

Upper Airway Cough Syndrome – Definition, Pathogenesis and Clinical Significance

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ABSTRACT

Chronic cough is a troublesome problem, which considerably reduces the quality of life of affected individuals. Standardized diagnostic protocols focus mainly to the three most frequent reasons of chronic cough, so-called diagnostic triad. They are diseases of the upper airways, gastroesophageal reflux and certain phenotypes of bronchial asthma.

Pathologies of the upper airways are frequently associated with chronic cough and interdisciplinary cooperation is needed to manage such patients. ENT specialist worldwide are now recognizing the connection between the upper and lower airway physiology, and this short review summarizes the recent understanding of neurophysiology of cough reflex, cough plasticity and analyses mechanisms responsible for up-regulation of cough in subjects with rhinosinusitis.

Postnasal drip, as it was previously suggested, is not the only mechanisms leading to the modulation of cough related neural pathways, but pathogenesis of chronic cough in subjects with rhinosinusitis is complex phenomenon. Understanding of pathogenetic mechanisms can lead to successful therapeutic interventions.

INTRODUCTION AND DEFINITION OF TERMS

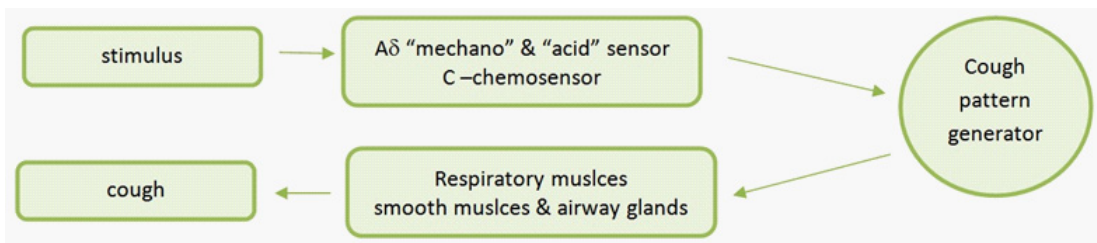
Cough is essential airway defensive reflex which protects the airways from accumulation of secretions, invasion of foreign bodies and chemical irritants – fulfilling its physiological role is of substantial importance for the human airways [1]. It is also one of the most common symptoms of respiratory diseases that lead to a consultation. Frequent causes of acute cough are typically upper respiratory tract infections (URTI), what is usually not difficult to manage at the level of primary care and the spontaneous resolution of cough is expected.

Chronic cough is completely different problem. Not particularly that one caused by chronic respiratory tract diseases (COPD, lung fibrosis or cancer) where the pathology of the airways and its relation to cough are obvious, but the syndrome of chronic cough. It is defined as dry unproductive cough, lasting for more than 8 weeks, with negative chest x-ray and negative findings during physical examination of the chest [2]. This type of chronic cough with no identified pathology in the lower airways is caused frequently by triad of diseases that produce conditions leading to the “up-regulation” of cough. They are gastroesophageal reflux, diseases of the upper airways and specific phenotypes of asthma.

American college of chest physicians defined upper airway cough syndrome (UACS), previously referred to as postnasal drip syndrome (PNDS), as one of several critical pathogeneses of chronic cough. In UACS patients, cough can be caused by a variety of upper respiratory disorders, including nasal and sinus diseases; it can also result from anatomic abnormalities and rhinitis. UACS is difficult to diagnose and to treat because it often coexists with other disorders that contribute to chronic cough [3] and it can seriously affect a patient’s quality of life [4]. This short chapter summarizes recent understanding of the pathogenesis of UACS and its main objective is to point out mechanisms responsible for enhanced cough response in subjects with upper airway diseases.

COUGH AS A REFLEX

Cough reflex is exclusively vagal phenomenon, with the polysynaptic reflex arch consisting of several parts. They are airway afferent nerves, afferent pathways and brainstem circuits responsible for processing of the afferent information. If the information is relevant and reaches the threshold to induce reflex response, cough motor pattern is generated by the brainstem centre, which activates efferent pathways and finally effectors of the cough reflex [5]. (Figure 1)



Airway Sensory Nerves

Afferent nerves innervating the airways belong to the vagus nerve, however there are some recent data suggesting that airways are innervated also by fibres derived from DRG. Neurons responsible for mediation and modulation of cough were identified using retrograde neuronal tracing and they are located in vagal nodose and jugular ganglia, while their terminals are broadly distributed within the airway mucosa in tussigenic areas in larynx, trachea and bronchi [5].

There are two main types of airway afferents responsible for cough – afferents responding to mechanical stimulation and afferents responding to the chemical agents [6].

