Published in final edited form as:

Pulm Pharmacol Ther. 2011 June ; 24(3): 344–352. doi:10.1016/j.pupt.2010.12.010.

Workshop: Tuning the ‘cough center’

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Abstract

The Workshop considered the mechanisms whereby the ‘cough center’ could be tuned by various afferent inputs. There were particular presentations on the effects of inputs from the nose, mouth, respiratory tract and lungs, cerebral cortex, somatic tissues and the pharynx. From all these sites cough induced from the lungs could be increased or decreased in its strength or modified in its pattern. Thus ‘tuning’ of cough could be due to the interaction of afferent inputs, or to the sensitization or desensitization of brainstem neural pathways. The pattern of response depended on the ‘type’ of cough being studied and, in some instances, on the timing of the sensory input into the brainstem. Cough inputs could also affect various ‘non-cough’ motor outputs from the brain, although this was not the main theme of the Workshop. The main conclusion was that cough is not a stereotyped output from the medullary ‘cough center’, but that its pattern and strength depend on many afferent inputs acting on the ‘cough center’.

Keywords

Cough; Expiration reflex; Exercise; Urge-to-cough; Gastroesophageal reflux

1. Introduction

John Widdicombe started by quoting Ranson [1] who wrote in 1921 that “it is clear that the respiratory center has connections with all the other afferent cranial and spinal nerves”. Since the ‘cough center’ is intrinsically interconnected with the ‘respiratory center’ (although neither term is much used nowadays), Ranson’s claim may be expected to apply also to the cough center.

It follows that a ‘simple’ afferent input, such as touching the finger, will *potentially* affect cough. This could be either by a ‘direct’ afferent connection to the cough center or indirectly by ‘affect’, the cerebral cortex being activated by awareness of the stimulus and in turn modifying cough. For each afferent input the questions that need to be asked are:

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1. Is the potential response sufficiently large to be measurable and physiologically important? The answer, possibly including the example above, may often be no.
2. Which 'cough reflexes' are affected? For example the 'classical' cough reflex (CR) starting with a deep inspiration, or the expiration reflex (ER) starting with an expiratory effort (both of which can be elicited from the larynx and tracheobronchial tree) or both? [2,3] (For convenience in this paper both will often be referred to as 'cough'.)
3. If there is a cough response is it positive or negative—stimulation/increased sensitivity or inhibition/decreased sensitivity of cough?
4. Is there a change in the motor pattern/integration of cough? [4–6].
5. Does the timing of the afferent input in relation to the phase of the respiratory cycle affect the response? There is increasing evidence for this phenomenon ([7–11], see also below), which might be expected to apply more to the short-latency (15–25 ms) ER than to the long-latency (500+ ms) CR.

The following sections will review the information for particular afferent inputs which have been shown to affect cough and its sensitivity (see also reviews [12–16]).

2. Tuning from the nose

Milos Tatar described how the upper respiratory tract serves many important functions, including the warming and humidification of inspired air and removal of particle and vapor-phase pollutants. The nose is also a major site of common allergic illnesses, the site of infection with common viruses and a site for mucosal irritation and nonallergic inflammation [17]. Inflammation of the nasal mucosa leads to sneezing, nasal itch, rhinorrhea and nasal blockage. Many of these symptoms are likely the result of nasal trigeminal sensory nerve stimulation by inflammatory mediators. Nasal challenge with the C-fiber stimulant capsaicin causes a different set of symptoms than those evoked by histamine, suggesting that these two stimuli may activate separate subpopulations of nasal sensory nerves [18]. Information arising from the irritation of the nasal mucosa represents a very important input to the respiratory and cardiovascular systems to initiate physiological responses. This input also serves as a potent activator of different defense responses from the upper airways [19].

Diseases of the nose and paranasal sinuses are among the most commonly identified causes of chronic cough. Depending on the population studied and the variations in the diagnostic algorithm, the diseases of nose and sinuses contribute to cough in 20–40% of patients with chronic cough and a normal chest radiograph [20]. The mechanisms of chronic cough in rhinosinusitis are not completely understood. Several mechanisms have been proposed, single or in combination: postnasal drip (PND), direct nasal irritation, inflammation in the larynx and lower airways and cough reflex neural sensitization [21].

There is a consensus that the cough reflex cannot be directly triggered from the nose. We addressed the mechanistic question whether the strength of the cough reflex can be modulated 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. We showed that the cough reflex is sensitized by the intranasal administration of sensory nerve activators in animal models and in humans [22].

