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# Chronic cough in subjects with upper airway diseases – analysis of mechanisms and clinical applications

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Cough is the commonest respiratory symptom leading to a medical consultation. Although acute cough which is usually associated with respiratory viral infection is not a problem to manage, chronic cough is frequently a diagnostic and therapeutic challenge as it does not respond to usual treatments. Specific group of chronic coughers are considered to have upper airway diseases, lately categorized as having upper airway cough syndrome. There is an increasing pool of evidence that upper airway diseases have significant involvements in the regulation of cough reflex, indicating that they must be taken into considerations as major triggers of coughing in the patients. Here we summarize current literature and experiences on the pathogenesis of upper airway cough syndrome, and discuss further clinical applications.

**Key words:** Cough; Rhinitis; Upper airways; Inflammation; Neuron

## INTRODUCTION TO THE TOPIC, GENERAL NOTES

Cough is the commonest respiratory symptom, and indeed it is one of the commonest among all symptoms resulting in medical consultations. Particularly, chronic cough is a diagnostic and therapeutic challenge. Just recently, it has been recognized for what it is–a syndrome with unique clinical presentations [1, 2]. Many studies from around the world have repeatedly reported that the commonest causes of chronic cough are gastro-oesophageal reflux, asthma with related syndromes, and upper airway diseases [3]. However, there still remains controversy regarding their related mechanisms [4], and 'what underlies chronic cough' needs vigorous discussion.

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Physiologically, cough is a polysynaptic reflex which results from the irritation of afferent nerve endings in the so-called tussigenic areas of the airways. Initiation of cough reflex is exclusively attributed to vagal neurons with the cell bodies in nodose and jugular ganglia; however, the reflex is also modulated by many other afferent inputs within the vagus nerve and out of it. This modulation is called 'cough plasticity' [5]. Particularly at the level of basic science, the last decade of research is devoted to the 'plasticity of cough'-modulation of reflex response both at peripheral and central levels [6]. As every process in the body, cough reflex is regulated. Although it is not unambiguously defined what "physiological" cough means, it can be easily concluded that adequately regulated cough reflex provides essential defence to the airways without causing physical damage or psychosocial detriment.

Dysregulation of cough reflex can take two forms. As first, it is the 'up-regulation' of cough when cough reflex is too strong or too long, or when it occurs at stimuli which have no tussive potential in healthy subjects [7]. It occurs in chronic diseases of the respiratory system, gastro-oesophageal reflux, or nasal diseases. Another form is 'down-regulation' of cough reflex, which leads to insufficient protection of the respiratory system. An example can be shown in patients after lung transplantation, patients with stroke, muscular atrophy, or unconscious patients, in which the attenuated cough reflex may lead to aspiration pneumonia [8]. Both extremes of up- and down-regulation, and their systematic research in animal models or in clinical settings have been of highest interest. The research has brought new insight into the mechanisms participating in the pathogenesis, and also identified new therapeutic targets. As an example, the identification of TRPV1 channel as a "cough receptor" has led us to the development of TRPV1 antagonists and the initiation of clinical trials [9].

In this review, we aim to summarize current literature and experiences to explain 'how upper airway diseases are related to the cough reflex'. We hope that the review would provide useful insights to understand the pathogenesis of chronic, and to identify new therapeutic targets.

## UPPER AIRWAY DISEASES AND CHRONIC COUGH: CLINICAL EVIDENCE

Upper airway disease is one of the most commonly identified causes of chronic cough. Despite the differences in studied populations and diagnostic protocols, it has been consistently reported to be the main cause for chronic cough (20-40%) among patients attending the specialized cough clinics [3, 10]. Moreover, epidemiologic studies on general community populations support the findings from clinics [11-13]. A longitudinal population-based cohort demonstrated that rhinitis was an independent risk factor (odds ratio 1.7) for developing chronic cough within 5 years [12].