Chemosensitive afferents are distributed all over the airways and lungs. These fibres are not activated during regular breathing cycle, but rather by different chemical stimuli such as inflammatory mediators, oxidizing substances or air-borne irritants. Majority of these fibres are non-myelinated C-fibres and their activation leads to the release of tachykinins [7]. The role of C-fibres in cough remains controversial and needs to be further clarified. Activation of C-fibres in anaesthetized guinea pigs by chemical stimuli does not induce cough. Conscious subjects respond to the activation of jugular C-fibres by coughing, however activation of nodose C-fibres has inhibitory effect on coughing in guinea pig model. Circumstantial evidence suggests that their effects in humans are comparable to those identified in guinea pigs [8]. Activation of jugular C-fibres by stimuli which does not reach the threshold for induction of cough reflex can induce specific sensation of urge-to-cough. This is complex cortical interpretation of airway irritation or discomfort, which proceeds (but not necessarily) the cough motor pattern [9].

Airway mechanosensors adapt to the lung inflation either rapidly or slowly, thus we can recognize two types – rapidly adapting receptors (RAR), which reduce the burst of action potentials during prolonged lung inflation and slowly adapting receptors (SAR), which rather adapt to this stimulation slowly [10]. The burst of action potentials appears after activation by relevant mechanical stimuli, such as lung volume changes (inflation/deflation), contraction of airway smooth muscles and oedema of the airway wall [6]. RARs and SARs are generally not sensitive to chemicals unless these substances are able to induce airway wall oedema, increase mucus output or induce changes of airway muscle tone. Reflex response to the activation of RARs is tachypnea and airway smooth muscle contraction, while activation of SARs participates on Hering-Breuer reflex [6].

Specific type of a mechanosensor was identified in the guinea pig airways. It is A δ mechanosensor with lower conduction speed (5m/s) located mainly in the extrapulmonary airways responding to mechanical stimulation and acid by burst of action potential. These stimuli are relevant to induction of cough in anaesthetized guinea pigs - interestingly, this type of nerve ending is different from RARs, SARs and C fibres and it originates in the vagal nodose ganglia. Based on the data from animal studies, this type of the nerve ending could be attributed to what is called “cough receptor” [11].

Evidence also supports the role of chemosensory fibres in the cough reflex in humans. Chemical substances known to be activators of airway chemosensors, such as bradykinin, citric acid and capsaicin, are also known as potent tussive agents in humans and animal models in conscious state [12]. These substances fail to induce cough in anesthetized subjects. Evidences lead to an assumption that cough induced by chemical agents depends on cortical activity, which is suppressed by general anaesthesia and this assumption correlates with the conception of urge-to-cough.

Based on the data about the most common stimuli inducing cough it is possible to conclude that humans are equipped by two types of cough reflex. Cough to mechanical stimuli and acid substances mediated via A δ nodose neurons [11], which developed as a protection against aspiration of “acidic” substances (reflux) and cough mediated by airway chemosensors, mainly C-fibres derived from the jugular ganglion. These fibres are sensitive to inflammatory mediators and chemical factors, for example capsaicin, bradykinin, adenosine and cinnamaldehyde [1].

Afferent Pathways and the Central Cough Pattern Generator

Afferent pathways carrying the information towards central nervous system run to the brainstem in the vagus nerve and superior laryngeal nerve entering the ventrolateral parts of medulla [13].

Cough pattern is generated in complex polyfunctional neuronal network localized in the brainstem. It is a neuronal network spreading in the rostrocaudal direction in the brainstem. These neuronal populations are responsible not only for airway defensive reflexes, but they also regulate normal breathing and its modification based on different signalling [14]. It is a holarchical, orchestrated and gated system, which processes afferent impulses from respiratory system. Information from the airway enters this network via nucleus of the solitary tract (nTS), which is the most important site where airway afferents connect to the second order neurons. If information reaches the threshold and is relevant for coughing, the neuronal network will initiate the motor pattern via activation of premotor and motor neurons. Neurogenesis of cough is further related to the lateral tegmental field, pontine respiratory group and lateral reticular nucleus [15]. The motor act of coughing consists of inspiratory phase, compressive phase when glottis is closed, but expiratory muscles produce high intrathoracic pressure, which will drive the expulsion of the air in expiratory phase [16].

Efferent Pathways and Effectors of the Cough Reflex

Efferent pathways and effectors are not specific only for cough but also for breathing, sneezing and other respiratory defensive reflexes. Motor drive is initiated in the premotor and motor neurons and is conducted to peripheral motoneurons via reticulospinal tracts to the particular segments of the spinal cord at the cervical, thoracic and lumbar levels. Final efferent signalling is conducted via phrenic, intercostal and lumbar nerves. Very important component is efferent innervation of pharyngeal and laryngeal muscles provided by vagus nerves and other cranial nerves. Airway smooth muscles and glands belong also to the effectors of the cough reflex and these are innervated by sympathetic and parasympathetic nerves [15].

Airway smooth muscle

Cough and bronchoconstriction are considered to be protective and defensive mechanisms of respiratory tract. Their afferent nerve tracts are separated, as they can be both induced simultaneously, but they are suppressed selectively.

