nasal airflow resistance [74].

Immersion of both feet in warm water (42°C) increased the temperature of the nasal mucosa from ~30°C towards core body temperature [151]. Lidocaine prevented this nasal mucosal temperature rise. This implicated a neural mechanism. Topical mucosal application of phenoxybenzamine, an  $\alpha$ -adrenergic receptor antagonist also increase the mucosal temperature. These data suggested that foot warming led to a decrease in systemic sympathetic activity that resulted in decreased norepinephrine release, default vasodilation, and so an increase in arterial blood flow through the superficial vascular plexus. Foot warming may have induced a transient, organ – specific parasympathetic vasodilator effect. Acetylcholine was not involved, although it is conceivable that small diameter VIP / NO sphenopalatine vasodilator neurons were activated.

**Crutch Reflex.** Five minutes of unilateral axillary pressure decreased the ipsilateral minimum nasal cross sectional area (median change = 0.09 cm<sup>2</sup>,  $P < 0.01$ ) [152]. This demonstrated that axillary pressure caused either a loss of sympathetic vasoconstriction in the anterior nasal valve, or increased parasympathetic tone. In either event, ipsilateral nasal obstruction (“congestion”?) was induced. The contralateral nasal minimum cross-sectional area was significantly increased (median change = 0.35 cm<sup>2</sup>,  $P = 0.01$ ) (median change = 0.35 cm<sup>2</sup>,  $P = 0.01$ ) suggesting a contralateral increase in sympathetic vasoconstriction. Systemic sympathetic effects were suggested by increases in heart rate and diastolic blood pressure, but systolic blood pressure was unaltered. The loss of parasympathetic cholinergic inhibition of the sinoatrial node may also have contributed to the increased heart rate.

**Additional Triggers.** Non-eosinophilic non-allergic rhinitis (NENAR) may be a disease of autonomic imbalance. The roles of systemic stimuli on nasal patency were assessed [153]. The nasal response to axillary pressure is much reduced in NENAR patients compared with normal controls, and the normal decrease in nasal resistance in response to standing is abrogated. Isometric exercise has little effect in normal subjects, but those with NENAR demonstrate an increase in nasal resistance. A similar effect is seen in response to the cold pressor test. Treatment with topical fluticasone propionate normalized the damaged nasal reflexes seen in NENAR, while placebo had no effect. However, the systemic, non-nasal autonomic reflexes imbalances were not affected by nasal treatment.

Blood oxygen saturation decreases during dental procedures. The use of external nasal dilator strips decreased patient discomfort, but this was not correlated with changes in oxygen saturation [154]. This suggests that the sensation of nasal patency may be separated from fear, pain and hypoventilatory effects. Tooth stimulation activates sympathetic reflexes with

elevation in heart rate and blood pressure and nasal mucosal vasoconstriction [155]. More intense and prolong tooth stimulation induced a second vasodilator reflex limited to the lips.

Infrared light emitted from a dark source and applied to the face or trunk induced the sensation of nasal congestion [156]. Entering a brightly lit area from a dark area stimulates sneezing in some subjects [157]. Mechanisms of these reflexes are unknown.

Trigeminal autonomic cephalgias are a headache class that includes cluster headache, paroxysmal hemicrania, short lasting neuralgiform pain with conjunctival injection and tearing (SUNCT), and a subset of migraine headache patients who develop unilateral cranial autonomic symptoms such as nasal congestion, rhinorrhea, conjunctival vasodilation and injection, lacrimation, and eyelid edema [158]. One open label study suggested that that this subset may have had better pain relief with sumatriptan than migraineurs without autonomic symptoms [159]. However, this 5-HT<sub>1B/1D</sub> receptor antagonist did not alter the migraine – associated autonomic responses. The absence of double blinding, randomization, placebo control, and study in migraineurs without unilateral cranial autonomic symptoms severely limits the value of this conclusion.

Patients with neurological degenerative diseases develop multiple system atrophy (MSA) with autonomic dysfunction and disabling orthostatic hypotension [160]. The absence of normal autonomic reflexes has uncovered a series of previously unknown reflexes. Meals induce profound hypotension. Conversely, commonly used nasal decongestants have substantial pressor effects, and ingestion of 500 mL of water can increase blood pressure by a previously unrecognized sympathetic reflex. Residual sympathetic tone can induce sustained supine hypertension that resolves after ganglionic blockade. These phenomena were not previously recognized because of the buffering capacity of the baroreflex, but were unmasked in these autonomic failure patients. Although unstudied, they may have nasal congestion as occurs in Horner's syndrome, and alterations of other nasal reflexes.

Alcohol induces nasal congestion, the sensation of laryngeal airway closure, and occasionally bronchoconstriction. Red wine followed by white wine are the most common causes [161]. Women are affected twice as often as men. Some men report profound nasal obstruction with malt – laden beers. The agents that trigger these responses are not identified, but may include tannins from grape skins, sulfite preservative, and volatile products of fermentation.

### **The Sexy Nose.**

Sex and the nose are intimately linked. Foreplay and coitus lead to increased sympathetic reflexes with nasal

constriction. This may last for some time before the normal nasal cycle or bilateral nasal congestion occur.

