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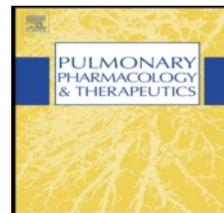
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Mechanisms of the cough associated with rhinosinusitis.

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ABSTRACT

The diseases of the nose and paranasal sinuses (rhinosinusitis) often in combination with asthma and gastroesophageal reflux are common causes of chronic cough in patients with normal chest radiograph. The relationships between rhinosinusitis and cough are incompletely understood. We investigated modulation of the cough reflex by the inputs from the nose. We demonstrate that the cough reflex is sensitized by the intranasal administration of sensory nerve activators in animal models and in humans. Cough reflex is also sensitized in the guinea pig model of allergic nasal inflammation and in patients with allergic rhinitis. In patients with allergic rhinitis the cough sensitization is augmented during the allergen season. We conclude that the cough reflex can be sensitized from the nose. Our data indicate that this sensitization is mediated by nasal sensory nerves. We speculate that by inducing the cough reflex sensitization rhinosinusitis contributes to chronic cough. If combined with environmental or endogenous cough triggers, the cough reflex sensitization is predicted to cause excessive coughing. The potential endogenous cough triggers may be associated with rhinosinusitis (postnasal drip, aspiration of nasal secrets) or secondary to a coexistent disease such as asthma or gastroesophageal reflux.

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The diseases of the nose and paranasal sinuses are among the most commonly identified causes of chronic cough^[1]. Depending on the population studied and the variations in diagnostic algorithm, the diseases of nose and sinuses are reported to contribute to coughing in 20-40% of patients with chronic cough who have normal chest radiograph (table 2 in ^[2]). The mechanisms of chronic cough in rhinosinusitis are incompletely understood. Several mechanisms have been proposed, single or in combination: postnasal drip (PND), direct irritation, inflammation in the lower airways and the cough reflex sensitization ^[3]. Here we discuss potential mechanisms of cough associated with rhinosinusitis with the emphasis on the cough reflex sensitization induced from the nose.

Sensitization of the cough reflex.

Sensitization of the cough reflex (cough reflex hypersensitivity) refers to a condition in which the cough reflex is more readily inducible. The sensitization of the cough reflex can be demonstrated as 1) the lowered intensity of a stimulus required to trigger cough or 2) enhanced coughing in response to a stimulus with the constant intensity. In clinical and laboratory experiments, the sensitization of cough reflex is detected by measuring the cough threshold or by evaluating changes in the number of coughs induced by a stimulus with defined intensity. The cough threshold is measured by a controlled inhalation of increasing concentrations of an aerosolized tussigen, commonly capsaicin or acidic solutions^[4, 5]. The cough threshold is defined as the lowest concentration of the tussigen required to induce a predetermined number of coughs (typically 2 and 5 coughs, denoted C₂ and C₅, respectively). The cough reflex hypersensitivity is found when the cough threshold in the patient group is lower than in the appropriate reference group.

The cough reflex hypersensitivity is often reported in patients with chronic cough attributed to disparate causes including nasal diseases ^[6, 7]. It is implied that the sensitization of the cough reflex contributes to coughing. In patients with sensitized cough reflex, the environmental and endogenous stimuli are predicted to be more effective to trigger cough. Thus the sensitization of the cough reflex results in the amplification of cough, similar to the amplification of pain in hyperalgesia. The observations that the cough sensitivity decreases with the successful treatment or natural resolution of cough also support the notion that the cough sensitization contributes to coughing^[6, 8, 9].

There is a consensus that the cough reflex cannot be triggered from the nose. We addressed the mechanistic question whether the cough reflex can be sensitized from the nose. Based on the general concept that the activation of nasal sensory nerves leads to sensitization of the cough reflex, we carried out a series of studies in humans and in animal models.

Sensory nerve activators in the nose sensitize the cough reflex.