Physiologic role of bronchoconstriction accompanying cough is not clearly known; it is assumed that it can potentiate the effect of cough expulsion, in which entrainment of mucus and pollutants it contains out of the airway and stabilises lumen in active cough expulsion. Narrowed airways are more rigid in comparison to relaxed state and thus it serves as a prevention from total collapse.

Upper airway muscles and respiratory muscles

Upper airway muscles do not contribute directly to airflow, but their activation needs to be synchronised with those respiratory muscles, which generate spontaneous breathing pattern and motor output of cough. Muscles of oral and nasal cavities, specifically muscles of nasal alae, muscles enabling opening of mouth, muscles of soft palate and genioglossus muscle, do participate in cough [17,18].

Laryngeal muscles

Cricothyroarytaenoideus posterior muscle (PCA) is a laryngeal abductor, whereas thyroarytaenoideus and arytaenoideus muscles are adductors. Role of cricothyroideus muscle (CT) is more or less controversial and resembles the abductors [19]. Throughout the inspiration phase of cough, the PCA and CT are activated, which causes decrease in resistance of upper airways and enabling inspiratory airflow. During narrowing of glottis both muscles show only minimal activity. During expiratory phase the PCA is active and adductors are suppressed. This phenomenon opens glottis and allows expulsion of air from lung whilst expiratory muscles are activated [19].

Diaphragm, intercostal and abdominal muscles

This group consist of external intercostal, scalenic, sternocleidomastoid, pectoral and subclavius muscles. External intercostal muscles have inspiratory function and internal intercostal muscles show expiratory activity. Many recent studies have confirmed that external intercostal muscles in the ribcage shorten during passive inflation and internal lengthen.

Expiratory muscles with significant respiratory function are localised in ventrolateral part of abdominal wall. Their contraction drags abdominal wall inwards and thus increasing intraabdominal pressure, resulting in diaphragm being pushed in cranial direction, lung volume decreasing and pleural pressure rising. Contraction of abdominal muscles contributes to exhalation via decrease of rib cage. Their intense activation contributes substantially to cough [18].

COUGH PLASTICITY

Recently, a term “cough plasticity” was introduced as the description of modulation of the neurogenesis of cough at the peripheral and central level. Cough, if precisely regulated, prevents aspiration and contributes to the airway cleaning. In terms of plasticity, cough can be up- and down-regulated. Up-regulation of cough (stronger or more frequent cough bouts) is usually present in majority of respiratory diseases and it may also develop as a consequence of extrapulmonary conditions, for example in UACS or GERD [20]. In turn, cough reflex can be suppressed (down-regulated) in elderly, new-borns, anaesthetized subjects, lung transplant recipients, paralyzed subjects or patients with neuromuscular disorders [21]. How plasticity works and what are the main mechanisms responsible for neuroplastic changes?

Interaction of Airway Sensors – Convergence

Pathological processes in the airways are usually complex and they activate more types of airway afferents. For example in inflammation - C fibres are activated by the presence of inflammatory mediators and A δ fibres are activated by accumulated mucus, airway wall swelling etc. at the same time. It was found that interaction of afferent nerve subtypes in the airways can lead to modulation of cough. Activation of jugular C-fibres may interfere with A δ fibres, thus potentiating the cough response. Synergistic interactions between C and A sensory drive leading to augmented cough response are based on the mechanism of convergence [22,23]. It was documented that activation of non-myelinated C-fibres induces release of tachykinins not only at the peripheral terminals in the airway mucosa, but also at the central projections site. Increased release of neurokinin on the sites of projections to second and higher order neurons in the brainstem can thus increase central synaptic transmission.

Change of the Nerve Fibre Phenotype

Second type of neuroplastic changes is related to the increased expression of cation channels which are responsible for activation of cough relevant afferents. These ion channels are TRPV1 and TRPA1 - abundantly expressed on airway terminals. Inflammation of various aetiologies leads to increased expression of ion channels, thus increasing irritability and responsiveness of airway sensors. Neuroplastic changes were observed in subjects with allergic airway inflammation [24,25] and also there are recent data about up-regulation of TRP channels in airway sensory nerves induced by respiratory viruses. Airway inflammation is a massive source of neurotrophic factors, which lead to the phenotypic changes in the neurons and for example previously only mechanosensitive A δ fibre may express TRPV1 protein extending its sensitivity to the chemical agents. Exposure of the nerve fibres to the neurotrophic factors also lead to the sprouting – growth and branching of nerve fibres in the airway mucosa [24].