However, the mechanisms of association between chronic cough and rhinosinusitis are not completely known. Previously, cough present in subjects with rhinitis had been attributed to the post nasal drip syndrome (PNDs). It was believed that mucus dripping down to the area of pharynx/laryngeal aperture may stimulate nerves, thus triggering cough [14]. However, the arguments against PND are many [15]. PND is a common phenomenon and only small proportion of those subjects complains about cough [16]. Conversely, patients with chronic cough attributed to nasal/sinus disorder (approx 20%) never experienced PND. It seems therefore unlikely that post nasal drip is the executive mechanism triggering cough.

Therefore, chronic cough in patients with upper airways problems was renamed to "upper airway cough syndrome" (UACS), reflecting its complexity rather than mechanistic explanation of PNDs [10, 17]. In general, UACS as a cause of chronic cough represents 'up-regulation of the cough reflex', in terms of physiology.

## UP-REGULATION OF COUGH REFLEX IN ALLERGIC RHINITIS

Older works by Irwin and other researchers suggested that cough occurs directly as a consequence of pathological process located within the nasal cavity and/or sinuses, by stimulation of nasal afferents [14]; however, this hypothesis has never been relevantly proven. We tried various direct stimulation of nasal afferents in animal models and humans (capsaicin, histamine, allyl isocyanate, air puffs) [18-21], and also experimentally induced rhinitis in guinea pigs [22]; but the direct responses to nasal stimulation were never cough, but only 'sneeze reflex'. Logically, if experimental stimulation of nasal afferent nerves does not produce coughing but cough is associated to upper airway diseases, then there must be specific mechanisms which are responsible for this relationship. The mechanisms could be complex, involving


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post nasal drip, microaspiration of inflammatory aerosol, nasobronchial reflex, lack of nasal functions with inhaling cold dry air and its further consequences in lower airways, or propagation of inflammation via systemic circulation [23]. There are also considerable issues of the central and peripheral neuroplasticity [17]. However, no clear explanation has been made.

Allergic rhinitis is an example to help our understanding the up-regulation of cough reflex by rhinitis. Cough reflex was sensitized in subjects with allergic rhinitis particularly during the pollen season [24]. Cough threshold in subjects with rhinitis measured by C2 and C5 parameters was significantly lower comparing to healthy volunteers [25]. Since the symptoms of allergic rhinitis in pollen sensitive patients were most prominent during the pollen season, the cough sensitivity was also at its highest in this period. Cough sensitivity correlated with the symptom magnitude, and nasal corticosteroids diminished this sensitization [26]. Sensitization of the cough reflex was also observed out of pollen season, which could be attributed to the repeated activation of sensory nerves. Repeated exposures to allergen may induce inflammation with release of mediators sensitizing the neural pathway at multiple levels.

Insights from allergic rhinitis guinea pig models confirmed the findings in humans. The original method described by Underwood [27] was further modified and validated as a model reliable for testing of the cough responsiveness in follow up fashion in awake animals [22]. Using the ovalbumin-induced allergic rhinitis models, cough sensitivity was found to be heightened, and it correlates with the presence and magnitude of nasal symptoms [22, 28]. Treatment of inflammation by local corticosteroids, antagonists of leucotriene cys-LT1 receptor or peroral rutinoscorbine decreased significantly the magnitude of nasal symptoms evaluated by scoring system, and also led to desensitization of the cough reflex back to pre-disease values [22, 28, 29].

Mechanistically, it is suggested that allergic rhinitis modulates two distinct types of cough–either cough induced by stimulation of putative TRPV1-expressing capsaicin-sensitive fibres, or cough initiated by capsaicin-insensitive mechanosensitive Aδ nodose fibres [30]. The latter, the mechanically-induced cough, persists in anaesthesia and thus can be optimally studied in anaesthetized animals. Coughing induced by laryngeal mechanical stimulation was more sensitized than coughing induced from trachea, as to number of cough efforts and intensity of the expiratory efforts in a cough bout provoked by mechanical stimulation of laryngopharyngeal or tracheobronchial mucosa by nylon fibre. In this experimental set-up, animals were either tracheotomised immediately after rhinitis was induced, or were allowed to remain with intact airways for 20 minutes, while ventilation was enhanced by CO2 admixture to the inhaled air. The data suggested that breathing through intact airways with increased respiratory drive necessary to pass the air through 'swollen nasal passages' may potentially contribute to the microaspiration of aerosol with mixture of inflammatory mediators to the distal portion of the airways [31].

