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Review

Brainstem mechanisms underlying the cough reflex and its regulation

Donatella Mutolo

Dipartimento di Medicina Sperimentale e Clinica, Sezione Scienze Fisiologiche, Università degli Studi di Firenze, Viale G.B.Morgagni 63, 50134 Firenze, Italy

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ABSTRACT

Cough is a very important airway protective reflex. Cough-related inputs are conveyed to the caudal nucleus tractus solitarii (cNTS) that projects to the brainstem respiratory network. The latter is reconfigured to generate the cough motor pattern. A high degree of modulation is exerted on second-order neurons and the brainstem respiratory network by sensory inputs and higher brain areas. Two medullary structures proved to have key functions in cough production and to be strategic sites of action for centrally active drugs: the cNTS and the caudal ventral respiratory group (cVRG). Drugs microinjected into these medullary structures caused down-regulation or upregulation of the cough reflex. The results suggest that inhibition and disinhibition are prominent regulatory mechanisms of this reflex and that both the cNTS and the cVRG are essential in the generation of the entire cough motor pattern. Studies on the basic neural mechanisms subserving the cough reflex may provide hints for novel therapeutic approaches. Different proposals for further investigations are advanced.

1. Introduction

Cough is a very important airway defensive act that functions to expel foreign or endogenously produced materials from the lower airways (Macklem 1974; Korpáš and Tomori 1979). It is usually an adequate reflex response to nociceptive stimuli, i.e. actually or potentially tissue damaging events (e.g. Woolf and Ma 2007; Loeser and Treede 2008) applied to the airways, but can also be initiated on voluntary command. Cough is one of the most common and troubling symptoms for which patients seek medical attention. It is usually purposeful and useful, but in case of persistent or chronic cough is without benefit or even with clear physical and psychological complications that considerably impair the quality of life. Available antitussive therapies have limited efficacy and unacceptable side effects. Thus further research is needed to find better antitussive drugs (Dicpinigaitis et al., 2014). On the other hand, an impairment of airway protective reflexes, including cough and swallowing, in some neurodegenerative diseases such as Parkinsonism, Alzheimer's disease and fronto-temporal dementia, or following ictus could lead to high risk of aspiration and consequent life-threatening conditions (e.g. Dicpinigaitis et al., 2014; Dutschmann et al., 2014; Bolser et al., 2015; Pitts et al., 2016; Cinelli et al., 2016). Admittedly, studies on animal models of chronic cough or neurodegenerative diseases could be more appropriate to disclose novel therapeutic approaches. Nevertheless, investigations on the basic neural mechanisms subserving the cough reflex performed on healthy preparations can provide useful hints for the development of antitussive or protussive strategies (see e.g. Cinelli et al., 2016; Mutolo et al., 2016).

The central mechanisms controlling breathing movements depict a respiratory cycle divided in three phases: inspiration, postinspiration and expiration (for review see e.g. Richter and Smith 2014). Post-inspiratory activity provides a mechanism to mechanically brake the expiratory airflow. It is of great importance for the mediation of various protective reflexes, such as glottal closure, sneeze, cough and swallowing, that ensure protection from penetration of potentially harmful foreign substances into the airways (Dutschmann and Herbert 2006; Dutschmann et al., 2014 also for further Refs.). Cough consists of a modified respiratory act that includes three phases: inspiratory or preparatory, post-inspiratory or compressive (glottal closure) and expiratory or expulsive (e.g. Korpáš and Tomori, 1979; Widdicombe 1986).

A distinctive aspect of human cough motor responses in acute and chronic conditions is the "urge-to-cough" caused by tickling sensations in the upper airways that lead to the behavioral act of coughing (Davenport 2008; Muroi and Undem 2011). Reflex and voluntary coughing present similarities, but differ in very important respects. The cough reflex is subject to a high degree of voluntary control, so that all possible cough motor patterns can be mimicked and the frequency and intensity of spontaneous cough can be modulated up to complete suppression (see Magni et al., 2011; Mazzone et al., 2011; Ando et al., 2014; Brandimore et al., 2015 also for further Refs.). Interestingly, the habitual voluntary suppression of cough may lead to pathological

E-mail address: donatella.mutolo@unifi.it.