Changes in The Activation Profile of the Nerve Fibers

Mechanisms of signal transduction in vagal afferents are not entirely understood [20]. Majority of inflammatory mediators affects airway sensory nerves in a term of either activation or modulation of their neurophysiological properties, mainly membrane excitability. For example, bradykinin induces single discharge of action potentials in airway A δ fibres. Administration of PGE₂ does not activate A δ terminals, however it increases the effect of administered bradykinin. Based on similar studies it was documented that not all inflammatory mediators can activate cough fibres. Bradykinin is an activator, but majority of them – prostaglandins and leukotrienes can “modulate” their membrane excitability, thus reducing the threshold for other tussigenic stimuli. The result of this interaction is augmented cough response [20]. (Figure 2)

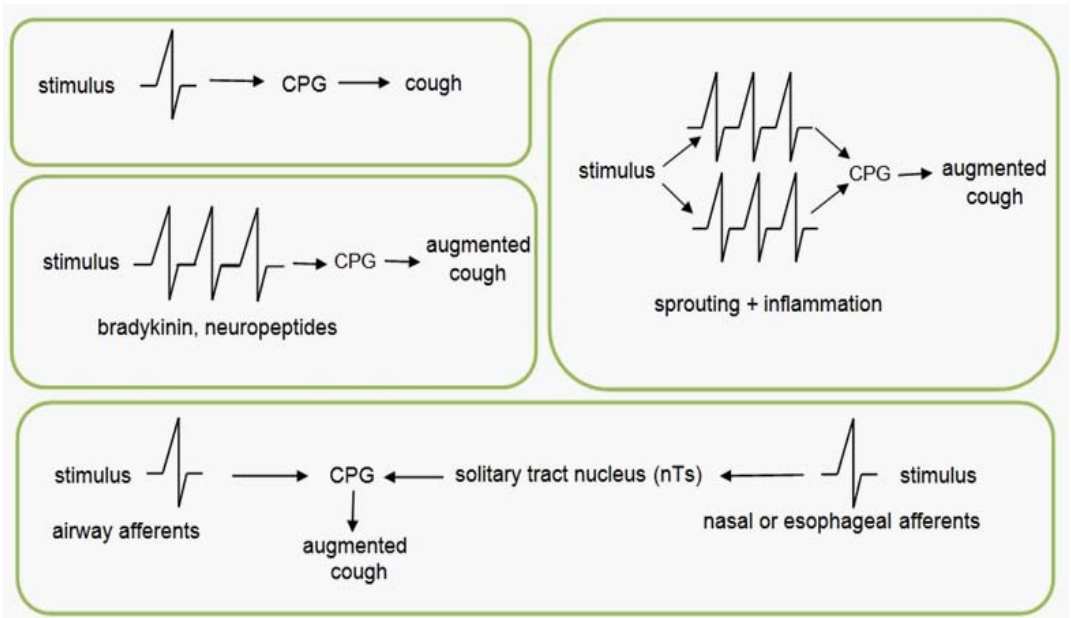


Figure 2: Pannel A: In physiological conditions, activation of the airway afferent leads to the action potential discharge, this afferent drive is processed in central cough pattern generator (CPG) and it afterwards produce cough motor act – “normal” physiological cough. Pannel B: The same tussive stimulus in case that peripheral afferents are sensitized by the presence of inflammatory mediators or neuropeptides produces more robust discharge of action potentials as a consequence of increased excitability - this information is evaluated in CPG and lead to production of augmented cough. Pannel C: Increased density of the airway nerve terminals (result of sprouting – additional growth and branching of the nerves) is exposed to the same tussive stimulus. More afferents become activated, stronger afferent drive reaches the CPG and the result is augmented cough. Pannel D: Stimulation of airways and organs outside of the tussigenic areas lead to the convergence of the afferent inputs to the nTs, and then depending on the type of interactions, CPG produces augmented cough response.

Central Neuronal Interactions

Central neuronal interactions seem to play substantial role in cough plasticity [26,27]. Cough is often present in subjects suffering from extrapulmonary diseases such as reflux or rhinosinusitis. Interactions of airway afferents with afferents innervating oesophagus or nose may potentiate cough response at the central level [28,29]. Cough in reflux patients could be an excellent example for such interaction of vagal afferents. Infusion of the acid to oesophagus does not induce coughing, but it potentiates the cough response induced by an airway challenge in healthy volunteers. Similar effect was observed in subjects with stimulation of nasal afferents in experimental settings. Stimulation of trigeminal terminals does not provoke cough, but facilitates cough induced from the lower airways [30,31]. Mechanism proposed for these central interactions is based on the convergence of afferent inputs.