First we evaluated the hypothesis that the afferent nerve activators applied into the nose sensitize the cough reflex in humans by using nerve sensor activators histamine and capsaicin. Histamine is a prototypic mediator of nasal inflammation that directly stimulates a

subset of nasal sensory nerves [18]. The TRPV1 selective agonist capsaicin is also an efficient activator of the nasal sensory nerves [18]. Intranasal administration of histamine and capsaicin failed to trigger cough in healthy subjects. 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. 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 [23,24].

Similarly, intranasal histamine did not trigger cough but sensitized the cough reflex in patients with allergic rhinitis. These data are consistent with the hypothesis that the activation of nasal sensory nerves sensitizes the cough reflex [25]. We next evaluated sensitization of the cough reflex in patients with allergic rhinitis but without nasal histamine. We found that the cough reflex was more sensitive in patients with allergic rhinitis compared with healthy subjects [26].

Our results strongly indicate that nasal sensory nerves are the neural pathways involved in the sensitization of cough. Results on vagal afferent systems lead to informed speculation that they can mediate central sensitization of the cough reflex [27]. 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 showed that the sensitization of cough from the nose can be induced even in anaesthetized animals, suggesting that the cough sensitization does not require intact cortical function [22].

Similar to human studies, intranasal administration of a sensory nerve activator sensitized the cough reflex in awake guinea pigs [28]. In this study, intranasal administration of capsaicin enhanced by 70% the cough induced by lung inhalation of citric acid. Intranasal ovalbumin substantially decreased the citric acid cough threshold in the guinea pig model of allergic rhinitis induced by repeated intranasal ovalbumin challenge in ovalbumin-sensitized animals [29]. Our preliminary data suggest a role for the leukotriene cys-LT1 receptor in the sensitization of cough by allergic inflammation in this model [29]. It is of note that the stimulation of cys-LT1 receptors induces sensitization of putative nociceptive trigeminal sensory neurones innervating the nose [30]. 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 anaesthetized guinea pigs the intranasal administration of capsaicin caused an approximately threefold increase in the number of coughs evoked by mechanical stimulation of the trachea [28]. Similar results were obtained in cats [28]. Thus the sensory nerve activators applied into the nose sensitize both the mechanically- and chemically-induced cough from the lungs. These data suggest that nasal sensory input modulates cough at the level(s) above the central projections of the cough-triggering nerves.

The nasal mucosa is a potential site for numerous irritant influences. Studied membrane receptors, which could be stimulated by inhaled irritants, are TRPA1 and TRPM8 receptors on afferent nasal trigeminal nerve endings. The modulating effects of the input from these receptors on the cough reflex are not known. Stimulation of TRPA1 receptors in the lower airway is a potent trigger for the cough reflex [31]. We can speculate that TRPA1 receptors in nasal mucosa can modulate the cough reflex by an effect similar to that of TRPV1. TRPM8, a menthol receptor stimulated by cold, is an important inhibitor of ventilation, especially in guinea pigs [32]. Cold applied to the nasal cavity and the face skin generates

the diving reflex with strong inhibition of ventilation and heart rate. Cold applied to the nasal mucosa can down-regulate the cough reflex [33].

3. Tuning from the mouth

John Widdicombe pointed out that patients believe that oral antitussives work; over £300 million is spent each year by patients in the UK and over \$2000 million in the US on over-the-counter oral treatments (including herbal) for cough [34]. These treatments are assumed to act in the mouth and pharynx, but there are few studies where the same dose is swallowed in a capsule as a control. The true control would be to remove the active chemical ingredient from the dose, leaving the same taste, smell and physical consistency, but this is impractical. Thus the subjects cannot be blind to the test.

An example is the report by Paul et al. [35] that received much media publicity. This showed that oral honey had a clear antitussive action in children with acute cough, significantly greater than the placebo; but the 'placebo' was placing an empty syringe in the mouth! The honey was given while the children were awake, but antitussive action was present after they went to sleep [35,36]. Similar oral antitussives such as sesame oil [37] and menthol [38] have been shown to continue their action during sleep, so the mechanism cannot be solely 'conscious/psychological'. Eccles [39] has called this a 'physiological' antitussive action, and suggested it is due to the release of endorphins in the upper brain with long-lasting actions (which would continue during sleep), a mechanism established for pain-relieving agents. This implies that during sleep the cerebral cortex exerts a tonic cough-sensitizing influence on the 'cough center' in the brainstem that can be inhibited by endorphins. What happens during dreams?