Apart from the nasal discharge with potential microaspiration and decreased nasal patency which were the dominant factors for cough in the previous paragraphs, there is also direct evidence that cough is sensitized more importantly by the neural mechanisms. Local pretreatment with 1% mesocain inhibited previously augmented cough responses in the guinea pig model. Therefore, the role of the nasal afferents in this process of sensitization is strongly suggested [32]. Inflammatory mediators released in early and late phases of allergic reaction are known as potent activators (histamine, bradykinin) and sensitizers (prostaglandins, leucotrienes) of nasal trigeminal afferents [33]. Concept of 'cough plasticity' proposed that cough is rather a "plastic" phenomenon, than a stereotyped and fixed response, and it could be modulated at peripheral and central levels [6, 34]. In the light of these concepts, we started to hypothesize that cough reflex could be considerably modulated by afferent drives from the nose.

## ROLE OF NASAL AFFERENTS IN MODULATING COUGH REFLEX

Terminals of the trigeminal afferents innervating nasal mucosa are commonly called 'gate-keepers', since these fibres are the first to detect substances entering the upper respiratory tract [35]. They could be classified into several categories based on their size, myelinization, mechano-, thermo- or chemosensitivity [33, 36, 37]. Among many classes of nerve fibres are the polymodal nociceptors (PMNs). Their activation induces protective reflexes and nocifensive behaviours. Although there are many types of PMNs, the most common are those that are activated by capsaicin through its receptor, transient receptor potential cation channel TRPV1. Recently, an interesting breakthrough was made when pharmacological experiments revealed that acrolein, the noxious unsaturated aldehyde enriched in photochemical smog and smoke, is a potent agonist of human and murine TRPA1 channels

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[38]. This transient receptor potential channel belongs to the TRP group, family A, member 1. TRPA1, like TRPV1, is expressed by trigeminal neurons and, moreover, both channels are most often found on the same neuron. Therefore we basically focused on these afferents.

First, we decided to study the effects of nasal capsaicin and histamine challenge on cough induced either by chemical tussive agent (cough mediated via TRPV1-expressing putative jugular fibres) or mechanical stimulation of the airway mucosa (Aδ capsaicin-insensitive nodose fibres). Histamine is an inflammatory mediator that directly stimulates a subpopulation of nasal sensory nerves. Capsaicin, TRPV1 selective agonist, is also efficient activator of nasal sensory nerves. Activation of nasal sensory nerves also initiates axon reflexes and retrograde release of tachykinins (substance P) which generate additional stimuli for the nerves. Furthermore, TRPV1-expressing trigeminal neurons also co-express histamine receptors, cys-LT1 and TRPA1, which are activated by various endogenous molecules. Therefore, nasal administration of capsaicin, as a model, likely activates large proportion of nerves that are also stimulated or sensitized during inflammation.

Consistently with the data from previous human studies [18, 19], intranasal administration of capsaicin failed to trigger coughing, but it significantly enhanced cough from lower airways in anaesthetized cats, and also in conscious and anaesthetized guinea pigs. Both histamine and capsaicin that were applied to the nose caused the sensitization of the cough reflex. The number of cough efforts induced by inhalation of defined dose of capsaicin was increased by 60-80%. Similarly, intranasal histamine did not trigger cough, but sensitized the cough reflex in subjects with allergic rhinitis [39].

It is known that cough and expiration reflex from vocal folds are distinct reflexes; however both of them belong to the category of airway defensive reflexes. We documented that expiration reflex evoked from vocal folds is enhanced in a model of allergic rhinitis, and in a model of nasal capsaicin challenge in anaesthetized animals. Histological samples taken from the larynx were negative with respect to allergic inflammation or any other pathology. These results suggest that up-regulation of expiration reflex is mediated probably by similar neural pathways. Teleologically, we speculated that cough reflex is up-regulated during stimulation of nasal afferents and nasal diseases in order to minimize the potential spread of the pathological process from the nasal cavity to other parts of the respiratory tract in the presence of nasal diseases or air pollutants stimulating nasal afferents.

