Experimental models and mechanisms of enhanced coughing

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Abstract

Enhanced coughing can be produced in a variety of animal models, including the guinea pig, cat, dog and pig. Typically, airway inflammation has been produced by sensitization, exposure to cigarette smoke, sulphur dioxide or angiotensin-converting enzyme inhibitors. In some of these models, inflammatory mediators such as bradykinin and tachykinins have been shown to contribute to the enhanced coughing. While most of these studies have focussed on peripheral mechanisms, increases in central excitability of the cough reflex have been shown to occur as a result of airway inflammation. As such, we propose that enhanced coughing in pathological conditions is the result of plastic changes in both peripheral and central neural elements. Furthermore, we present a modified model of the neurogenesis of cough that takes into account peripheral and central plasticity induced by mediators of inflammation.
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1. Introduction

The morbidity of chronic cough in humans is likely a product of the enhanced frequency and intensity that occurs as a result of increased excitability of this behaviour. Clearly, the sensitivity of cough in response to inhaled irritants in patients with a variety of pulmonary disorders is enhanced [1,2], but the frequency and intensity of cough can be elevated as well [3,4]. The mechanisms by which the sensitivity, spontaneous frequency and magnitude of cough are increased in airway disease are poorly understood.

Most of the mechanistic information on the cough reflex has been generated from animal models in which there is little or no airway pathology. The role of airway pathological changes in modifying the mechanics, regulation and pharmacology of cough is not well understood. The purpose of this review is to highlight current progress in this area, identify important topics for future investigation, and propose an integrative model of the central neurogenesis of cough in the presence of airway inflammation.

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2. Guinea pig

2.1. Allergic animals

Most of the information that we have on enhanced coughing has been generated in this species from models featuring allergic animals. Dose-dependent increases in coughing have been produced by a passive sensitization paradigm [5]. Allergic cough in this study was sensitive to an H_1 receptor antagonist, pyrilamine, and to cortisone. Codeine was ineffective to suppress cough, but the dosage employed was low (4 mg/kg) [5]. In another study cough was elicited in actively sensitized guinea pigs by acute exposure to antigen aerosols [6]. Allergic cough appeared to be more sensitive to suppression by antihistamines and salbutamol than did capsaicin-induced cough, but both types of coughing were sensitive to codeine (30 mg/kg) and anticholinergics [6]. However, another study found no effect of codeine at doses up to 56 mg/kg (p.o.) on antigen-induced cough in sensitized animals [7].

Several studies have shown increased coughing in response to inhaled capsaicin one or more days after antigen challenge in sensitized animals [8–11]. Increased coughing in these preparations was associated with airway eosinophilia as well as increases in other inflammatory cells as

detected by bronchoalveolar lavage (BAL) and/or histo-logical examination of airway epithelia [8,11]. The study of Xiang et al. [11] additionally showed that capsaicin-induced cough was augmented in sensitized but unchallenged animals, even though no significant change in inflammatory cell counts was detected by BAL. The mechanism for this effect of sensitization is unknown. Lui et al. [8] did not find an increase in capsaicin-induced cough in sensitized unchallenged animals although their method of sensitization was very similar to that of Xiang et al. [11].

Tachykinins appear to have a role in augmented cough in allergic guinea pigs. Enhanced cough to capsaicin after sensitization and antigen challenge was suppressed by NK_1, NK_2, and NK_1/NK_2 receptor antagonists [11,12]. Further-more, neutral endopeptidase (NEP) activity was suppressed 72 h after antigen challenge in allergic animals [9]. Liu et al. [8] showed that the NEP inhibitor, phosphoramidon, potentiated capsaicin-induced cough in naïve but not in allergic animals. This finding supports the results of Katayama et al. [9] that NEP activity is already suppressed in allergic animals. The suppression of NEP activity shown by Katayama et al. [9] was reversed by administration of the mucolytic agent, carbocysteine, over the 72 h period following antigen challenge. This drug also reversed the increased cough excitability induced in allergic animals when given 2 days after antigen challenge [9]. The effect of carbocysteine was not due to suppression of infiltrating inflammatory cells as cell counts via BAL were not affected by the drug. The exact mechanism by which carbocysteine had these effects is unknown. However, the results of Katayama et al. [9] and Xiang et al. [11] strongly support an important role of tachykinins and NEP in the enhanced coughing produced by capsaicin in allergic animals.