There is thus a *prima facie* case for believing that oropharyngeal afferents can lessen cough, either via the brainstem 'cough center' or via the cerebral cortex. If so, the afferents have not been identified. Nor is it clear whether they need to be stimulated or inhibited when they exert their antitussive effect. Menthol and clove oil, given either as oral solutions or by inhalation, are popular antitussives and have both local anesthetic and sensory receptor stimulant properties, although which is important has not been determined [40,41]. There seem to be no studies on the possible action of oral local anesthetics such as lignocaine on cough and its sensitivity (although they are effective antitussives when given into the lungs).

The possibility that the physical properties of the oral dose may be important was raised at the workshop. Subjects are aware of the 'stickiness' and 'fluidity' of the doses (although they may not use these terms), so these properties must be influencing afferent input to the brain and cerebral cortex. Temperature may be another factor, since hot drinks also inhibit cough, although the same drinks at room temperature also depress cough to a smaller extent [42].

There seem to be few studies on the afferentation of the tongue, apart from those on taste receptors. The tongue sensory nerves contain at least two types of membrane capsaicin receptor (TRPV1, TRPA1) [43], but their reflex actions have not been described. Capsaicin is an ingredient of some popular oral cough treatments (e.g. Fisherman's Friend); there may be an analogy with the lungs, where some capsaicin-sensitive receptors stimulate cough and others inhibit it [12,13,15].

Although oral care lowers the sensitivity to inhaled cough stimulants [44] the underlying mechanisms have not been worked out, but they could include diminished afferent inputs from the mouth.

4. Tuning from the esophagus

Giovanni Fontana pointed out that it is widely recognized that symptoms of gastroesophageal reflux (GOR), either oesophageal or extraoesophageal, are frequently reported by patients complaining of chronic cough. At least two distinct and not mutually exclusive mechanisms have been invoked to explain how reflux can provoke a cough response: aspiration of gastric contents and a vagally-mediated oesophageal-tracheobronchial reflex. When aspiration predominates, gastrointestinal symptoms of reflux are generally prominent and include heartburn, regurgitation, 'water-brash', sour taste; chest pain, globus sensation and pharyngolaryngeal symptoms (e.g. dysphonia, hoarseness and sore throat) may also be present. It is noteworthy, however, that aspiration cannot be invoked as the unifying pathogenetic mechanism in all cases of cough in refluxers. Carney et al. [45] found no evidence to support such a mechanism in a group of cough patients by measuring lipid-laden macrophages in sputum as a marker for aspiration. Convergence of vagal afferents from the oesophagus and respiratory tract in the brainstem has led to the possibility of an oesophageal-tracheobronchial reflex. This is supported by the findings that sensory nerves in the esophagus respond to mucosal irritation by acid. For instance, a study by Irwin et al. [46] using dual-channel pH monitoring showed correlation of cough with distal and proximal oesophageal acid exposure. In addition, acid infused into the distal oesophagus of patients with chronic cough increased the frequency of coughing [47] and cough reflex sensitivity [48]. This acid-induced cough reflex arc could be blocked with oesophageal lidocaine infusion [47]. Oesophageal acid exposure is probably not the sole cause of cough in patients with GOR, and an abnormal oesophageal motility has also been recognized as an important factor in the pathogenesis of "oesophageal" cough [49]. The fact that oesophageal acid had no effect on cough reflex sensitivity in patients with objectively confirmed reflux disease without cough [48] suggests that the oesophageal-tracheobronchial reflex may be sensitized in patients with chronic cough.

Whether central or peripheral mechanisms are responsible for sensitization of the cough reflex is unknown, although some authors advocate both mechanisms [50]. The situation is further complicated by the fact that many patients with reflux never complain about cough [51]; furthermore, coughing can produce reflux in some patients in whom extra-oesophageal causes of cough had been excluded [52]. Recent data [53,54] seem to contribute significantly to clarifying whether reflux is involved in the genesis of respiratory reflex responses. Indeed, it has been observed that some subjects with no appreciable respiratory disorders, as well as some patients with various respiratory diseases, exhibit cough attacks during slow and forced vital capacity maneuvers (SVC and FVC) [53,54]. These expulsive efforts evoked by maximal lung emptying ("deflation cough", DC) are well known to those involved in lung function assessments and are thought to represent a technical pitfall limiting the reliability of these measurements. Interestingly, it has also been observed that patients with DC also present symptoms of GOR and that DC is inhibited by prior administration of an antacid drug but not by beta-adrenergic agent administration. The finding points to a causative role by acidic reflux in the genesis of expulsive respiratory reflex responses such as the DC.