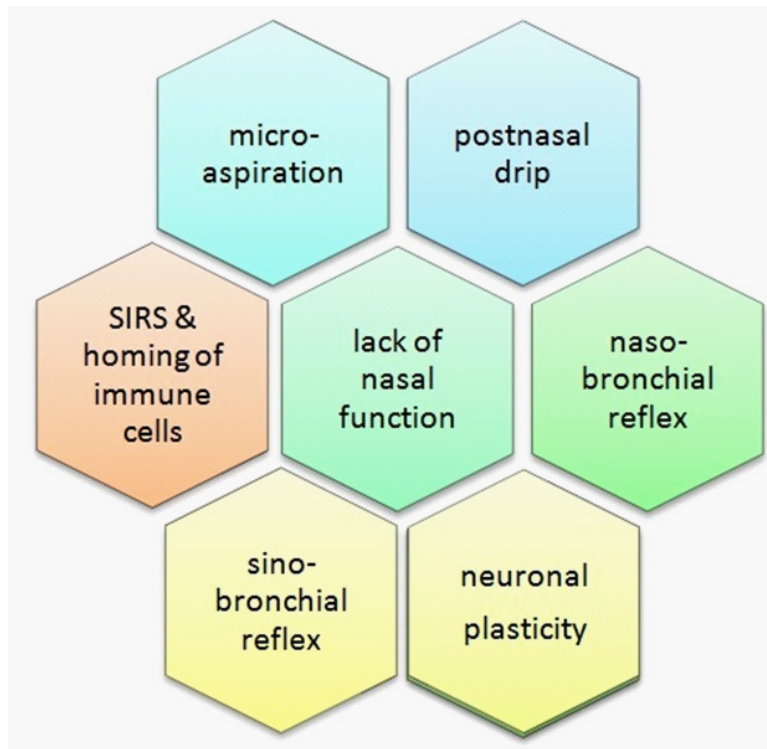
COUGH AND UPPER AIRWAY DISEASES

Upper respiratory tract infections (URTI) are the most common causes of acute cough and they are in more than 90% of patients caused by viruses [32,33]. In case of normal immune profile of an individual, acute cough due to URTI is usually self-limiting phenomenon, and it resolves with time.

Diseases of the upper airways are also the most commonly identified causes of chronic cough in adults. 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 [34].

As it was previously supposed by clinical branch of cough researchers, cough in upper airway diseases was believed to be a caused directly by activation of the nasal afferents by either inflammatory mediators or mucus excess [3]. The recent understanding of the airway sensory system provides substantial evidence that it is not possible to induce cough by stimulation of any afferents in the upper airways (nose, sinuses), because these “cough relevant” afferents are located in the larynx, trachea and main bronchi [17,30,31,35]. If cough belongs to spectrum of clinical presentation of these diseases, there must be mechanisms responsible for it.

Pathogenesis of UACS was systematically studied and it has been recognized, that simple mechanistic theory of “postnasal drip syndrome” is not the only mechanism provoking coughing in subjects with rhinitis. Understanding of the concept of the cough reflex regulation and cough plasticity that was described above make us understand why and how the subjects with upper respiratory tract diseases cough. Complex pathogenesis involves combination of mechanisms illustrated on the figure [36] (Figure 3).



Cough Sensitivity in Subjects with Upper Airway Diseases

Cough reflex sensitivity is defined as **the lowest concentration of tussive agent inducing cough**. The values are further classified into C2 and C5 – the lowest concentrations of tussive agent inducing two or more coughs or five or more coughs respectively. The test of cough sensitivity is performed by inhaling gradually increasing concentrations of tussive agent – TRPV1 agonist capsaicin. This parameter is usually changed in airway diseases and all states characterized by up-regulation of cough. Heightened cough reflex sensitivity means that lower concentration of capsaicin is required to produce cough [37].

It was repeatedly confirmed that patients with upper airway diseases, mainly allergic rhinitis, but also common cold, have heightened cough sensitivity [38-41]. Cough reflex is sensitized in subjects with allergic rhinitis during the pollen season and also out of it [39]. Cough sensitivity in rhinosinusitis correlates with the symptom magnitude and nasal corticosteroids diminish this sensitization [42]. Sensitization of the cough reflex out of pollen season could be attributed to the repeated activation of sensory nerves. Repeated episodes of the exposure to allergen induce inflammation with release of mediators sensitizing the neural cough pathways at multiple levels.

A study performed in children with common cold and allergic rhinitis showed that inflammation located in the upper airways leads to significant reduction of the cough threshold [41]. The data obtained in capsaicin cough challenge are suggestive for modulation of cough sensitivity which was reported also for adults with different type of upper airway diseases [36].

Insight from animal models confirms that sensitivity of cough reflex is heightened during experimentally induced allergic rhinitis in guinea pigs sensitized by ovalbumin and the cough sensitivity correlates with the presence and magnitude of nasal symptoms [42,43]. Treatment of inflammation by local corticosteroids, antagonists of leukotriene cys-LT1 receptor or peroral rutinascorbine decreases significantly magnitude of nasal symptoms evaluated by scoring system, and also led to desensitization of the cough reflex back to pre-disease values [41].

How Can the Upper Airway Disease Affect Coughing?