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processes in poorly draining lung regions and has been implicated in the Lady Windermere syndrome (see e.g. Reich and Johnson 1992). This review is focused on reflex cough evoked by stimulation of the tracheobronchial tree and the brainstem neuronal mechanisms that generate or modulate the cough motor pattern.

2. Cough afferent pathways

2.1. Cough-related afferent fibers

Cough-related receptors (for review see Sant'Ambrogio and Widdicombe, 2001; Canning et al., 2014) mainly located in the large extrapulmonary airways (trachea, carina, main bronchi) belong to the wide family of pulmonary Aδ rapidly adapting receptors (RARs), possibly including the so-called "cough receptors" described in the guinea pig larynx and rostral trachea (Canning et al., 2004, 2006a, 2006b). RARs are a heterogeneous family of polymodal receptors and some of them are particularly sensitive to mechanical stimulation of the airway mucosa and to chemical irritant stimuli such as citric acid, ammonia and cigarette smoke. RARs in the intrapulmonary airways very rarely evoke cough, but usually provoke other reflexes, such as hyperpnea/tachypnea, augmented breaths, bronchoconstriction and laryngeal closure. Cough-related afferents may also originate from bronchopulmonary C-fibers (Coleridge and Coleridge 1986; Widdicombe, 1998; Lee and Pisarri 2001; Canning et al., 2006b, 2014; Canning and Mori 2010, 2011; Chung 2015). In anesthetized animals, C-fiber stimulation has consistently failed to evoke coughing. In addition, the cough reflex can be inhibited owing to the activation of a subset of pulmonary C-fibers in dogs, cats and guinea-pigs (Tatar et al., 1988, 1994; Hanacek et al., 2006; Widdicombe and Singh, 2006; Canning and Mori, 2010; Canning et al., 2014; but see also Mutolo et al., 2008a). However, some studies suggested that in anesthetized guinea pigs (Mazzone and Canning, 2002b; Mazzone et al., 2005) C-fiber activation does not evoke cough, but produces changes in the cough reflex and airway autonomic outflow by amplifying the action of other airway afferent nerves, namely mechanically-sensitive vagal afferents. Thus, C-fibers may be especially relevant to coughing associated with airway inflammation and inhalation of environmental irritants. Further support for the inhibitory role of vagal C-fibers on mechanically-induced cough in anesthetized cats has recently derived from the results of the study by Simera et al., 2016. The "cough receptors" (Canning et al., 2004, 2006a,b) are innervated by slowly conducting Aδ-fibers and are sensitive to punctate mechanical stimuli and acid, but unresponsive to changes in luminal pressure, to capsaicin, bradykinin or hypertonic saline and, like Aδ RARs, do not express transient receptor potential vanilloid type 1 (TRPV1) channels under normal healthy conditions. Recent results on the antitussive effects of long-acting muscarinic receptor antagonists (LAMAs) are consistent with the possible role of this type of receptors in cough production both in awake and anesthetized rabbits (Mutolo et al., 2016). However, their presence in the tracheobronchial tree of this animal species remains to be ascertained. As a consequence, other receptors in addition to the TRPV1, as suggested by others (Birrell et al., 2014), should be taken into consideration in the mediation of LAMA antitussive effects, such as acid-sensing ion channels and mechanoreceptors of cough-related airway sensory afferents.