Additional observations ([53]; Fontana GA and Lavorini F, unpublished results) seem to add to the possibility of reflux as a causative factor of cough. In a small subset of patients with DC, real time changes in oesophageal pH, the motor pattern of DC and the effects of progressively increasing expiratory loads on the frequency of DC efforts have been investigated. Oesophageal pH was measured by a standard oesophageal catheter connected to a calibrated, custom-made device for real time pH recordings. Respiratory flow and volume were obtained by means of a heated pneumotachograph. Each patient produced several control SVC maneuvers during which the motor pattern of DC and the ongoing pH

changes were recorded. Patients were then requested to perform a series of full expirations with an added expiratory load corresponding to 2, 3 and 5 cm H₂O, during which DC and oesophageal pH were similarly recorded. In all patients maximal lung emptying consistently led to the appearance of DC which was usually accompanied by a fall in oesophageal pH corresponding to about 1.5 pH units; in most cases, the pH drop shortly preceded (by about 0.5 s) the appearance of DC. Expiratory loading of variable magnitudes caused obvious and proportional reductions of DC frequency up to complete inhibition of the phenomenon with the maximal expiratory load.

These preliminary findings are in keeping with the possibility that deflation cough is most frequently preceded by oesophageal acidification, suggesting a causative relationship between the phenomena. The mechanism by which expiratory loading inhibits DC and oesophageal acidification remains to be understood.

5. Tuning from the lungs

Jan Hanacek introduced the topic, and gave a general review of the principles involved in tuning the cough center from lung afferents. Detailed reviews of some of the inputs and their actions have been given [12–16].

When we are considering tuning the “cough center” by inputs from the lung it is necessary to realize some essential facts: (1) all types of afferent nerve fibers may send information to the cough center from all structures in the airways and lungs; (2) there are dynamic changes of airway and lung nerve endings discharge related to breathing movements, and to other physiological and pathological changes in the airway and lung tissues; (3) environmental influences and inherent properties of the afferent limb of the cough reflex arc important factors which may modify their complex influence on the cough center; (4) the cough reflex is not active in healthy persons but they can cough voluntarily; (5) the central integration of activities from airway and lung afferent nerve endings is poorly understood; (6) the nucleus tractus solitarius (NTS) is a strategic site for modifying cough through short-term or long-term plasticity [55].

Reflex cough (RC) is induced by many kinds of noxious stimuli which directly or indirectly stimulate cough-related nerve fibers. Different types of airway and lung afferent nerve endings are activated to different levels. The result is different intensities and qualities of afferent inputs directed to the CNS generally, and to the respiratory and cough centers specifically. Afferent inputs to the cough center from the airways and lungs can be profoundly changed, qualitatively and quantitatively, by “plasticity” of afferent nerve fibers. There are many separate airway and lung afferent nerve endings, the activities of which are involved in forming complex afferent inputs to respiratory and cough centers.

5.1. The concept of tuning the cough center

The concept is based on the supposition that cough regulation may involve not only excitatory mechanisms but also inhibitory ones [14,16]. It is also likely that there are similar mechanisms in the regulation of pain and cough [56].

The main pulmonary sources of afferent inputs related to tuning the cough center are (A) cough receptors (CRs) themselves, (B) rapidly adapting pulmonary stretch receptors (RARs), (C) slowly adapting pulmonary stretch receptors (SARs), (4) bronchial and pulmonary C-fibers (C-fibers), and (D) Aδ-fibers [57,58]. There may also be changes in phenotypes of existing nerve endings or the growth of new branches of nerve fibers. These changes may be induced by pathological processes, giving the sensors new properties. There may also be currently unrecognized subtypes of airway afferent nerve endings.

The final effects of these afferent nerves on the cough center (Fig. 1) may be (A) *excitatory*, an intensification of output from the center; (B) *inhibitory*, the suppression of the output; or (C) *transformational*, the transforming of cough to some other pattern of reflex.

Activity in the various types of excitatory afferent input may be increased in several ways (Fig. 1). (A) By an excitatory effect, causing an augmentation of cough, which can be the result of stimulation of excitatory pathways. Examples are: substance P synthesis in airway afferents with plasticity of the cough; stimulation by allergens or irritants leading to modulation of sensor glutamate content; stimulation (e.g. exposure to allergens, irritants) leading to modulation of glutamate content; release of mediators from central terminals of vagal afferents, with stimulation of second-order neurones in the NTS [59] and increased cough [60]; and (B) increased sensitivity of cough-exciting lung afferents by many different kinds of stimuli. In practice it is usually difficult to distinguish between the two mechanisms.