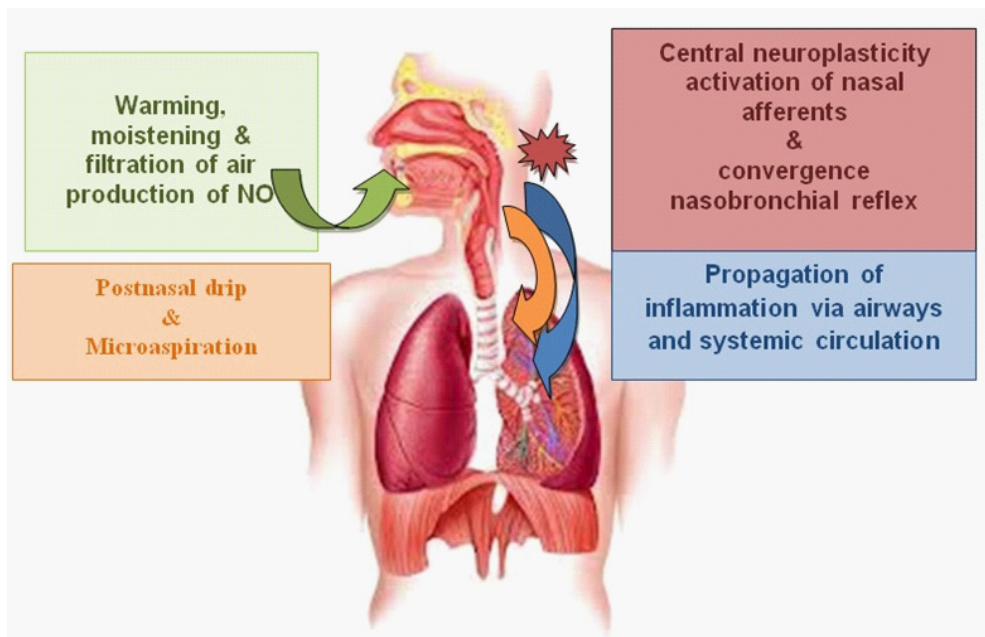
Reactivity of nasal mucosa is typically uniform and there is not particular difference depending on the provoking factors. Viruses, bacteria, allergy, cold, irritant exposure – they all initiate very similar responses, with similar consequences for the upper and lower airways, even though they are more or less intense from case to case [44].

Very important information that matters when it comes to the upper – lower airways relationship is that the nose is the first port of entry to the respiratory system and it provides numerous protective and defensive processes to protect itself and the lower airways. It moistens, warms and filters inhaled air and participates in many processes optimizing the functions of the lower airways. Sinuses also contribute to the lower airway physiology by producing optimal amount of NO, which regulates the bronchial smooth muscle tone and bronchial reactivity [45].

Pathological processes affecting the nose and sinuses lead to

1. Sneezing – a powerful reflex that eliminates mucus and irritants from the nose by forced expiration
2. Nasal discharge of different nature (watery, mucous, serous, purulent) with the main purpose to dilute and eliminate the noxa from the mucosa (rhinorrhoea)
3. Reduction of nasal patency to decrease further inhalation of any irritants deeper to the airways and/or sinuses [45].

To achieve dilution and increase mucus output, nasal vessels and glands are activated by immune, neural and humoral signalling. Therefore, the most common upper airway symptoms are sneezing, rhinorrhoea and nasal congestion with reduced nasal patency. All of these mechanisms may influence cough reflex arch either at the peripheral level (sensors) or central level (brainstem circuits, cortex) [36]. Consequences of mentioned processes in the upper airway with potential impact on the cough neural pathways are: lack of nasal function in complete nasal obstruction, postnasal dripping of the nasal secretions, microaspiration of the inflammatory “aerosols” or “droplets” and robust activation of nasal afferents with reflex consequences [36] (Figure 4).



Mechansims Influencing Cough Sensitivity

Complete obstruction of the nasal passages - lack of nasal functions

Nasal obstruction is subjective phenomenon; however, it can be objectively measured by rhinomanometry or by constructions of flow volume curves. In case of complete nasal obstruction subjects switch to oral breathing which is not optimal for air conditioning and is typically present during exercise or speech.

Persistent oral breathing leads to inhalation of cold dry air, which is not optimally filtered in the upper airways. Deposition of inhaled irritants and particulate matter, together with changes of osmolality of superficial fluid may lead to the functional and/or morphological impairment of the lower airway mucosa with increased cough reflex sensitivity [35]. Additional warming and moistening of inhaled air required in the lower airways lead to the lack of superficial mucosal fluids with consecutive hypertonicity, which modulates activity of cough related pathways [46]. Inhalation of poorly filtered and unconditioned air may lead to initiation of inflammation either based on immune system signalling or via neurogenic inflammation induced by inhaled irritants [47,48].