Based on the studies on the convergence of airway putative fibers mediating cough and bronchoconstriction in the nucleus tractus solitarius (nTs) by Brendan Canning and Stuart Mazzone in 2002 [40], we postulated the hypothesis that up-regulation of cough in nasal diseases has a central neural component through convergence. Convergence of afferent inputs to the brain stem creates opportunities for anatomical and functional interaction of neuronal populations which regulates cough. Airway afferents, including "cough fibres", are connected to the second order neurons in the solitary tract nucleus, which is the site of 'cough plasticity' [34], and the critical brainstem component responsible for coughing in guinea pigs [5]. Although the primary sensory fibres from the nasal cavity are interpolated to second order neurons mainly in sensitive nucleus of trigeminal nerve, these afferents have connections to the chemosensitive areas such as the area postrema, and also nTs [36]. With the detection of *c-fos* gene and the gene product, we have shown that intranasal administration of substances with nocifensive potential (capsaicin) induces the activation of neurons in the trigeminal sensitive nucleus and also in nTs, which may interfere with modulation of inputs to "cough generator". Expression of *c-fos* is an indirect marker of neuronal activity because *c-fos* is often expressed when neurons fire action potentials. Upregulation of *c-fos* mRNA in a neuron indicates recent activity. Increased *c-fos* positivity was detected in the VRG-ventral respiratory group (ncl. ambiguus and retroambigus), which contain the expiratory motoneurons and premotoneurons. This activation can hypothetically explain the increased strength of expiratory efforts in cough induced during nociceptive stimulation of the nasal mucosa. Similar distribution of *c-fos* positivity was detected in the brainstem of guinea pig models with experimental allergic rhinitis, however the counts of *c-fos* positive neurons in trigeminal sensory nucleus, nTS and also VRG were significantly higher suggesting for robust neuronal activation in this model of airway hyperresponsiveness [41, 42].

## AN URGE-TO-COUGH COMPONENT

Nasal challenges with other airway irritants–TRPA1 agonists, allyl-isothiocyanate (AITC) and cinnamonaldehyde, were conducted in healthy volunteers. TRPA1 channel is abundantly expressed on trigeminal afferents, and electrophysiological studies confirmed its role as an airway irritant sensor. This channel is relevant for majority of air born pollutants, electrophiles, reactive


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and oxidizing substances, and also endogenous molecules, such as inflammatory mediators or products of oxidative stress [43]. Both of the tested agonists after nasal administration failed to sensitize cough reflex and move cough threshold significantly in healthy subjects, but nasal AITC challenge significantly modulated the 'urge-to-cough' [20]. This finding showed us completely new perspective in cough sensitization from the nose.

'Urge-to-cough' is a subjective interpretation of airway irritation, which proceeds cough motor pattern. It represents cortical conscious contribution to the airway defence. It is difficult to say, whether it is voluntary cough, because subjects may cough to a request, if you ask them to without any perceived airway irritation. Taken together these facts, 'urge-to-cough' is specific sensation of airway irritation, which leads to coughing [44, 45].

Both of the agonists (AITC and cinnamonaldehyde) exert specific olfactory sensations of horseradish or cinnamon, respectively. While the cinnamon was quite well tolerated, AITC produced except burning unpleasant olfactory sensation. TRP channels are expressed on the olfactory terminals as well, and little is known about trigemino-olfactory interactions. We speculated that unpleasantness of olfactory stimulus may contribute to facilitation of the 'urge-to-cough'.