Suppression of inhibitory pathways may be due to several hypothetical factors. (A) Suppression of activity in pulmonary C-fibers known to inhibit cough [61]; (B) suppression of the CR at a central brainstem level [62–64]; (C) in theory cough inhibitory neural mechanisms could be made hyposensitive centrally or peripherally, although this possibility does not seem to have been studied.

Stimulation of cough inhibitory pathways should inhibit cough, although this has been little studied. (A) During exercise cough may be inhibited [65], and pulmonary C-fiber receptors are thought to be activated during exercise [66]. This effect could be due to release of GABA in the NTS [55]; (B) in theory cough inhibitory neural mechanisms could be made hyposensitive centrally or peripherally, although this possibility does not seem to have been studied. (C) There may be an analogy with the regulation of pain at the level of the dorsal horn by release of endorphins—the ‘gate theory’ [56].

Suppression of cough-excitatory pathways should inhibit cough. There are several hypothetical possibilities: (A) depression of glutamate release from sensory afferents in the NTS, e.g. by dopamine acting on D2 receptors [63], or by adenosine acting on A1 receptors [64]; (B) long-lasting depolarization of cough sensors in the airways due to intense pathological processes; (C) visceral pulmonary neuropathy with a decreased sensitivity of cough sensors; and (D) the use of antitussive or anti-inflammatory drugs.

5.2. Conclusions

An enormous literature has been surveyed showing how afferents from the lungs may ‘tune the cough center’. No attempt was made to cite all the relevant papers, but many will be found in recent reviews [12–16]. It is clear that the ‘cough reflex’, however defined, is not a stereotyped response with a single pattern, but is a range of responses which can be modulated by a large variety of neural inputs.

6. Tuning from the cerebral cortex: behavioral modification of reflex cough

Paul Davenport described his recent research with Karen Wheeler-Hegland. It is a well established that human subjects can generate a voluntary cough [67–69]. It is also well known that both voluntary and reflex cough can be cognitively sensed [70–72]. In addition it is well established that reflex cough can be involuntarily induced by tussive chemical agents [73]. The interaction between reflex and cognitively controlled cough is poorly understood [67,68,71]. We hypothesized that capsaicin can be inhaled at a dose that elicits a reflex involuntary cough that can be modulated by conscious behavior but cannot be suppressed. It is known that air puff stimulation of sufficient magnitude of the posterior pharyngeal wall

will elicit both a reflex cough and an urge-to-cough (UtC) [74]. Thus, we further hypothesized that mechanical air puff stimulation of the posterior pharyngeal wall at a pressure that elicits an UtC will also elicit somatosensory cortical evoked potentials.

Voluntary control of reflex cough was tested in healthy young adult subjects. They inhaled 200 μ M capsaicin which induced repetitive coughing in all subjects [70]. The subjects initially provided a baseline response by simply inhaling the capsaicin while we recorded the airflow cough response. The subjects were then instructed to perform three tasks in a randomized order. They were required to produce small-coughs, long-coughs or no-coughs in response to capsaicin inhalation. We analyzed the cough airflow pattern for compression phase and cough peak expiratory airflow across the four conditions. We also recorded lateral abdominal muscle EMGs for each of the four conditions. Peak integrated EMG activity was measured across conditions.

The preliminary results from a limited number of subjects ($n = 5$) showed in the baseline trials that 200 μ M of capsaicin elicited multiple reflex coughs in all subjects. Cognitive modulation of capsaicin reflex cough resulted in an increase in compression phase for all three conditions compared with baseline. Small-coughs had a decreased cough peak expiratory flow rate and increased number of coughs. Long-coughs had the same cough peak expiratory flow rate as baseline but fewer coughs. The cough plateau phase was also increased in the long-cough condition. The no-cough condition resulted in complex behaviors that ranged from delayed coughs to throat clearing. When coughs occurred in the cognitive no-cough condition, the compression phase was increased and the cough peak airflow was decreased. The results of these preliminary studies show that 200 μ M capsaicin that elicits a reflex cough cannot be fully suppressed by cognitive behaviors. These results also show that cognitive behavior can modulate reflex cough. Thus, there is an interaction between higher brain center cognitive and voluntary control systems and involuntary reflex cough motor centers.