Postnasal drip

Literature data about postnasal drip share conflicting evidence, as majority of patients with clinically diagnosed PND do not cough. It is also difficult to establish diagnosis of PND based on the finding of the mucus on the dorsal pharyngeal wall dripping down to the hypopharynx [49,50]. Since the term postnasal drip (PND) is rather associated with chronic upper airway diseases (rhinosinusitis) it may appear also in URTI [51,52]. Increased production of mucus in the nose

and sinuses in URTI subjects leads to the nasal discharge. Only 30% of secretion is transported forward to the nostril and drips out of them. 70% of the mucus produced in the nose and sinuses moves to the nasopharynx and pharynx as a consequence of anatomical conditions and orientation of mucociliary transport [38,44]. Previously, it was thought that dripping of the mucus down to the laryngeal aperture can reach the larynx, trachea, or eventually more distal airways. Studies using radiolabelled material applied to the sinuses demonstrated that mucus does not reach the larynx. Radiolabelled marker was detected in the upper gastrointestinal tract 24 hours after its sinonasal administration [53]. There are effective laryngeal reflexes, which probably provide sufficient defence and prevent the mucus against entering the lower airways [36].

Even though, postnasal drip can activate mechanosensors in the pharynx and hypopharynx by its presence on the mucosa's surface. Inflammatory mediators, cells and their products which are present in the mucus can activate or sensitize the chemosensors, as well [54].

Incomplete nasal obstruction with microaspiration

The lack of objective evidence about transportation of the macroscopic amount of mucus from nose to tussigenic areas together with the benefits of nasal decongestants on cough in common cold subjects led to postulation of a hypothesis of microaspiration [54]. Similar hypothesis of aspiration of refluxate in "gaseous" form was implied for reflex related coughing [55]. Hypothesis explains that increased resistance of nasal passages increases the turbulent pattern of the airflow. These conditions may lead to formation of polydisperse aerosol, which is inhaled deeper to the airways.

Indirect evidence was obtained in animals with experimentally induced rhinitis. Animals were either tracheotomised immediately after rhinitis was induced, or were allowed to breathe through the nose 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 contribute to the microaspiration of aerosol with mixture of inflammatory mediators to the distal portion of the airways [35].

Similar results were reproduced in healthy human volunteers with histamine induced nasal discharge and obstruction; both parameters were objectively measured and quantified. Subjects were instructed to breathe through the nose with a force to overcome increased resistance, and the other group was instructed to breathe through the mouth wearing a nose clip. Intensified nasal breathing augmented cough response probably by the mechanism of microaspiration of inflammatory aerosol [35]. These results are supported by the observation that medication reducing nasal mucosal swelling and secretion also reduces coughing [54].

Nasobronchial/sinobronchial reflex

Reflex interactions between the nose and lower airways are frequently subjected to discussion. There are conflicting evidences whether sinobronchial and nasobronchial reflexes exist. While

some authors describe the rise of lower airway resistance in the subjects with activation of nasal trigeminal afferents, some other authors failed to prove their existence [56-58]. The data are indicative for existence of nasobronchial/sinobronchial interactions, but rather in the subjects with already present airway hyperresponsiveness.

Nasobronchial reflex (lower airways narrowing provoked by nasal irritation) can modulate coughing. It was previously believed that bronchoconstriction can activate cough related fibres by the mechanical forces produced by the change of the airway lumen. Nowadays it was recognized, that cough and bronchoconstriction are different reflex processes, but they may potentiate each other by the mechanism of central convergence and synergistic interactions of cough and bronchoconstriction related pathways [59].

Sinus diseases or abnormal ventilation of the sinuses may lead to reduced production of nitric oxide, which is synthesized in sinuses and reaches the lower airways with every inspiration. Physiological levels of nitric oxide modulate bronchomotor responses and prevent bronchoconstriction [60].

The role of central neuronal pathways – convergence

It was previously suggested by clinical respirologists that cough can be elicited directly, by activation of nasal afferents. This assumption was not correct. The upper airways are innervated by trigeminal nerve and stimulation of these nerve endings in the nasal mucosa by mechanical and chemical stimuli (capsaicin, AITC, cinnamaldehyde, histamine) fail to provoke coughing in experimental and clinical settings [36,43]. Primary responses to this stimulation are sneezing, itching/irritation, nasal congestion and rhinorrhoea. Animal models, studies in human healthy volunteers and subjects with upper airway diseases indicate that it is not possible to induce coughing from the upper airways [31].

It is known that inflammation in the upper airways potentiates either cough induced by stimulation of putative TRPV1-expressing capsaicin-sensitive fibres, or induced by mechanosensitive A δ nodose fibres [10]. Recent understanding of the airway sensors and their neurophysiology together with the evidence about peripheral and central cough plasticity may explain pathogenesis of UACS.

