Cold, Dry Air, and Hyperosmolar Challenges in Rhinitis

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Introduction

Rhinitis implies inflammation of the nasal mucosa. Inflammation is caused by many stimuli, including ambient conditions. The environmental conditions can also act as a trigger of symptoms. The interaction of environmental temperatures and humidity, especially dry conditions, and nasal inflammation are reviewed in this chapter. Also reviewed is the hyperosmolar challenge, which can serve as a surrogate for cold, dry air (CDA) challenge.

Many individuals experience symptoms of rhinitis, primarily rhinorrhea and nasal congestion, on exposure to cold, windy environments [1]. Some individuals are exquisitely sensitive to CDA; for example, patients with nonallergic rhinitis react to CDA more vigorously than do healthy individuals [2]. There has also been an interest in the nasal reaction to CDA, to understand the physiology of the nose.

The prevalence of cold-air-induced rhinitis is not clear, but in a 1980/81 survey of 912 police officers in Paris, France, 5.4% reported this problem [3]. A database of 206 individuals with objectively confirmed perennial allergic rhinitis and 150 with seasonal allergic rhinitis indicated that cold air is considered a stimulus for nasal symptoms in 55% and 28% of the individuals, respectively [4]. Additionally, individuals who go skiing almost uniformly have rhinitis, and hence the placement of tissues on the lift lines is commonly seen.

Nasal inhalation of CDA causes drying of the nasal mucosa, resulting in increased toxicity and osmolarity of nasal secretions [5]. Hyperosmolar stimuli can trigger nerves, leading to reflex stimulation of the parasympathetic system. In support of this concept, unilateral challenge with CDA leads to bilateral cholin-
logic secretory response via a nasosinal reflex, and this secretory response can be reduced by topical treatment with atropine [6, 7]. The complex structure of the nasal vasculature performs air conditioning by dilatation of the resistance vessels and increasing blood flow [8]. Passive vasodilatation of the nasal vascular bed in response to CDA is mediated by the parasympathetic system [9–11]. These effects lead to increased speed of airflow, increased evaporation of water from the nasal mucosal surface, and hence increased osmolarity of nasal secretions.

The Conditioning Capacity of the Human Nose

A major function of the nose is to condition the temperature and humidity of inspired air [12]. In the healthy state, the reserve of the nose to perform this function is enormous. Prior investigations of nasal conditioning have led to several observations. First, exhaled air is fully humidified [12]. Second, its temperature is slightly below body temperature because of a mucosal temperature gradient caused by inspiration. This gradient leads to a recovery of heat and water estimated to be 30% of that needed for conditioning of inspired air [13, 14]. Inspiring hot, dry air interferes with the establishment of the gradient and allows for less recovery of heat and water during expiration [14]. Third, there is wide individual variability in the temperature recorded in the nasopharynx [12–14]. Fourth, despite the wide variability in nasopharyngeal temperature, the relative humidity is 100% [12–14]. Finally, ventilation between 10 and 40 litres has no effect on the temperature and humidity of inspired air [13].

The theoretical model of Hanna and Scherer predicts that the blood temperature distribution along the airway wall, and the total cross-sectional area and perimeter of the nasal cavity, are the two most important parameters of the human air-conditioning response [15]. Other factors, such as the thickness of liquid on the airway surface, blood perfusion rates, and the thickness of the mucosal-submucosal layers, are thought to be less important. As discussed below, parts of this model can be supported, but others cannot.

A part of the importance of nasal air conditioning is its impact on the lower airway. Air that is not fully conditioned when it exits the nasal cavity requires further conditioning by the lower airways [16]. This fact has been amply demonstrated and relates to minute ventilation, tidal volume, and the temperature and water content of the inspired air [17]. Transferring this function from the nose to other parts of the airway for prolonged periods may alter the airway physiology. This notion is supported in part by several lines of evidence: epidemiologic studies by Annens et al. showed that subjects reporting nasal sensitivity to CDA had a more rapid decline in FEV1 over 5 years, compared to those without such sensitivity [18]; inhalation of the same volume of dry air through the mouth, in contrast to the oronasal route, causes a greater reduction in FEV1 in asthmatics [19]; temperature changes can affect ciliary activity in vitro; and subjects requiring a tracheotomy or endotracheal intubation for protracted periods of time have changes in the tracheal epithelium [12]. Also, studies of the lower airways of elite athletes, who exercise in cold environments for prolonged periods of time, have changes in structure.