Air puff stimulation of the posterior pharyngeal wall was tested in an additional group of young adult subjects ($n = 7$). Air puff delivery was accomplished via a specially adapted rubber mouthpiece [74]. The mouthpiece tube served as a conduit for passage of a flexible endoscopic camera covered with a thin sheath that provided both hygienic cover of the camera and a longitudinally-oriented air puff delivery port. The sheath was connected to a pressurized air-tank in series with an air-chamber connected to a manometer, allowing for quantification of air puff pressure. A customized control device delivered air puffs upon manual trigger by the researcher. A modified Borg category scale was used to quantify UtC. Participants were seated comfortably in a reclining chair. They put the mouthpiece in place, and the sheath-covered camera was placed through the oral cavity, posterior to the uvula to approximately 5 mm from the posterior pharyngeal wall. The air puffs were delivered with increasing air pressure intensity in a stepwise fashion, until the maximum pressure the participant could tolerate was reached. "Maximum" was defined as the pressure at which an air puff produced coughing. Four trials of 50 air puff stimuli that elicited an UtC greater than 1 but did not elicit a motor cough were then delivered, with 2–3 min of rest, and sips of water between trials. All participants could detect the air puffs. Throughout each trial the participants were asked to rate their UtC [71]. Instances of cough were recorded for each trial in a categorical manner.

The results show that there was a threshold pressure for the UtC which was less than a pressure that elicited a motor cough. The air puff pressure when no-cough was elicited had an UtC perception rating that was significantly lower than the higher air puff pressure that elicited a motor cough. An evoked potential was observed in all subjects at an air puff pressure that elicited an UtC but did not elicit a motor cough. The evoked potential was

characterized by a short-latency positive voltage dipole localized over the somatosensory cortex. Longer latency, second-order processing evoked potential peaks. The results of this study demonstrate that air pressure mechanical stimulation of the posterior pharyngeal wall elicits both an UtC and a motor cough response that is a function of the pressure stimulus magnitude. Similar to the UtC response to capsaicin [70,71], the air puff UtC occurs at a lower pressure stimulus level than the motor cough threshold. The evoked potential responses demonstrate that the cognitive awareness of an UtC is associated with activation of somatosensory higher brain centers that process interoceptive information and cognition.

The results of both of these studies demonstrate an interaction between cognitive and voluntary neural control systems and involuntary reflex cough motor centers. It is apparent that reflex cough is generated in involuntary control centers, presumably in the brainstem [75]. Voluntary mechanisms interact with reflex cough centers by descending modulation of the reflex motor pattern [67,69,72]. Stimulation of a reflex cough also produces a simultaneous sensory activation of higher brain centers, in particular the somatosensory cortex [76,77], which is presumably involved in the cognitive sensation of an UtC.

7. Tuning from somatic tissues

Federico Lavorini introduced this topic. Reflex influences from chest wall, limbs and cutaneous nerve afferents have repeatedly been demonstrated to affect breathing [78]. Moreover, some studies support the view that afferent inputs from these tissues to the brainstem can also powerfully “tune” the cough reflex, either by stimulating or inhibiting it ([12]; see also [15] for further Refs.). Stimulatory somatic inputs to cough seem to occur during various skin diseases characterized by pruritus, neurogenic inflammation and increased levels of mediators with a protussive effect [79]. Conversely, inhibitory somatic inputs to cough may arise from chest wall joint receptors which have been shown to stimulate breathing and decrease the intensity of cough, thus supporting the view that there is no positive correlation between increased breathing and cough sensitivity [80,81]. Interestingly, afferents from cutaneous nerve receptors may have both excitatory and inhibitory actions on cough, presumably depending upon the nature of the stimulus [82–84].

Inflammatory processes of the skin may influence sensitivity of airway nerve endings mediating cough. For instances, patients with atopic dermatitis but no clinical sign of respiratory disease display an increased cough sensitivity to capsaicin [85]. Similar findings have been observed in patients with localized scleroderma [86]. In contrast, patients with *Psoriasis vulgaris* have cough sensitivity to capsaicin similar to that of healthy subjects [85]. The increased cough sensitivity observed in patients with atopic dermatitis and localized scleroderma could be related to subclinical inflammatory changes present in the airways and/or in the lungs, even in the absence of clinical findings of bronchial hyperresponsiveness [85]. In this connection, it is noteworthy to recall that patients with atopic dermatitis typically have marked pruritus, a factor that could exert a reflex influence on cough sensitivity by the irritation of skin-sensitive nerve endings [79]. It has been shown that mast cells are structurally associated with C-fiber sensory nerves in both the skin [86] and the lungs [87]; thus it could be speculated that neuropeptides, such as substance P and calcitonin-gene related peptide, released by sensory nerve endings may induce mast cell activation. Mast cells, in turn, will release mediators that promote inflammation at the level of these anatomical districts [79]. In this connection it seems worthwhile recalling that patients with idiopathic chronic cough may show an increased density of substance P in the airway nerves [88].