Menthol and other aromatic compounds are frequently used in over-the-counter remedies for cough and cold. Animal and human studies conducted with menthol, cineole, camphora suggested their antitussive potentials. As it will be discussed later, we have confirmed that these substances suppress the cough probably via nasal trigeminal afferents. All of these substances exert nice and pleasant olfactory sensations, and therefore we decided to test also the urge-to-cough after nasal challenges of menthol isomers, eucalypthol and thymol–a component of thyme. Molecular background for both menthol and eucalyptol is the TRPM8 channel, while thymol is an agonist of TRPV3 channel, which is abundantly expressed on skin, tongue and basically neurons originated from DRG, including trigeminal afferents [46].

As results, menthol, eucalypthol and thymol nasal challenges significantly desensitized the cough reflex. The concentration required to induce the urge-to-cough was higher when comparing to nasal vehicle challenges. Perception of airway irritation produced by standardized capsaicin test was attenuated by these pleasant feelings [20, 47]. The effects on other parameters were variable; C2, C5 and total number of coughs obtained during provocation were more impressive for menthol, while urge-to-cough suppression was the most significant for nasal thymol challenge.

Interestingly, (+) menthol isomer, which is less effective in vitro, has stronger effect on selected cough parameters, when comparing to (-) menthol isomer with highest biological activity in vitro. Since the subjects we not informed completely about the purpose of the study, they could not be completely blinded due to specific smells of tested agent; however, they were not able to recognize eucalypthol, and menthol isomers just by the smell. The subjective interpretation suggested that (+) menthol smells better to them than (-) menthol, which has typical medicinal smell.

However, there are currently no published data about the contribution of olfactory signalling to the modulation of cough, and this could be definitely proven on subjects with complete lack of olfactory functions. Interesting is a question of placebo effect of these substances. There are studies suggesting that 80% of the drug effect is provided by placebo and the rest of it is biological activity [48].

## DOWN-REGULATION OF COUGH FROM NOSE

Most published data suggest that nasal sensory nerves are involved in sensitization and 'up-regulation' of the cough by nasal inflammation and trigeminal afferent stimulation [18, 19, 22, 24]. In contrast to other sites–such as mouth, pharynx, respiratory tract and lungs, cerebral cortex and somatic tissues, or hypercapnia and/or hypoxia, that may down-regulate cough center [49], little evidence is available to support desensitization of cough from the nose. Biological processes are frequently regulated by antagonistic systems, and the workshop in London Cough meeting in 2010 discussed whether there is a neural pathway which can desensitize cough from the nose.

Recent study with menthol nasal challenges shared evidence that, in general, this neuronal pathways does exist in animals and even in humans, and that menthol reduces the perception of airway irritation and therefore the subjects coughed less to defined concentrations of capsaicin [20].

The previous experiments in animals and studies with human volunteers have shown that 'inhalation' of menthol supresses cough, however, direct mechanism of its action was not known [50, 51]. Now, the identification of TRPM8 receptor, the channel relevant for menthol and innocuous cold, brought a novel breakthrough to the molecular pharmacology of menthol and other compounds with cooling effects [52, 53]. Single cell RT-PCR

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analysis of trigeminal and vagal neurons showed that menthol receptors, TRPM8, are abundantly expressed mainly in the upper airways, while they are less frequently expressed in nodose and jugular neurons [54]. These data are consistent with other studies which showed distribution of the TRPM8 expressing neurons mainly within trigeminal populations [55] and their low proportion within the vagal afferents innervating the lower airways of rats [56] and mice [57].

Menthol vapors administered selectively to the nose but not to the lower airways significantly suppressed cough induced by citric acid in anaesthetized guinea pigs. Series of those studies in anaesthetized guinea pigs with separated upper and lower airways and selective nasal cold, menthol and icilin (TRPM8 superagonist) challenges showed that antitussive action of menthol is mediated predominantly by nasal trigeminal afferents expressing TRPM8 channel [54]. Recent evidence indicates that TRPM8 may be expressed in two distinct populations of cold-sensitive dorsal root ganglion (DRG) neurons and trigeminal neurons, one sensitive to menthol but not capsaicin and the other sensitive to menthol, capsaicin, ATP, and acidic stimuli; the former were suggested to be cold receptors and the latter nociceptors [58]. Our data obtained from trigeminal neurons single cell RT-PCR reaction can confirm this finding, as we have seen both groups of neurons–$TRPM8^+/TRPV1^+/TRPA1^+$ - considered as being nociceptors, and a subpopulation expressing TRPM8 only $TRPM8^+/TRPV1^-/TRPA1^-$. We suppose that cough inhibitory pathway mediated by menthol nasal challenge could employ just these $TRPM8^+/TRPV1^-$ neurons [54].