Cold, Dry Air Challenge

Exposure to unconditioned air also has been shown to affect the nose itself. Nasal congestion is a physiologic response to breathing of cold air [20]. Prolonged exposure of rats to cold environments results in nasal mucosal damage, with decreased goblet cells and intraepithelial glands as well as fibrotic changes [21, 22]. Intermittent exposure of guinea pigs to cold air induces upregulation of mucociliary receptors and increased responsiveness to methacholine and antigen provocation, but not to histamine provocation [23]. The use of nasal continuous positive airway pressure (CPAP), which involves high flows of dry air, for treatment of sleep apnea leads to significant rhinitis, which is in part reduced by heated humidification of the inspired air. Additionally, subjects who have had total laryngectomy and hence are no longer passing air through their nose undergo structural changes in their nasal mucosa [14]. These lines of evidence suggest that the mucosa of the upper and lower airway changes in response to the air-conditioning demands dictated by the environment.

When air is inspired through the nose, not only the warming process, but also the humidification process leads to cooling of the mucosal surface [24], because vaporization of water from the epithelial lining fluid into the airstream requires heat. With water leaving the epithelial-lining fluid, transient increases in the osmolarity of this fluid occur. With increasing ventilation rates through the nose or when the ambient air is at a temperature much lower than room air (and, consequently, water content), the nasal heat and water losses are increased and the cooling as well as the drying effects on the nasal mucosa are greater.

The anatomy of the nasal mucosa is of major importance in the ability of the nasal passages to condition air while retaining homeostasis of mucosal heat and water. One of the characteristic mucosal structures is the dense, subepithelial capillary network. These capillaries have fenestrations that are polarized toward the luminal surface [25]. Blood flow through this network provides heat, and the fenestrae probably facilitate water transportation into the interstitium, the epithelial cells, and the epithelial lining fluid. The other important structural elements of the nasal submucosa are the venous sinusoids, which lie below the subepithelial capillary network. These blood vessels have the ability to rapidly pool large volumes of blood because they are supplied by many arteriovenous anastomoses and because their draining veins (cushion veins) can contract and stop the blood outflow [26]. Blood pooling leads to engorgement of the nasal mucosa, and this increases the airstream contact surface.

There is no agreement on which the structural element of nasal mucosa mainly contributes to water transportation and air humidification. The abundance of seromucous submucosal glands, especially in the anterior portions of the nasal cavity, suggests that their secretions could provide most of the water needed for humidification [27]. Cauna contended that the role of humidification belongs to water from the fenestrated subepithelial capillaries, which continuously diffuses through the epithelium [28]. However, Ingelstedt, who injected fluorescein intravenously in normal human subjects, was not subsequently able to detect it in their nasal secretions [29]. Fluorescein is supposed to move freely across capillaries into the adjacent tissues, and its absence in these experiments suggests that transudation does not occur. However, it is not known whether fluorescein can cross the nasal basement membrane and diffuse between epithelial cells. Osmotic drives generated by water loss during the inspiratory phase may move water from the intraepithelial spaces...
Evidence for Hyperosmolarity Occurring Because of Water Loss from the Nasal Surface

An experimental model of nasal provocation with CDA was developed in 1985 [36]. Nasal inhalation of CDA led to hypertonicity of the nasal lining fluid [5, 37]. Secretions produced by inhalation of hot (40–45°C) dry air through the nose were more hyperosmolar than those for the respective CDA challenge [38]. These studies suggest that hydration of the nasal mucosa and water loss caused by CDA challenge are important factors for determining the osmolarity of nasal secretions. Individuals who do not develop a symptomatic response to CDA do not have increased post-CDA osmolality [5], indicating that they have a greater capacity to achieve osmotic homeostasis. No change in the number of epithelial cells in nasal lavage fluids was observed after CDA provocation in nonresponders, whereas, the number of epithelial cells in nasal lavage fluids increased sixfold immediately after CDA provocation in CDA-reactive individuals. It is possible that the epithelial detachment occurred as a result of mucosal desiccation, due to the inability to compensate for dry-air-induced water loss [39].