In anaesthetized animals, Javorka et al. [80] showed that, during stimulation of airway, lungs and chest wall receptors by high-frequency jet ventilation causing inhibition of spontaneous

breathing, mechanical stimulation of the nasal, laryngeal and tracheal mucosa was still able to provoke defensive responses, such as sneezing and coughing. Noticeably, the inspiratory component of all the evoked reflexes was inhibited, and the overall intensity of coughing and sneezing reduced [80]. In healthy humans, chest wall vibrations applied bilaterally over the 7th–10th intercostal spaces significantly inhibit the volume and time components of the breathing pattern [89]. By using a similar technique, Kondo et al. [81] showed that cough threshold to citric acid was significantly increased during chest wall vibrations, suggesting that inputs from intercostal muscles and/or costovertebral joints have an inhibitory effect on cough sensitivity. Taken together these results point at the possibility that signals arising from chest wall joint and muscle receptors exert an inhibitory influence on the cough reflex.

In contrast, Lee and Eccles provided evidence that application of high-frequency vibration at the level of the jugular notch [90] or the manubrium sternum [91] induces cough in patients with acute upper respiratory tract infection (URTI) but little or no-cough in healthy subjects. The authors hypothesized that the vibration stimulus may induce cough by stimulation of “irritant” receptors in the trachea and bronchi, and speculated that the enhanced cough response, as demonstrated by vibration, observed in patients with URTI compared with healthy subjects, was due to hyperreactivity of the cough reflex, perhaps related to the presence of inflammatory mediators around sensors that mediate cough [90]. The reasons for the conflicting findings of Javorka et al. [80], Kondo et al. [81], Homma [89] and Lee and Eccles [91] are not immediately clear; it is possible that neck and chest vibration causes either inhibition or facilitation of cough depending upon different physical parameters of chest vibration.

The adaptive responses to exercise include hyperpnea, activation of airway, lung, and chest wall receptors, and airway water and heat loss [92]. In theory, all exercise-related adjustments can modulate cough through influences on the neural substrates subserving it, from sensors to brainstem to cortex. However, information on the effects of exercise on the sensitivity and intensity of cough is scarce and often contradictory. For instance, cough and bronchoconstriction are common features of asthmatic subjects after exercise [93] and coughing may also appear in some normal subjects mainly after exercise in cold weather [94]. However, questioning athletes provides anecdotal evidence that subjects with cough may find it reduced during exercise, suggesting downregulation of cough [16].

Recently, Lavorini et al. [65] have investigated the effect of steady-state exercise and voluntary isocapnic hyperpnea on the sensitivity of the cough reflex and the sensation of an urge-to-cough (UtC) evoked by ultrasonically nebulized distilled water (fog) inhalation in healthy subjects. They showed that both cough sensitivity and UtC are suppressed by voluntary hyperpnea and steady-state exercise [65]. Similar results were obtained when subjects performed a static “handgrip” exercise at 30% of their maximum voluntary contraction (Fontana GA and Lavorini F, unpublished observation). Thus, the complex reflex and non-reflex mechanisms from exercising limbs, thoracic muscles, and/or higher nervous mechanisms evoked by exercise and voluntary hyperpnea can down-regulate the sensitivity of the cough reflex and the perceptual magnitude of the UtC to fog inhalation. It may be that convergence of cortical and reflex stimuli on brainstem neural network’s subserving breathing and cough production inhibits cough sensitivity. The role played by factors such as varied aerosol distribution or mental distraction also needs to be defined.

8. Tuning from the alimentary system

Don Bolser introduced the studies he was conducting with Teresa Pitts. Systematic coordination between cough and swallow are vital for protection of the airway. Their current model for cough proposes that the brainstem central pattern generating network for

breathing is rapidly reconfigured to produce the cough motor pattern. Our understanding of the central mechanisms in the production of swallow is limited in comparison. However, they have proposed that cough and other airway protective reflexes such as swallow are coordinated by a brainstem network that includes populations of neurones (or assemblies) that cooperate to exert definable control over the entire neural system and therefore the behavior itself [95]. They have termed these populations of neurones ‘behavior control assemblies’ (BCAs) and also have proposed that BCAs exist for different behaviors that interact to ensure that the airway is adequately protected. They also hypothesized that in healthy individuals the BCAs would ensure that different behaviors are discretely expressed. That is, one airway protective behavior would be initiated and completed before other behaviors were expressed.