Sexual intercourse is a poorly recognized and underappreciated trigger factor for attacks of asthma and/or rhinitis and the morbidity caused to the ego and self-image of these patients. Some subjects can develop an overactive cholinergic reflex with nasal discharge that responds to anticholinergic drugs. Acute severe asthma may require emergency department visits [162]. These events can strain a relationship and lead to high anxiety. Late asthmatic responses have been reported, suggesting that the asthmatics may have been undertreated. None of the patients developed wheezing, dyspnea, a fall in peak expiratory flow rates, or rhinitis after climbing two flights of stairs, an exercise considered equivalent to energy expended during sexual intercourse. Thus, sexual excitement rather than exercise appeared to be the cause of postcoital asthma and rhinitis. Adequate pharmacotherapy along with counseling of the patients and their spouses restored normal sexual function and control of asthma and rhinitis. Postcoital asthma and rhinitis can easily be overlooked due to patient embarrassment and lack of physician awareness.

Sex and nonallergic rhinitis played an influential role in Sigmund Freud's development of concepts of neurosis and psychoanalysis. Freud's closest friend and confidant was an eccentric ENT surgeon, Dr. Fliess [163]. Fliess postulated that "reflex nasal neurosis" was based on an important physiological connection between the nose and the genitals, and described specific genital spots located on the nasal inferior turbinate. His tools were his clinical observations that he reduced to descriptive classifications. In contrast, Freud, the academic, analyzed these clinical observations of psychological phenomena through the prism of his theory of sexuality.

This unlikely pair developed a joint research project in 1893 to study the clinical problem of "neurasthenia" [164]. This study became more of a dialogue and was never carried out. One outcome was the psychological component of Freud's psychoanalytic theory. The other was Fliess's theory of vital periodicities. He believed that the symptoms of his reflex nasal neurosis followed regular 28-day cycles like female menstruation, and proposed a 23-day male menstrual cycle that he centered specifically on the nasal turbinate.

Although these theories have been largely discredited, we remain with the issue of "neurasthenia" in its various guises, and psychosomatic syndromes. The latter include sudden anosmia [165], recalcitrant nose picking [165], Intractable psychogenic sneezing [105-107], and the neurocognitive need to explain nasal symptoms in the context of affective or psychological dysfunction [166].

Why should rhinitis have had such strong influences on Freud and Fliess? Cases of coital reflex nasal obstruction, the anxiety they produced, and nasal symptoms that changed during throughout the menstrual period and in pregnancy probably played important roles. The anxiety and frustration of allergic rhinitis, and presumably nonallergic rhinitis, decrease quality of life and promote sexual dysfunction [167]. Changes during the menstrual cycle have been evaluated using peak inspiratory nasal flow, acoustic rhinometry, anterior rhinomanometry, mucociliary clearance time and a rhinitis questionnaire [168]. Anterior rhinomanometry and mucociliary time were significantly reduced at the time of ovulation compared to the onset of menstruation ( $p < 0.05$ ). These obstructive changes coincided with the high serum estrogen levels found at ovulation. Changes in mucosal hyperresponsiveness were also examined [169]. The nasal mucosa became hyperreactive to histamine at the time of ovulation. Hyperresponsiveness was not different from the menstrual level during the luteal phase.

Relationships such as these have not been identified in earlier studies [170,171], perhaps because of limitations in assay techniques. However, receptor binding studies did not identify nasal mucosal receptors for estradiol or progesterone.

## **Conclusion**

A wide variety of reflexes have nasal afferent and either nasal, tracheobronchial, or systemic efferent sympathetic or parasympathetic connections (**TABLE 2**). Our understanding of these nasal afferents will improve as we apply new information about subsets of Type C and A $\delta$  nerve fibres that are characterized by specific combinations of ion channels, G protein – coupled excitatory and inhibitory autoreceptors, other sensors, and their combinations of neurotransmitters. Recognition that these afferents may be regulated by neurotropic cytokines, pollutants, pollen grains, and allergic and nonallergic inflammation is important in order to determine optimal, individualized treatment plans. Unfortunately, there are few drugs for blocking these afferent nasal nerves short of surgical extirpation. Afferent nerve axon responses appear to stimulate the immediate defense mechanism of glandular secretion when induced by relatively low intensity pain of hypertonic saline. Other sets of afferents may be activated by histamine (itch), capsaicin, and other agents, and lead to different local mucosal responses. These actions are very different in humans from the widely studied rat neurogenic inflammation mechanisms. Nasonasal cholinergic, parasympathetic reflexes also lead to glandular exocytosis and can be effectively blocked by topical anticholinergic agents. The naso-broncho-cardiac or diving reflex is an ancient one that persists in humans. It may have been retained to function at the time of birth. Systemic temperature,

pressure (e.g. crutch reflex), and other stimuli can affect the nose by stimulating or suppressing autonomic sympathetic or parasympathetic tone. There is still considerable work to be done to define the neural pathways of these and the other reflexes that have been discussed.

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