Human Model for the Study of Dry-Air and Hyperosmolar Challenge

Models of nasal challenge with dry air or with hyperosmolar stimuli (hypertonic saline, mannitol) have helped investigators to understand the pathophysiology of CDA-induced nasal inflammation [40]. The model of nasal CDA challenge developed by Togias is characterized by: (a) breathing of air through a nasal CPAP mask placed over the nose; (b) subfreezing air temperatures (0–10°C); (c) moderately high airflow (around 26 l/min); and (d) a 10–15 min duration of challenge [36]. Subjects were asked to inhale through the nose and exhale through the mouth to maximize the potency of the stimulus. Nasal inhalation of warm, moist air (around 37°C, 100%

Relative humidity) was used as a negative control. Braat and colleagues [41] used air at −10°C with a relative humidity of <10% via a porpoise-shaped nose cap. The dosage was increased in steps as follows: 12.5, 25, 50, 100, 200, and 400 liters/min. This involved CDA provocation steps of 1, 1.2, 2.4, 8, and 16 min with a flow of 12.5 for the first step and 25 l/min for the following steps. With this model, they could differentiate patients with nonallergic, noninfectious, and perennial rhinitis from control subjects.

Hyperosmolar challenge of the nose involves the instillation of 10 ml of hypertonic mannitol solution (around 800 mosmol/kg) into the nose (in the form of a nasal lavage), where it remains for 10 s [37, 42] before being expelled. This can lead to nasal symptoms (burning is the most prominent symptom) and histamine release in returned nasal lavage fluids. One can access the capacity of the nasal mucosa to correct acutely the hypertonic load by measuring the osmolality of the mannitol solution before instillation and after it is expelled from the nose [37]. Hypertonic saline spray with increasing concentrations (0.9–22% NaCl solutions) have been used in a stepwise protocol for challenge of the nose [43, 44]. Furthermore, localized hyperosmolar nasal provocation can be done by application of a filter paper disk soaked with NaCl solution on the septal or conchal mucosa [45, 46].

For experimental research, quantitative measurements with high reproducibility are essential [47]. The interpretation of the results demands a basic knowledge of the techniques employed as well as of the study design. All provocation studies require careful selection of subjects, and the disease state and the symptomatic status of the subject must be clearly defined by subjective and objective parameters. The selected subjects should be free of other underlying diseases and of the need for medications that may confound the interpretation of results.

Assessment of the Response

Subjective

Symptoms produced after nasal challenge can be recorded by different techniques, such as, symptom scores or a visual analog scale. Congestion and rhinorrhea are easy to assess by the subject and yield valuable information. Counting of sneezes by the investigator provides an objective symptom assessment.

Objective

1. Nasal airway resistance (NAR): Rhinomanometry measures NAR by quantitatively measuring nasal airflow and pressure. Active anterior rhinomanometry is most frequently used because it is well tolerated by the patients. Unfortunately, the correlation between the objective and subjective response is weak.

2. Nasal peak inspiratory flow: This is the simplest technique for detecting changes in nasal patency for repeated measurements before and after a nasal challenge.
It can also be used at home to monitor the airflow or the response to treatment over a more prolonged time period.

3. **Nasal volume**: The geometric cross-sectional area and nasal volume can be measured using acoustic rhinometry.

4. **Nasal secretions**: Several methods have been used for collecting and quantifying nasal secretions: suction, blowing, dripping, lavage, and absorption. Blown secretions can be quantified by weighing of handkerchiefs. An amount of nasal secretions can be obtained by placement of disks on the nasal mucosa for a fixed period of time. Disks used for secretion collection are first kept in Eppendorf tubes, and the disk-tube combinations are weighed before the collection of secretions. After collection, the disks are replaced in the Eppendorf tubes and weighed. The precollection weight is then subtracted from the postcollection weight for determining the weight of secretions generated in a fixed period [48]. Nasal lavage samples secretions from a large mucosal area, whereas, disks sample secretions from a localized area. Importantly, the collection of nasal secretions is useful for the assessment of both cellular and biochemical changes in nasal secretions and change in the osmolarity of nasal secretions.