First we evaluated the hypothesis that the afferent nerve activators applied into the nose sensitize the cough reflex in humans by using sensory activators histamine and capsaicin. Histamine is a prototypic mediator of nasal inflammation that directly stimulates a subset of nasal sensory nerves^[10]. The TRPV1 selective agonist capsaicin is also an efficient activator of the nasal sensory nerves^[10]. A large proportion of the TRPV1-positive

trigeminal neurons innervating the nose expresses a variety of receptors relevant for detection of stimuli associated with inflammation. For example, nasal trigeminal neurons functionally express the histamine H1 receptor, the leukotriene cys-LT₁ receptor^[10-12], TRPA1 channel (activated by various endogenous inflammatory molecules) and the P2X purinergic receptors for ATP (Taylor-Clark, unpublished observations). Thus intranasal administration of capsaicin likely stimulates large proportion of nerves that are also stimulated or modulated by nasal inflammation. Local and reflex consequences of the sensory nerves activation with histamine and capsaicin (such as substance P release from peripheral terminals and reflex vasodilation) may generate additional stimuli effective to further stimulate nasal sensory nerves^[13, 14]. In addition, direct effects of histamine on the cells other than sensory nerves likely lead to generation of more endogenous sensory stimuli.

Consistent with the extensive data from human studies^[15, 16] intranasal administration of histamine and capsaicin failed to trigger cough in healthy subjects^[17, 18]. The effective activation of nasal sensory nerves by histamine and capsaicin was confirmed by the occurrence of sensations and symptoms typically described after intranasal administration of these agents. The cough was induced by inhalation of a tussigen aerosol during the time window of the most pronounced nasal symptoms evaluated by a composite score.

Both histamine and capsaicin applied into the nose caused sensitization of the cough reflex in healthy subjects (Tab. 1)^[17, 18]. Following the intranasal administration of capsaicin or histamine, the number of coughs induced by inhalation of a defined dose of capsaicin was increased by 60-80%. Similarly, intranasal histamine did not trigger cough but sensitized the cough reflex in patients with allergic rhinitis (Fig.1A)^[19]. This data are consistent with the hypothesis that the activation of nasal sensory nerves sensitizes the cough reflex.

It is unlikely that the sensitization of cough after intranasal sensory nerve activators was due to aspiration of nasal content into the lower airways, although this possibility cannot be entirely excluded. To address this issue we carried out a study comparing the cough sensitization after maneuvers designed to minimize and maximize aspiration of nasal content^[19]. At one occasion the precautions to minimize the inspiration of nasal content were taken: following the intranasal administration of histamine the subjects wore the nasal clip and breathed through the mouth. On a different occasion the same subjects performed an intensified nasal breathing following intranasal histamine to maximize the inspiration of the nasal content into the more distal airways. The degree of cough sensitization at the two occasions was similar suggesting that inspiration of nasal content plays limited (if any) role in cough sensitization induced by intranasal histamine.

Cough reflex is sensitized in patients with allergic rhinitis.

We next evaluated sensitization of the cough reflex in patients with allergic rhinitis^[20, 21]. Chronic nasal symptoms attributable to sensory nerve activation in patients with rhinitis implicate that the inflammation leads to repeated activation of sensory nerves. As discussed below, the repeated activation and mediators associated with inflammation can induce sensitization at multiple levels of sensory pathways. Thus we predicted that the cough reflex is more sensitive in patients with allergic rhinitis than in healthy subjects.

The grass pollen-sensitive patients with allergic rhinitis were studied out of pollen season. All patients included in the studies were free of nasal symptoms at the time of investigation. We found that the cough reflex was more sensitive in patients with allergic rhinitis compared to healthy subjects (measured by the capsaicin C_2 cough threshold, Fig. 1B)^[20]. This finding was reproduced in a separate study in which the capsaicin C_5 threshold was evaluated in another groups of patients and healthy subjects^[21]. In this study, the concentrations of capsaicin causing five coughs (C_5 , geometric mean and 95 % CI) were 132.4 (41.3 – 424.5) μM and 13.1 (6.0 – 28.6) μM in healthy subjects (5M/7F, mean age 23 yrs) and patients with allergic rhinitis (5M/7F, mean age 23 yrs), respectively ($P < 0.05$). We conclude that the cough reflex is sensitized in patients with allergic rhinitis.

Since the symptoms of allergic rhinitis in pollen-sensitive patients are most prominent during the pollen season, we hypothesized that the sensitization of cough is most pronounced in this period. Fifteen patients were evaluated out of pollen season (January-February) and in the grass pollen season (May-June) in a paired study^[20]. The capsaicin cough C_2 threshold was reduced in the pollen season vs. out of the pollen season, 0.11(0.3-0.33) μM vs. 0.84(0.14-5.2) μM , respectively ($p < 0.05$). Thus the cough reflex in patients with allergic rhinitis is further sensitized in the period when the nasal inflammation is more active.

Sensitized cough reflex and coughing.