Work done with animal and human models describes the concept *phase preference* for the expression of breathing and swallowing [96–100]. The most common pattern is for the swallow to occur during the phase transition from inspiration to expiration. This pattern promotes airway clearance of any material which might linger after the completion of the swallow. However swallows can occur during the inspiratory or expiratory phase of breathing and are least likely to be expressed during the transition from expiration to inspiration. However, for the coordination of cough and swallow they propose the concept of *phase restriction*. This governing principal may restrict the swallow to occur only during the E₂ phase of the cough cycle, when active airflow is minimal.

Fig. 2 is an example of the interaction between cough and swallow in the cat [100]. The animal was anesthetized and electromyograms (EMG) were placed in pharyngeal and laryngeal muscles which contribute to the expression of both behaviors. Thyropharyngeus (ThPh) is a part of the pharyngeal constrictor complex which moves the food/liquid into the esophagus. The geniohyoid (GeHy) is a part of the laryngeal elevator complex. Cricopharyngeus (CrPh) is the major muscle in the upper oesophageal sphincter. The thyroarytenoid (ThAr) is the major muscle for laryngeal adduction. Transversus abdominus (TA) is an abdominal muscle active during the expiratory phase of breathing. The parasternal (PS) is an accessory muscle active during the inspiratory phase of breathing. The protocol was to mechanically stimulate the trachea for 5 s, inject 3 ml of water into the oral-pharyngeal cavity, and continue the tracheal stimulation for another 15 s. Stars represent the expression of cough and arrows indicate the occurrence of swallows.

This example supports the afore mentioned hypothesis of phase restriction, all swallows occurred during the E₂ phase of cough or after coughing had ceased, and there was no overlapping expression of the behaviors that would result in swallows occurring during periods in which cough airflow was high. Future work will focus on defining the “rule-set” which governs the coordination of these behaviors. Also, analysis has begun to model the neural networks which make-up the BCAs responsible for the expression of these behaviors and supports protection of the airways.

9. Conclusions

The different sections and discussions at the Workshop in general confirmed the accuracy and perceptiveness of Ranson’s [1] statement. There was no time to discuss in detail some other examples of afferent inputs that have been shown to ‘tune’ the cough center, although some are mentioned in the sections above. They include the external ear [101], the nasopharynx ([11,102,103] and see above), the heart [104], the abdominal viscera [105], the eye [106] and the skin ([79,81–83,107], and see above). Nearly all the results described by applied to the ‘classical’ cough reflex, starting with an inspiration and usually induced by capsaicin or citric acid aerosols. Tuning the expiration reflex has been less studied.

'Tuning' is an imprecise word; it could include stimulation, inhibition, sensitization, desensitization (see above) or modification of pattern of respiratory muscular contraction. The last aspect has been identified in clinical situations [4–6] but has been little studied experimentally. In addition there is increasing evidence that the tuning of the cough center may depend on the timing of the afferent input that affects it (see Refs. above). These are fields open for research.

Some tissues can be shown to have both excitatory/sensitizing and inhibitory/desensitizing actions on cough, presumably depending on the stimulus and the afferent nervous pathway. This applies for example to the skin [82–85,107], C-fiber receptors in the lungs [12,13,15], temperature and humidity in the respiratory tract [108,109], the pharynx [102,103], chest wall vibration [80,81,90,91], exercise [65,94] and the cerebral cortex (voluntary initiation and suppression of cough). An example of particular interest is the nose. Abundant evidence shows that nasal irritation and inflammation sensitize cough induced from the lungs [see above], but cold water in the nose *inhibits* cough [33], probably as part of the diving reflex; this makes teleological sense, as cough should be inhibited during diving. These results are not surprising in view of the multiple innervations of the tissues, but they may complicate analysis and interpretation.

Of course, Ranson's statement is a two-edged sword. If all afferent inputs can potentially affect cough, cough can potentially affect all afferent inputs, reflexes and motor systems. This is well established for cough afferents reflexly controlling the cardiovascular (heart and blood vessels) and respiratory (breathing, airway smooth muscle, vascular bed and glands) systems. But other examples exist. These include: (A) cough inhibits cutaneous pain, the 'cough trick' [107] and cutaneous irritation can potentiate cough [79,84,85]; (B) cough can cause lachrymal secretion while eye irritation can sensitize cough from the lungs [106]; and (C) cough can cause arousal from sleep [110] and the cough reflex is depressed in sleep [111]. These examples raise interesting possibilities of feedback loops. They have scarcely been explored.

Acknowledgments

We are grateful to Proctor & Gamble UK (Dr. David Hull) for their support, including financial, for this Workshop.

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Fig. 1.
Scheme – tuning the ‘cough centre’ by inputs from the airway and lung (explanation in the text).

Fig. 2.
For description, m see text.