5. **Biological markers**: Biological markers in the collected secretions can be measured for understanding the underlying pathophysiology. These include histamine and other mast-cell- associated mediators, cytokines, plasma protein, and glandular secretory products. It is important to know the stability of each marker after recovery, as well as the validity of each measurement, when interpreting changes in the levels of these markers. The amount of markers obtained reflects their levels on the mucosal surface, which may not be the true amount of the released substances. However, the level of mediators obtained at fixed time intervals best reflects the total amount of the mediator collected.

6. **Cells**: Cells can be obtained from the nasal cavity by multiple techniques. The epithelial layer can be scraped or brushed. Nasal scrapings and brushing allow mucosal sampling from a wide area of the nasal cavity and contain a large number of epithelial cells. Blown secretions are simple and painless to collect, but are dependent on the spontaneous exfoliation of cells. The specimen reflects activity only in the upper level of the nasal mucosa and yields low cellularity. Nasal lavage samples the entire nasal cavity and reflects changes in the upper mucosa only. Nasal biopsy provides information about structural elements and cellular contents of the epithelial layer and the deeper submucosa. A wide range of histochemical or immunohistochemical techniques can be employed for light microscopy.

**Comparison Between Dry-Air and Hyperosmolar Challenge**

Hyperosmolar provocation in the human nose activates nasal glands [42, 44, 49]. However, plasma extravasation has not been demonstrated [44, 49]. Unilateral stimulation of the nasal mucosa with hyperosmolar stimuli results in bilateral secretory response [46]. Treatment of the ipsilateral site to the hyperosmolar challenge with topical anesthetic (lidocaine) inhibits both the ipsilateral and the contralateral secretory response. Repetitive, unilateral application of capsaicin for several days before hyperosmolar challenge inhibits both the ipsilateral and the contralateral secretory response [45]. This demonstrates that a hypertonic stimulus can activate sensory nerves and induce central reflexes with effenter glandular responses in both nasal cavities.

Hyperosmolar provocation results in the release of histamine and leukotriene C₄ [42], generating the hypothesis that hyperosmolarity leads to mast cell activation. Human lung mast cells release inflammatory mediators upon exposure to a hyperosmolar medium in vitro [50, 51]. However, mast cell tryptase cannot be detected after hyperosmolar nasal challenge [49].

The similarities between the nasal response to a hyperosmolar stimulus and to CDA are: (1) Individuals who develop nasal symptoms after CDA challenge are more responsive to challenge with hyperosmolar mannitol [37]; (2) CDA provocation in CDA-sensitive subjects can activate nasal glands [49, 52]; (3) In cold-air-sensitive individuals, CDA activates sensory nerve endings and produces a central secretory reflex [7]; and (4) CDA provocation in the CDA-sensitive subjects leads to mast cell activation [36, 49, 53]. The difference between the nasal response to a hyperosmolar stimulus and that to CDA is that plasma extravasation has been demonstrated after CDA challenge, but not after hyperosmolar challenge [35, 36]. Late-phase responses after nasal provocation with CDA have been shown [54]. Unfortunately, no one has examined the occurrence of a late response after nasal challenge with hyperosmolar stimuli.

**Assessment of the Ability of the Nose to Warm and Humidify Air**

**Nasal Probe**: We developed a probe with a thermistor and a humidity sensor that is placed in the nasopharynx [55]. We selected the nasopharynx for these studies because it represented the end result of nasal conditioning. Although the exact location for conditioning of air within the nose will shift, such a shift occurring before the exit of air from the nose would not be expected to influence the lower airway. The technique involved placing a nasal CPAP mask over the probe with head straps. Air from the compressed air tanks was passed through a flow meter into a cold-air machine. CDA at 0% relative humidity was then delivered to the patient's nose via the mask at flow rates of 5, 10, and 20 l/min. The air temperature was approximately 19°C, 10.5°C, and 0.8°C at 5, 10, and 20 l/min, respectively [56]. The subjects were instructed to breathe in and out through the mouth. Nasopharyngeal temperatures at 5, 10, and 20 l/min for subjects during exposure to CDA were 33.4 ± 0.7°C, 30.5 ± 1.1°C, and 25.9 ± 1.4°C, respectively [55]. The difference between the water content of air prior to entry into the nose and that in the nasopharynx was the water gradient (WG) across the nose, which
represented the amount of water evaporated by the nose to condition air. After exposure to CDA, the WG at 5, 10, and 201/min. was 297.6 ± 12.6 mg, 509.1 ± 32.0 mg, and 794.1 ± 62.1 mg, respectively. Individuals showed wide variability in their ability to condition air. This ability did not correlate with the baseline nasal airway resistance, nasal volume, nasopharyngeal mucosal temperature, or body temperature. Proctor et al. speculated that prior viral infections may have altered the epithelium, thus producing the variability [56]. However, it could reflect an intrinsic capacity of the nasal surface to condition inhaled air. A recent study showed that siblings condition air similarly, suggesting a hereditary component to nasal conditioning [77].