The mechanism by which capsaicin-induced cough is potentiated in allergic guinea pigs may also involve alterations in the phenotype of sensory afferents. Myers et al. [13] have shown that substance P and calcitonin gene-related peptide production is induced by sensitiz-ation and antigen challenge in large diameter vagal afferent neurones. This population of vagal afferents is composed of low threshold mechanoreceptors that are insensitive to capsaicin and do not normally express tachykinins [13]. As such, allergic animals may recruit mechanoreceptors as a source of tachykinin release in response to non-noxious stimuli [13].

Liu et al. [8] found that enhanced capsaicin-induced cough in allergic animals was insensitive to the beta-adrenoreceptor agonist, procaterol, in bronchodilator doses. Furthermore, these investigators found that atro-pine suppressed capsaicin-induced cough in naïve animals, but not enhanced cough in allergic animals. Their results, when compared to the results of Bolser et al. [14] for cough elicited in allergic animals by antigen challenge, suggest that the pharmacologic mechanisms of antigen- and irritant-induced cough may differ significantly.

Codeine, administered orally, suppressed augmented capsaicin-induced cough in sensitized, challenged animals but had no effect when given by inhalation [11]. However, in this study the dose of codeine administered by inhalation (0.01%) was at least an order of magnitude lower than the ED_{50} for inhibition of capsaicin-induced cough in normal animals (0.76% [14]). Interestingly, these investigators showed significant effects of oral codeine on the increased capsaicin-induced cough responses of both sensitized and sensitized challenged animals, but not in normal guinea pigs [11]. These results could mean that sensitization increased the sensitivity of the animals to the cough suppressant actions of codeine. However, no dose-response to codeine was conducted in this study.

2.2. Cigarette smoke exposure

Chronic mainstream or sidestream cigarette smoke exposure can enhance coughing in response to irritant aerosols [15–17] in guinea pigs. Coughing induced by histamine or methacholine aerosols in mainstream ciga-rette smoke-exposed guinea pigs was not enhanced over that of control animals [15]. On the other hand, challenge with aerosols of bradykinin elicited significantly greater coughing in animals that were chronically exposed to mainstream cigarette smoke [15]. Spontaneous coughing occurred in mainstream smoke-exposed but not air-exposed animals [15]. Furthermore, sensitized animals that were exposed to mainstream smoke spontaneously coughed more than nonsensitized guinea pigs [15]. Chronic exposure to mainstream cigarette smoke elicited eosinophilia and neutrophilia that were similar to those produced in sensitized animals [15]. Furthermore, chronic mainstream smoke-exposed animals had greater amounts of calcitonin gene-related peptide immunoreactivity in tracheal tissue [17].

Enhanced irritant-induced cough due to cigarette smoke exposure was not mediated by cyclo-oxygenase products because it was insensitive to indomethacin [17]. The neutral endopeptidase inhibitor, phosphoramidon, did not enhance coughing elicited by acute smoke exposure in animals chronically-challenged with cigarette smoke. However, cough induced by both capsaicin and acute smoke was significantly reduced by inhalation of an aerosol of tachykinin NK_1 and NK_2 receptor antagonists [15]. Indeed, microinjection of a tachykinin NK_1 receptor antagonist into the nucleus of the tractus solitarius (NTS) blocked the cough enhancement produced by chronic sidestream smoke exposure [16].

2.3. Angiotensin-converting enzyme (ACE) inhibitors

Chronic systemic treatment with several different ACE inhibitors potentiates irritant-induced and spontaneous cough in the guinea pig [18–20]. Not all ACE inhibitors had the same efficacy to enhance cough. Acute

administration of enalapril potentiated cough induced by capsaicin but not by citric acid [21]. Indeed, acute inhalation of enalapril did not elicit spontaneous cough [22], but chronic administration of this ACE inhibitor did augment citric acid-induced cough [19]. Chronic administration of imidapril had no effect on citric acid-induced cough [19]. In another chronic study, captopril but not enalapril, quinapril or alacepril potentiated citric acid-induced cough [21]. The reasons for these apparently differing responses may be related to differing dosing regimes and/or duration of treatment in chronic studies.

The mechanism(s) of enhanced coughing induced by ACE inhibitors may involve several different mediators. For example, ACE-induced enhanced cough can be partially suppressed with indomethacin, which is consistent with a mechanism involving prostaglandins [19]. Hirata et al. [18] showed that administration of enalapril for at least 20 days elicited spontaneous cough that was suppressed by a bradykinin B1, but not a B2, receptor antagonist. Furthermore, bradykinin B1 receptors were upregulated in tracheal tissue in this model.

2.4. Sulphur dioxide

Chronic exposure to SO_2 can enhance coughing in response to capsaicin in the guinea pig [22]. In this model, inhaled phosphoramidon elicited coughing and enhanced capsaicin- or substance P-induced cough in normal animals [22]. However, phosphoramidon did not enhance cough in SO_2-exposed animals [22].