Local nasal pre-treatment with 1% trimecaine inhibited previously augmented cough responses in animal models. Intranasal administration of irritants which activate trigeminal nerves enhances urge-to-cough [43]. Therefore, the role of the nasal afferents in this process of sensitization is strongly suggested [27]. Inflammatory mediators released during the nasal inflammation are known as potent activators (histamine, bradykinin) and sensitizers (prostaglandins, leukotrienes) of nasal trigeminal afferents [61,62]. Intranasal administration of different chemical substances known as activators of trigeminal afferents in animal and human studies documented that if cough is induced simultaneously from the lower airways, it is significantly augmented. In the light of cough plasticity concept, we started to hypothesize that cough reflex could be considerably

modulated by afferent drive from the nose. Parameters of cough sensitivity are typically shifted towards lower concentrations. Total and cumulative count of coughs is increased together with considerably enhanced urge-to-cough [36,43].

Also urge-to-cough is enhanced in subjects with UTRI [63,64], similarly to the subjects with nasal irritants challenges.

Does virus make you cough?

Virus infection typically destroys the epithelial tight junctions, leads to the epithelial damage and shedding. This makes the airway afferents more exposed to the tussive factors of endogenous and exogenous nature. The role of inflammation in the activation of the cough reflex has been explained already, but recently, interesting data were published about the role of the virus infection in cough. Objective evidence of this “virus-induced” cough hypersensitivity relies on challenge experiments. A shift in the cough dose response curve with a lower threshold in URTI, has been demonstrated to capsaicin challenge in adults and also in children [38,41]. Recovery of the cough reflex to a more normal level is seen as the infection abates.

It is known that activation of TRPA1 and TRPV1 channels expressed on the nasal trigeminal afferents up-regulates the cough response while activation of “menthol receptor” TRPM8 channel down-regulates it [65,66].

Recently published data showed that respiratory viruses have the ability to up-regulate cough reflex. The authors showed for the first time that rhinovirus can infect neuronal cells. Furthermore, infection causes up-regulation of TRP channels by channel-specific mechanisms. The increase in TRPA1 and TRPV1 levels is mediated by soluble particles of the virus whereas TRPM8 expression appears after the virus terminated its replication. There is hypothesis that increased expression of the TRPV1 by the virus is an integral part of the virus life cycle. Expression of TRPV1 increases coughing of affected individual, which makes the virus to spread to another host across the population [65]. (Table 1)

Table 1: Summary of mechanisms influencing cough reflex in subjects with upper airway disease.

Proposed mechanism	Cough reflex targets
Complete nasal obstruction → lack of nasal functions in oral breathing	Inhalation of cold dry and unfiltered air *
	Damage of the superficial mucosal layers with increased penetration of tussigenic factors to the nerves *
	Neurogenic and/or immune factors initiated inflammation
Overproduction of mucus & postnasal drip	Activation of mechanosensitive A δ fibres in the pharynx and laryngeal aperture *
	Activation/sensitization of chemosensitive C fibres by mediators and signal molecules in the mucus
Incomplete nasal obstruction → nasal breathing with increased nasal resistance	Formation of polydisperse aerosol of secretions and inflammatory mediators, cells and their products - microaspiration to the lower airways *
	Activation/sensitization of chemosensitive C fibres
Nasobronchial/sinobronchial reflex	Modulation of activity of airway afferents by increased tone of the smooth muscle cells
Irritation of nasal trigeminal afferents by ongoing inflammation	Convergence of trigeminal and vagal afferent drive with up-regulation of cough pattern generator activity
Virus induced neuroplastic changes	Peripheral plasticity of putative cough fibres in the airway – increased expression of TRPV1 and TRPA1 ion channels

THERAPEUTICAL IMPLICATIONS

Mechanisms by which rhinosinusitis affects cough reflex are many, but all of them are consequences of nasal disturbances – increased secretion, reduced patency, inflammation and so on. Cough sensitivity correlates with magnitude of nasal symptoms and severity of inflammation, therefore combating these two are the underlying conditions for management of UACS. Since there are not unified guidelines worldwide, recent papers recommend following therapeutic strategies. Their differences are very likely related to the different distribution of causes leading to the sinus/nose diseases with subsequent up-regulation of cough reflex.

Corticosteroids, antihistamines and also cysLT1 antagonist montelukast were tested in animal models together with rutinascorbine, and these studies documented clear relationship between successful treatment of nasal pathology which leads to the improvement of cough. Recent paper by Yu and co-workers analyses different approaches to the medication of UACS and it is summarized in the Table 2.

The strategy of the treatment is subjected to the cooperation between cough clinics experts and ENT specialists.

Table 2: Guidelines for treatment of UACS in different countries.

	USA	UK	Europe	Australia	Japan	China
Allergic rhinitis	new generation A+D	NS	New generation A+D	NS+A	A	NS +A +D
Nonallergic rhinitis	First generation A+D					First generation A+D
Chronic rhinosinusitis	First generation A+D NS ATB			NS ATB/purulent	Low dose of 14/15 – member ring macrolide	NS First generation A+D ATB

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