Surface Temperature: Multiple factors can contribute to the amount of water delivered to inspired air. Among these, the geometry of the nasal cavity and the temperature of the nasal mucosa appear to be key factors [15]. Keck and colleagues measured intranasal temperature at different locations in 50 volunteers, after inspiration, and found that the greatest increase in temperature was observed in the nasal valve area [57]. We studied the effects of raising the nasal mucosal surface temperature by immersion of the feet in warm water [58–60]. Increased nasal mucosal temperature improved the ability of the nose to condition inspired air without a significant change in the volume of the nasal cavity [61]. Application of a topical vasoconstrictor drug, oxymetazoline, decreased the nasal mucosal temperature [62] and the temperature of inspired air at the oropharynx [24]. Application of an alpha-adrenergic receptor antagonist, which increased the temperature of the nasal mucosa, had no impact on the ability of the nose to condition air [62]. Furthermore, we reduced the nasal volume without altering the mucosal temperature by placing subjects in the supine position, and we studied this effect on the nasal conditioning capacity. Contrary to the theoretical model, in the supine position, subjects were less able to condition CDA compared to the upright position [63]. Based on these observations, the theoretical model of Hanay and Shurer is only partially supported [15]. It is quite possible that surface temperature and nasal volume are only partially responsible for the water transportation capacity across the nasal mucosa. There are many complex factors (e.g., electrolyte transport across the nasal mucosa, tight junction transport, or aquaporin function) which have not been assessed.

Nasal Inflammation: We previously showed that subjects with seasonal allergic rhinitis, out of season, had a reduced ability to warm and humidify air compared with normal subjects [55]. We studied the effect of allergic responses induced by either seasonal exposure or nasal challenge with antigen on nasal conditioning of CDA. An allergic response caused by either seasonal exposure or allergen challenge increased the ability of the nose to condition inspired air [64]. The allergen challenge-induced observation was subsequently confirmed in subjects with perennial allergic rhinitis [65, 66]. We also showed that subjects with asthma had a decreased ability to condition air [67]. The more severe the asthma, the worse was the ability of the nose to condition air, indicating that the reduced nasal conditioning capacity of subjects with asthma could adversely affect the lower airway.

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Parasympathetic Nervous System: The parasympathetically driven glands in the nose, approximately 45,000 per nasal cavity, are the major contributors to the volume of surface secretions [27, 68]. Local application of atropine sulfate significantly inhibits rhinorrhea in nasal lavage fluids, suggesting that parasympathetic neuronal activity occurs during the nasal response to CDA [35]. We were concerned that, although ipratropium bromide treated the rhinorrhea, it might worsen the ability of the nose to condition air. It had been shown that subcutaneous injection of 1 mg atropine decreased the ability of the nose to humidify air [69]. However, application of homatropine or ipratropium bromide to the nasal surface did not impair its humidification function [70, 71]. We studied the effect of treatment with ipratropium bromide on the ability of the nose to condition CDA. Ipratropium bromide improved the conditioning of inspired air, despite the fact that the secretary response measured after the end of cold-air exposure was decreased [72]. This experiment suggested that glandular secretion was not a major contributor to nasal conditioning, and blocking of secretions did not adversely affect the ability of the nose to warm and humidify air.

Mechanism of CDA-Induced Rhinitis

CDA challenge to the nose led to mast cell and glandular activation [49, 52] and plasma extravasation [35] (Fig. 1). This was observed only in cold-air-sensitive individuals, but not in nonsensitive controls and correlated well with the development of nasal symptoms [48].

Inhalation of CDA stimulates sensory nerves and generates a cholinergic secretory response. The cholinergic secretory response was demonstrated by the reduction of the contralateral secretory response after ipsilateral CDA provocation when the contralateral nostril was pretreated with atropine [7]. Furthermore, atropine was shown to reduce rhinorrhea scores and a biomarker of glandular activation after CDA challenge, without affecting exudation [35].