Recently, Poussel and colleagues [59] published interesting findings that nasal stimulation by water down-regulates cough in anaesthetized rabbits. This finding is of high importance because it underlines the sense of physiology of airway defence. They suggest that nasal stimulation by water down-regulates tracheal defensive reflexes in anaesthetized rabbits, as stimulation of nasal afferents with distilled water is likely to desensitize airway defensive reflexes at central level, as shown by inhibition of expiration and cough reflex. They explained this observation by teleological sense, because cough and its full inspiration phase would be undesirable during diving [59].

Inhalation of menthol vapors also inhibits breathing rate in laboratory animals and in humans [60, 61], and it also decreases the drive to breathe [62, 63]. It is generally accepted that the respiratory and cough control share the same neuronal network and the stimuli that increase ventilatory drive also typically potentiate cough and *vice versa*, and the depression of ventilation is related to the depression of cough, as it was shown in animal model with veratrine induced apnoea and models of hypercapnia/hypoxia in anaesthetized animals [64, 65]. This is quite interesting concept, but it is not known so far, how this could be applied to the human physiology, and whether this hypothesis is valid still only for anaesthetized or also conscious animal models.

## CLOSING REMARKS: CLINICAL APPRAISAL

Chronic cough has been associated with complex etiology, but it is now considered to be rather 'one syndrome' mainly mediated by cough hypersensitivity. Clinical observations on the demographics of chronic cough patients have suggested us a potential clue to the pathogenesis of the disease (a universal biologic factor - cough hypersensitivity), as they are mainly middle-aged females regardless of their populations. Then, how upper airway diseases underlie chronic cough? First, we speculate that nasal inflammation would be a major 'trigger' in the subjects who already developed cough hypersensitivity either by inherited (genetic) or acquired factors. The acquired factors could be medical conditions to increase the risk of gastroesophageal reflux or asthma. Then, the treatments for rhinitis like corticosteroids or anti-histamines will resolve the main trigger and also return the reflex to normal ranges. Of course, the investigations and management of the 'underlying conditions related to cough hypersensitivity' should be sought at the same time. Second, upper airway disease itself may be the cause for developing cough hypersensitivity; then, the endotype of upper airway diseases could be highly relevant, as not every patient with nasal disease complains cough.

Then, how could this update in knowledge provide us therapeutic applications? In the current practice, we already 'desensitize' the cough reflex by management of nasal inflammation. Local corticosteroids, antihistamines or leukotriene antagonists will abolish majority of nasal symptoms, limit the amount of secretion and the extent of nasal obstruction, therefore influencing all discussed mechanisms. Also, inhibited release of inflammatory mediators will less irritate the nerves, thus influencing the neural contribution to upper airway cough syndrome too. Secondly, furher application would be nasal afferent modulation as suggested by recent findings. For example, the role of aromatherapy with menthol cineole, thymol, or


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other natural remedies would be applied, as it can diminish the urge to cough component, and desensitize the cough reflex by trigeminal or even olfactory signaling. Now, our future attention is focused on histamine receptors antagonists, particularly H3 and H4 antagonists, which appear to be very promising in the management of the upper airway cough syndrome.

Herein we reviewed current literature and our experiences regarding the association between upper airway diseases and cough. The pool of the data is highly indicative for strong associations. There is still much to be elucidated regarding the mechanisms; however, it seems clear that nasal afferents play crucial roles in the regulation of cough reflex. The knowledge would be helpful in our understanding of chronic cough, and would provide future therapeutic advances.

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