In a series of studies we demonstrate that the cough reflex in healthy subjects is sensitized by the intranasal administration of sensory nerve activators^[17, 18]. These results are consistent with the hypothesis that the activation of nasal sensory nerves sensitizes the cough reflex. We also show that the cough reflex is sensitized in patients with allergic rhinitis^[20, 21], and is further sensitized in this group by intranasal sensory activator histamine^[19] and during the period of more active nasal inflammation^[20]. Our results may help to explain the mechanisms contributing to chronic cough associated with rhinosinusitis.

Our results are highly indicative that nasal sensory nerves are the pathways leading to sensitization of cough. The wealth of data from the somatosensory^[22] and vagal^[23, 24] systems allows for an informed speculation that central sensitization of the cough reflex mediated by nasal sensory nerves underlies the observed cough sensitization. In this scenario the afferent inputs from the nose feed into the central regulatory circuits of the cough reflex in a manner rendering the cough reflex hypersensitive. It has been demonstrated that the cough reflex triggered from trachea is sensitized by the stimulation of sensory nerves innervating distal parts of the respiratory system (lungs) in animal models^[23], or even from the esophagus in humans^[25] and guinea pigs (BJ Canning, personal communication). The sensitization of cough by the nasal trigeminal sensory pathways is perhaps more complex than the vagally-mediated sensitization, since the trigeminal and the cough-triggering vagal sensory nerves terminate in different areas of the brainstem. Interestingly, we show that the sensitization of cough from the nose can be induced even in the anaesthetized animals, suggesting that the cough sensitization does not require intact cortical function (see below).

The situation is more complex in patients with allergic rhinitis. Our data discussed thus far predict that the sensitization of cough reflex mediated by acute sensory nerve activation occurs in the symptomatic patients (Fig 1A). However, in the patients without symptoms (such as the patients with allergic rhinitis out of the allergen season) the absence of the symptoms indicates limited nasal sensory activity. Yet the cough reflex is strongly sensitized in this group (Fig 1B)^[20, 21]. It seems unlikely that the nasal sensory nerves in patients without symptoms are stimulated in a manner that is sufficient to maintain the cough sensitization but insufficient to trigger the symptoms. Rather, we speculate that the cough sensitization is induced by sensory activation during the period with symptoms and then outlasts the sensory activation. Inflammatory mediators, neurotrophic factors and other signals emanating from the nose during symptomatic period could, in theory, initiate long-lasting neural plastic changes in the circuits regulating the cough reflex^[26, 27]. Mechanistic studies are needed to evaluate this speculation.

Nasal provocation with histamine induces significantly stronger sneezing responses in subjects with allergic rhinitis compared with healthy subjects – a sensitized sneezing reflex^[28, 29]. We noted that intranasal histamine was more effective in reducing the capsaicin cough threshold in patients with allergic rhinitis than in healthy subjects^[17, 19]. The simplest explanation is that the nasal sensory nerve pathways are sensitized, resulting in increased sensory feeding into the cough and sneeze regulatory areas. It is noteworthy in this context that nasal inflammation induces lasting changes in expression of molecules predicted to positively regulating activation and excitability in nasal afferent nerves^[30, 31]. However, a separate sensitization of cough and sneezing at the higher regulatory levels of cough and sneezing reflexes is also a viable option.

Another explanation is that the cough reflex is sensitized in patients with allergic rhinitis because of allergic inflammation in the lower airways and lungs. This possibility cannot be excluded. Numerous studies have shown that the inflammation in the lower airways and lungs in patients with allergic rhinitis is in many aspects similar to that in asthmatics (exemplified by^[32]). However, the studies in asthmatics failed to consistently show lowered capsaicin or citric acid cough thresholds^[33-35]. Since this is in contrast with the dramatic sensitization of cough in allergic rhinitis (Fig. 1B), this mechanisms likely plays only a limited role.

We chose allergic rhinitis as a model of a well-defined nasal inflammation allowing for selection of a relatively homogeneous patient population (skin prick test pollen-sensitive patients). Although the cough reflex was sensitized in allergic rhinitis, none of the patients complained about coughing. The increased cough reflex sensitivity is consistently found in patients with chronic cough and the effective treatment of cough is accompanied by normalization of the cough hypersensitivity. These observations advanced the hypothesis that the cough reflex hypersensitivity is the mechanism causing the cough. However, the cough reflex hypersensitivity has been also reported in other groups of patients who do not suffer from chronic cough. For example, the cough reflex sensitivity to capsaicin is increased in the GERD patients who do not complain about cough^[36, 37]. Interestingly, the magnitude of the cough threshold reduction in the GERD patients is comparable to that found in chronic coughers, and the cough threshold

reduction in allergic rhinitis appears to be even larger. The cough hypersensitivity without cough was also found in other diseases^[38, 39].