3. Cats

3.1. Experimental tracheitis

Hanacek et al. [23] have created an experimental tracheitis in cats by affixing a suture to the intrathoracic trachea. Within 1 week the animals displayed spontaneous coughing and mucus hypersecretion. Histological examination of the trachea revealed hyperaemia and cellular infiltrates restricted to the region of the suture. At 2 weeks post-surgery, cough number and tracheal pressures during both the inspiratory and expiratory phases of cough were significantly increased relative to control animals when the mechanical stimulus was applied to the inflamed site in the trachea [23]. Interestingly, only cough number was elevated when this behavior was elicited by laryngeal stimulation, even though the larynx was not inflamed. When stimuli were applied to the lower airways, cough number was not elevated but the magnitude of tracheal pressure changes during inspiration was increased [23]. These specific effects on cough elicited from regions of the airways that were not inflamed indicate that the inflammation resulted in central plasticity of cough pathways.

4. Dogs

4.1. Allergic animals

Anaesthetized dogs sensitized and acutely challenged with aerosol ragweed antigen had an enhanced cough response to mechanical stimulation of the trachea [24]. The cough response consisted of an increase in cough number (number of coughs per stimulus trial) and a transient decrease in oesophageal pressure in the first few minutes post challenge. This pattern was very similar to that produced by challenge with inhaled histamine [24]. Furthermore, the decrease in oesophageal pressure during cough may be due to the increased airways resistance and decreased dynamic compliance that occurred after antigen challenge in this model [24]. Antigen exposure did not elicit spontaneous cough in this preparation and mechanical stimulation of the trachea did not produce enhanced cough in animals that were sensitized but not challenged.

4.2. Sulphur dioxide

No systematic and objective analysis of cough has been conducted in dogs exposed to sulphur dioxide. However, chronic exposure to this irritant elicits mucus hypersecretion, airway obstruction, eosinophilia and spontaneous coughing in this species [25,26].

5. Pigs

5.1. ACE inhibitors

Acute administration of enalapril enhanced citric acid-induced cough in pigs [27,28]. The enhancement of coughing was not blocked by a bradykinin B2 antagonist, although citric acid-induced cough in the absence of enalapril was inhibited by this treatment [28]. The ACE-induced enhanced cough was suppressed by combined treatment with tachykinin NK_1, NK_2, and NK_3 receptor antagonists [28], supporting a role for tachykinins in the mechanism of cough enhancement in the pig.

6. Discussion

It is clear from this survey of the literature that enhanced coughing can readily be elicited in several different animal models. The inflammatory processes associated with some of these models have been shown to alter the phenotype and/or excitability of airway sensory afferent neurones [13,34–37], which in turn may lead to increased sensory input to the central control mechanism for cough. Depending on the model, the potentiation of coughing involved the actions of one or more of a variety of inflammatory mediators including bradykinin, histamine,

prostaglandins and tachykinins. The mechanism(s) by which these mediators, as well as other aspects of the inflammatory process alter the excitability and phenotype of airway sensory afferents represents an important area of investigation.

The information summarized in the preceding paragraph implies a system in which enhanced coughing can be the result of alterations in primarily peripheral mechanisms. Such a scenario would relegate the central nervous elements that produce cough to 'followers' of the peripheral events resulting from airway inflammatory processes. However, it is clearly recognized that central hyper-responsiveness can occur in other systems, such as the neurogenic mechanism for pain [38,39], and that these central mechanisms have clinical relevance [39]. Increased sensory afferent activity resulting from tissue damage can produce activity-dependent plasticity in central pathways [40]. There is evidence that central plasticity of the cough reflex occurs following airway inflammation [16]. Chronic exposure to environmental tobacco smoke produced increased citric acid-induced cough that was suppressed by microinjection of a tachykinin NK_1 receptor antagonist into the nucleus tractus solitarius (NTS [16]). Microinjection of this antagonist into the NTS of air-exposed animals did not inhibit coughing, indicating an inflammation-specific change in sensory neuropharmacology in the NTS. The central plasticity was presumably the result of an increase in airway afferent discharge due to airway inflammation. However, it is possible that circulating nicotine or its metabolites altered NTS neuropharmacology in this preparation.