Despite the larynx being often disregarded in cough studies since the trachea is in most cases cannulated, laryngeal receptors are a very important source of airway defensive reflexes and, in particular, of the cough reflex. Cough-related laryngeal receptors apparently display analogies with those located in the tracheobronchial tree (Korpáš and Tomori, 1979; Widdicombe 1986, 2003; Sant'Ambrogio, 1993; Sant'Ambrogio and Widdicombe, 2001 also for further details). Cough-related laryngeal receptors innervated by myelinated Aδ-fibers are activated by mechanical and chemical stimuli and are often called "irritant receptors". They possibly include "cough receptors" (Canning et al., 2004, 2006a,b). A large proportion of "irritant" type receptors respond to water or water solutions lacking chloride ions. C-fiber activation has also been reported to have a role in cough production. It seems plausible that specific second-order neurons for cough-related laryngeal afferents exist. In this regard, note the putative model (Fig. 7) by Widdicombe (2003) on the central pathways for the cough reflex, where laryngeal RARs project to their own laryngeal relay neurons, that have distinct connections with the cough generating mechanism. However, although the central pathways have not been investigated in detail, they are probably similar to those displayed by tracheobronchial cough afferents (Kalia and Mesulam, 1980; Nomura and Mizuno, 1983; Mifflin, 1993). In addition, "irritant" receptors may evoke many other airway protective reflexes such as glottal closure, apnea, bronchoconstriction, mucus secretion, the expiration reflex, the swallowing reflex and cardiovascular reflexes (Korpáš and Tomori, 1979; Widdicombe, 1986; Mutolo et al., 1995; Sant'Ambrogio and Widdicombe, 2001; Jean, 2001; Nishino et al., 2004; Mazzone and Undem, 2016). The expiration reflex closely resembles cough responses, but it consists of a pure expiratory effort evoked by the mechanical stimulation of the vocal fold mucosa in the absence of a preparatory inspiratory phase (Korpáš and Tomori, 1979; Korpas and Jakus, 2000; Sant'Ambrogio and Widdicombe, 2001). The expiration reflex can be also evoked by the stimulation of the tracheobronchial tree (Widdicombe 1954; Tatar et al., 2008; Poliacek et al., 2008b). Glottal closure and the expiration reflex may be regarded as the first level of airway defense since they prevent penetration of foreign bodies into the airways. Other laryngeal afferents display a marked respiratory modulation and are the source of different respiratory reflexes (see e.g. Widdicombe 1986; Sant'Ambrogio, 1993). A comprehensive review on laryngeal afferents and related reflexes is beyond the scope of the present report.

2.2. Central cough pathways

Both neuroanatomical and electrophysiological studies in both cats and rats have demonstrated that the main central termination sites of RAR primary afferents are the medial subnucleus of the NTS and, especially, the lateral aspect of the commissural subnucleus, where also RAR second-order neurons (RAR cells) are located (Kubin and Davies, 1988; Ezure et al., 1991, 1999; Lipski et al., 1991; Kubin and Davies, 1995; see for review Kubin et al., 2006). RAR cells were excited by ammonia inhalation and displayed monosynaptic EPSP in response to low-intensity vagal stimulation. Other studies in the rabbit (Mutolo et al., 2007, 2009) using excitatory amino acid (EAA) receptor antagonists implicate that cough-related afferents activated by the stimulation of the tracheobronchial tree terminate in caudal portions of the NTS consistently with previous data in the cat. The results obtained in the guinea pigs both by anatomical tracing studies and by microinjections of EAA receptor antagonists (Canning and Mori 2010, 2011) led to the suggestion that afferent fibers activated in response to stimulation of the tracheal mucosa "cough-receptors" terminate mainly in more rostral and lateral NTS sites (lateral to the commissural subnucleus and, perhaps, in the medial subnuclei). The difference with previous findings in the cat, rat and rabbit was attributed by Canning and Mori (2010) mainly to the different site of tussigenic stimulation (trachea vs. tracheobronchial tree).

Interestingly, no evidence was found by Canning and Mori (2011) for a permissive effect of slowly adapting receptors (SARs) in the cough reflex, as suggested by other studies (Sant'Ambrogio 1982; Hanacek et al., 1984, 2006). The role of pulmonary stretch receptors and, in particular, of volume-related feedback in the regulation of the cough reflex is controversial (Nishino et al., 1989b; Javorka et al., 1994; Romaniuk et al., 1997; Bolser and Davenport 2000). In a recent study, Poliacek et al. (2016) found that modified lung inflations during coughing and/or additional expiratory airflow resistances altered the spatio-temporal characteristics of the cough motor pattern through