The observations that the cough reflex hypersensitivity is not always accompanied by cough force the conclusion that the cough reflex hypersensitivity alone is not sufficient for clinical presentation of chronic cough. Rather, the increased cough reflex sensitivity contributes to chronic cough by amplifying the cough triggered by endogenous and, perhaps less likely, environmental stimuli. While the cough reflex sensitivity is predicted to worsen the cough, it is unlikely to be its only causal mechanism.

Sensitization of cough reflex in animal models of rhinitis

To gain further mechanistic insight we developed animal models of cough sensitization. Similar to human studies intranasal administration of sensory nerve activator sensitized the cough reflex in awake guinea pigs^[40]. In this study, intranasal administration of capsaicin enhanced by ~70% the cough induced by inhalation of citric acid (Tab.1). Intranasal administration of allergen in the sensitized guinea pigs also induced sensitization of the cough reflex (Fig.2). Intranasal ovalbumine substantially decreased the citric acid cough threshold in the guinea pig model of allergic rhinitis induced by repeated intranasal ovalbumine challenge in the ovalbumine-sensitized animals^[41]. Our preliminary data suggest the role of the leukotriene cys-LT₁ receptor in the sensitization of cough by allergic inflammation in this model^[41]. It is of note that the stimulation of cys-LT₁ receptor induces sensitization of the putative nociceptive trigeminal sensory neurons innervating the nose^[11].

The cough to inhaled aerosols of acid and capsaicin is presumably initiated by the activation of the TRPV1-expressing capsaicin-sensitive afferent nerve fibers. In the guinea pig the majority of the capsaicin-sensitive bronchopulmonary afferent nerve fibers conduct action potentials at <1 m/s (C-fibers)^[42, 43]. The chemically-induced cough is difficult to evoke in anesthesia and is therefore optimally studied in the awake animals^[44]. In contrast the cough evoked by the mechanical stimuli to the airways is initiated by the capsaicin-insensitive A-fibers in the large airways. In the guinea pig this fiber type has been identified as the nodose "touch-sensitive" A δ -fiber^[45]. The mechanically-induced cough persists in anesthesia and can be optimally studied in the anesthetized animals.

Given that the afferent pathways mediating mechanically-induced cough (A-fibers) are distinct from the pathways mediating cough to inhaled capsaicin and acid (C-fibers), we investigated whether the mechanically-induced cough is also sensitized from the nose. We found that in the anesthetized guinea pigs the intranasal administration of capsaicin caused approximately threefold increase in the number of coughs evoked by mechanical stimulation of the trachea^[40]. Similar results were obtained in cats^[40]. Preliminary data in the guinea pig indicate that the sensitization of cough from nose is prevented by local anesthetic (not shown).

Thus the sensory nerve activators applied into the nose sensitize both the mechanically- and chemically-induced cough. This data suggest that nasal sensory input modulates cough at the level(s) above the central projections of the cough-triggering nerves. Interestingly, preliminary reports on mechanically-induced cough in humans indicates

that the coughing to mechanical stimulus (vibrations applied from the body surface) was enhanced in patients with acute upper respiratory tract infection with cough^[46, 47].

Potential mechanisms triggering cough in patients with rhinosinusitis and cough

As discussed above, the cough reflex hypersensitivity is predicted to amplify cough by increasing the efficiency of endogenous and environmental stimuli to trigger cough but is unlikely to cause chronic coughing by itself. There is an ongoing discussion in the literature whether diseases of the nose actually trigger cough^[48, 49]. This confusion is also reflected in the recommendation of the term upper airway cough syndrome (UACS) to be used when discussing cough that is associated with upper airway conditions^[3].