The results of Hanacek et al. [23] in a model of cat tracheitis provide further evidence that central cough plasticity in response to airway inflammation can occur and that it can be highly specific. The selectivity of local tracheal inflammation on specific features (number and intensity) of cough indicates that enhancement of the excitability of airway sensory afferents does not simply produce a generalized excitation of cough. Specific central pathways can be modified that cause selective changes in one or more aspects of the behaviour. In particular, the regulation of laryngeal cough was modified, even though the larynx itself was not affected by the inflammation. These results suggest that the central mechanisms for the laryngeal cough share some, but not all, regulatory control with that of tracheobronchial cough. This concept differs from our current hypothesis for the regulation of tracheobronchial and laryngeal cough by means of two separate functional gating mechanisms (Fig. 1). Furthermore, our current conceptualization of the gating mechanism holds that it controls both cough excitability (and thus cough number) as well as the magnitude of expiratory efforts [41]. The results of Hanacek et al. [23] indicate that the gating mechanism for laryngeal cough can be selectively modulated, suggesting that it is functionally subdivided into a mechanism for controlling cough number and the magnitude of expiratory efforts (Fig. 1). There is currently no evidence that the tracheobronchial gating mechanism can separately control cough number and expiratory motor drive during cough. The exact neural circuitry responsible for these gating mechanisms is currently unknown. However, we propose
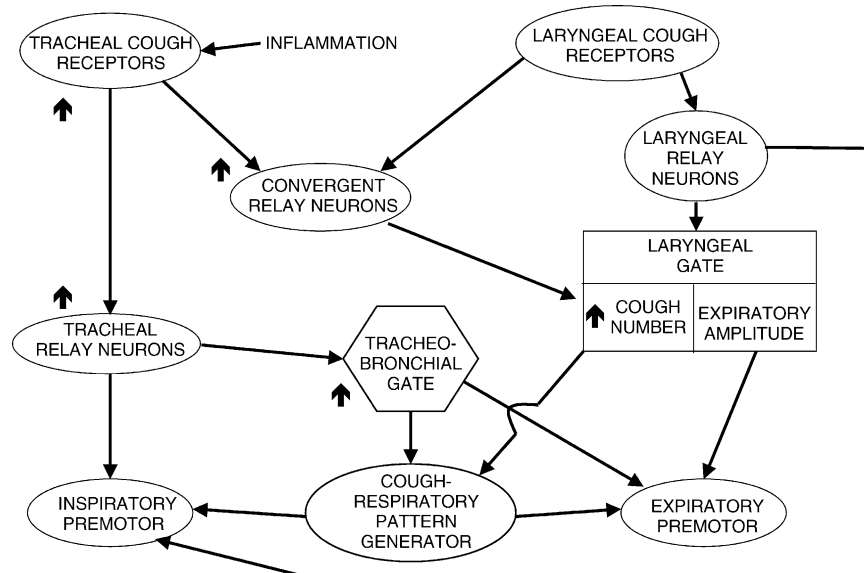

Fig. 1. Model of the peripheral and central elements of the neurogenic mechanism for cough, highlighting the proposed effects of inflammation. The model is modified from Bolser and Davenport[29] and depicts: (a) augmented tracheal cough receptor[30] activity, (b) laryngeal cough receptors, (c) tracheal and laryngeal relay neurones (interneurones), (d) convergent relay neurones in the NTS and medial reticular formation that receive synaptic input from both tracheal and laryngeal interneurons, (e) a tracheobronchial gating mechanism, (f) a laryngeal gating mechanism that is functionally subdivided into elements controlling excitability of the cough/respiratory pattern generator[31] and the magnitude of expiratory motor drive, and (g) inspiratory and expiratory premotor neurons. Pulmonary slowly adapting stretch receptors facilitate laryngeal cough and have a permissive effect on tracheobronchial cough [32,33]. These elements have been omitted from the model for clarity.

that interneurones in the caudal NTS and adjacent medial reticular formation (Fig. 1, [42]) could provide a substrate for convergence of tracheobronchial and laryngeal sensory information that would account for the results of Hanacek et al. [23].

The dynamics of peripheral and central plasticity of cough are unknown, but the presence of both may have important clinical implications. For example, resolution of peripheral inflammation may not completely resolve chronic cough in some disorders. Enhanced excitability of central pathways that persists beyond the initial peripheral insult may result in spontaneous cough and/or increased sensitivity to previously innocuous stimuli. Future therapeutic approaches to chronic cough may involve more complex regimes that include both specific peripheral therapy as well as specific centrally-acting drugs designed to suppress central plasticity in cough motor pathways. The advantages of such an approach would include a faster response time to therapy as well as a lower proportion of patients identified as idiopathic. A necessary prerequisite for this scenario is a continued effort to more completely understand both peripheral and central mechanisms our current models of enhanced cough.

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