Although the nasal reaction to cold air has been found to involve both mast cell activation and sensorineural stimulation, the clinical significance of the former pathway is unknown. For example, a topical antihistamine (azatadine base) had been shown, previously, to inhibit allergen-induced symptoms and release mast cell mediators in individuals with allergic rhinitis [73]. However, it had no effect on either symptoms or histamine release after CDA provocation [74]. Furthermore, the use of topical glucocorticosteroid (beclomethasone), for 7 days, significantly reduced histamine release, but not in the TAME-esterase activity, albumin levels, or in symptoms after CDA challenge [34]. These results indicate that histamine may not be essential for the development of the immediate nasal reaction to CDA. The clinical response to CDA seems to be mediated primarily by neural mechanisms, with a sensory element that is located in the nasal mucosa and an effector element that is mostly cholinergic. In support of this concept, objective measures of the nasal reaction (decreased nasal patency and secretion weight) to CDA have been
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Nasal symptoms are reduced successfully with intranasal capsaicin treatment, which defunctionalizes nociceptor C-fibers [75]. Also, intranasal anticholinergic agents reduce rhinorrhea in skiers [76].

During cold-air breathing, there is loss of heat and water from the mucosal surface, resulting in mucosal cooling and hyperosmolarity of nasal secretions. The effect of cooling on the mucosa is unknown. Evidence has shown that hyperosmolarity is a known trigger for mast cell and sensory nerve activation in the human nose. Water loss leading to hypertonicity is more likely to be the key stimulus rather than heat loss.

One hypothesis for CDA-induced symptoms of rhinitis is that the respiratory mucosa of individuals with CDA sensitivity cannot compensate for the loss of water that occurs on exposure to the stimulus, leading to epithelial damage. Cruz et al. found a sixfold increase in nasal-lavage epithelial cells in the CDA-sensitive group after CDA, but not after exposure to warm, moist air [39]. This finding shows that epithelial cell shedding accompanies clinical responses to CDA in the human nose, supporting the above hypothesis.

Why does cold-air-induced rhinitis affect a subgroup of individuals more than others? Neither the presence of atopy nor nasal responsiveness to histamine has predicted CDA responsiveness [37]. The osmolarity of the epithelial lining fluid was increased after CDA provocation in a CDA-sensitive group, but not in an insensitive group [5]. In addition, when nasal challenge with a hyperosmolar solution was performed in both groups, CDA-sensitive subjects released significantly more histamine in nasal lavage fluids than did CDA-insensitive subjects [37]. The underlying difference between CDA-sensitive and CDA-insensitive individuals probably relates to the ability of the mucosa to cope with conditions that demand an increased water supply to inhaled air or to the epithelial surface, whether after the inhalation of dry air or after application of a hyperosmolar stimulus. The airway mucosa of CDA-sensitive individuals cannot compensate for the water loss that occurs under extreme conditions, leading to epithelial damage [39], whereas, CDA-insensitive individuals have an adequate water supply to the epithelial surface under stressful conditions, resulting in no reaction to the stimulus.

Conclusion

Nasal provocation tests with cold air have been used for the study of one of the major functions of the nose, the nasal conditioning capacity, and pathophysiology of cold-air-induced rhinitis and its treatment. Because one of the mechanisms underlying cold-air-induced rhinitis is hyperosmolarity of the epithelial lining fluid, a nasal provocation test using hyperosmolar stimuli has been developed. These tests help us to better understand how the environment interacts with the nasal mucosa, and it may improve treatment strategies for rhinitis in the future.
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Basic Biology of Mucous in the Respiratory Tract

Mucous Composition

Mucous composition varies among different respiratory tract sites and species. The large airways typically produce a thick, tenacious, viscoelastic mucus that coats the airway surface in a gel-like layer. In the large airways, mucus is produced by Clara cells of the secretory bronchial epithelium. The mucus film serves several functions that include gas exchange, water transport, and protection of the airway surface. In the nasal cavity, mucus is produced by goblet cells located in the epithelium. The nasal mucus is thinner and more watery than the bronchial mucus. In the nose, the mucus film is important in trapping inhaled particles and pathogens, as well as facilitating the delivery of inhaled medications.