One proposed mechanism for triggering cough in rhinosinusitis is the postnasal drip (drainage of secretions from the nose or paranasal sinuses into the pharynx). In this scenario the cough-triggering nerves located in the hypopharynx or larynx are stimulated by secretions emanating from the nose and/or sinuses dripping down into these areas^[50]. The arguments against postnasal drip as a sole cause of cough in rhinosinusitis are twofold. Postnasal drip is a common phenomenon, and only a small fraction of patients with the postnasal drip also complains about cough^[51]. Conversely, a proportion (reported ~20%) of patients with chronic cough attributed to rhinosinusitis do not experience postnasal drip. It seems therefore unlikely that postnasal drip is the exclusive mechanism triggering cough. Cough in rhinosinusitis could be also conceivably triggered by aspirated secretions stimulating cough receptors in the lower respiratory tract; however, there are limited data to support this mechanism^[3]. As is the case with postnasal drip, the aspiration or inhalation of nasal secretions likely occurs also in patients who do not have chronic cough. Enhanced sensitivity to environmental factors has also been linked to chronic cough in rhinosinusitis^[52].

The analysis of the mechanisms triggering cough in rhinitis is further complicated by the fact that rhinosinusitis often coexists with other common causes of chronic cough such as gastroesophageal reflux disease and eosinophilic airway diseases including asthma. Thus the potential cough triggers may be unrelated to the nasal disease (discussed elsewhere in this issue). Rhinitis is also very often part of the asthma presentation^[53] and chronic sinusitis and postnasal drip can be caused or worsen by gastroesophageal reflux^[54] introducing even more complexity into the analysis.

The treatment aimed at rhinosinusitis improves chronic cough in many patients who also present with other conditions potentially causing chronic cough (i.e asthma or GERD). That the rhinosinusitis causes sensitization of the cough reflex may explain the beneficial effect of this therapy. We speculate that the sensitization of cough reflex in combination with one or more cough triggers results in some unfortunate individuals in clinically relevant coughing termed chronic cough associated with rhinitis.

Table 1. Intranasal administration of sensory stimulants enhances cough induced by inhaled tussigens in humans and guinea pigs.

Subjects	Intranasal sensory stimulant	Number of coughs induced by inhaled capsaicin median (IQR) ¹		overall $\Delta\%$	n
		after intranasal saline	after intranasal stimulant		
Healthy subjects	capsaicin ²	5(3-7)	8(6-10)*	+60	20
Healthy subjects	histamine ³	4(2.5-5.5)	7.5(4-11.5)*	+87	12
Allergic rhinitis	histamine ³	4.5(4-6)	9(7-12)*	+100	14

Animals	Intranasal sensory stimulant	Number of coughs induced by inhaled citric acid median (IQR) ⁴		overall $\Delta\%$	n
		after intranasal saline	after intranasal stimulant		
Awake guinea pigs	capsaicin ⁵	3(2-5)	5(3-7)**	+67	23

¹ Cough was induced by four consecutive single-breath inhalations of the C₂ concentration of capsaicin after intranasal administration of a sensory stimulant^[17-19].

² Bilateral intranasal administration of 25 μ l capsaicin (750 μ M)^[17]

³ Bilateral intranasal administration of 100 μ l histamine (8mg/ml)^[18, 19]

⁴ Cough was induced by inhalation of citric acid aerosol (2 minutes, 0.3M)^[40]

⁵ Bilateral intranasal administration of 15 μ l capsaicin (50 μ M)^[40].

*p<0.05, **p<0.01, sensory stimulant vs. saline.

FIGURE LEGENDS

Fig. 1. (A) Intranasal administration of histamine enhances cough in patients with allergic rhinitis. Cough was induced by inhalation of defined suprathreshold dose of capsaicin after intranasal administration of saline or histamine in a paired randomized study (n=15).^[19] **(B) Cough reflex sensitivity is increased in patients with allergic rhinitis.** Cough threshold (C2, geometric mean [95%CI]) was determined as the lowest concentration of inhaled capsaicin causing at least two coughs in 24 control subjects and 23 pollen-sensitive patients with allergic rhinitis out of pollen season^[20].

Fig. 2. The cough reflex is sensitized after intranasal allergen in the guinea pig model of allergic rhinitis. Ovalbumin-sensitized animals (n=36) received repeatedly (6x) intranasal ovalbumin in 7 days intervals. The cough reflex sensitivity was determined by inhalation of doubling concentrations of citric acid (0.05-1.6M) 60 min after the last intranasal instillation of ovalbumin. *Inset:* cough threshold expressed as the lowest concentration of citric acid causing at least two coughs (C2, mean[95%CI]). There was no change in the cough threshold in control animals that received identical treatment except saline was used in place of ovalbumin in a parallel study (n=24, not shown). Note that curves show cumulative number of coughs. **p<0.01. Data from^[41].

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