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Review

Cough-related neural processing in the brain: A roadmap for cough dysfunction?

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ABSTRACT

Cough is a complex respiratory behavior essential for airway protection, consisting of sensory, motor, affective and cognitive attributes. Accordingly, the cough neural circuitry extends beyond a simple pontomedullary reflex arc to incorporate a network of neurons that are also widely distributed throughout the subcortical and cortical brain. Studies have described discrete regional responses in the brain that likely give rise to sensory discriminative processes, voluntary and urge-related cough control mechanisms and aspects of the emotive responses following airways irritation and coughing. Data from these studies highlight the central nervous system as a plausible target for therapeutic intervention and, consistent with this, a careful appraisal of the many and varied clinical disorders of coughing control would argue that more diversified therapies are needed to treat patients with cough dysfunction. In this paper we explore these concepts in detail to highlight unanswered questions and stimulate discussion for potential research of cough in the future.

Contents

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1. Introduction

The traditional view has held that cough is principally a reflex action controlled by regions in the caudal brainstem (Baekey et al., 2001; Canning and Mori, 2010; Ohi et al., 2005). However, there is increasing recognition that the control of coughing is a complex process influenced by sensory, motor, affective and cognitive mechanisms (Davenport, 2009; Mazzone et al., 2007, 2011b) and contemporary views posit a role for many brain regions in the expanded list of functions that extend beyond the stereotypical cough motor event. Importantly, these contemporary views provide prospective explanations for the expression of cough in clinical contexts and point toward regions in the central nervous system as potential therapeutic targets. There is merit in considering new research directions to develop cough treatments because efforts to antagonize reflex cough often do not produce measurable clinical outcomes and will remain problematic due to the inherent risks of curtailing such an important mechanism for airway clearance. Similarly, inhibitors of cough processing in the brainstem are also problematic given that many of the brainstem cough neural components are integral to normal respiratory rhythm generation and regulation. Although not devoid of possible side effects, the higher brain should be considered as a viable target for treating cough dysfunction in disease.

The main objective of this review is to develop a pathway for future research into the central control of coughing in clinical conditions. In order to achieve this objective the review will first explore the sensory, motor, affective and cognitive attributes of cough. The second section of the review will list the brain regions ascribed with a role in cough control and then discuss how activation in these regions can be related to different attributes of cough function. The final two sections will discuss the functional neuroanatomy of cough in the context of clinical conditions and what this means for cough therapies. In doing so, we aim to raise questions for potential future research.

2. The phenomenology of cough

2.1. Defining cough

A widely accepted definition of cough is a defensive airway reflex consisting of a modified respiratory act aimed primarily at generating the high flow velocities required for removal of mucus or any other foreign body from the lower respiratory tract. It typically begins with a preparatory inspiratory phase, characterized by an enhanced contraction of the diaphragm and abductor muscles of the larynx, followed by a brief expiration against a closed glottis (compressive phase) and finally a continued forceful contraction of the expiratory muscles with the glottis open (expulsive phase) (Fontana and Lavorini, 2006).

However, the definition of cough above merely describes the basic motor events of a typical cough and excludes respiratory responses in which the motor events differ (such as no initial inspiration or partial/absent glottal closure), which for all intents and purposes would be considered a cough in the clinical setting. The definition also excludes entirely the sensory, affective and cognitive components of cough. Cough is also often defined or described as a reflex, characterized by the involuntary respiratory motor events described above but occurring as a consequence of sensory inputs to the brainstem arising from the airways. Indeed, reflex cough is the primary defense mechanism that protects the airways from inhaled or locally produced irritants, aspirates and pathogens, thereby maintaining normal pulmonary function (Bessac and Jordt, 2010; Bolser and Davenport, 2002). Although this description includes a sensory component to coughing, it relegates the process to being uncontrollable (i.e., reflex in nature), and devoid of any conscious awareness of airways irritation or behavioral regulation of the cough motor act. This is clearly not the case as there is strong evidence that an awareness of irritation (giving rise to the perceived need to cough) precedes many coughs and furthermore the cough motor output can be voluntarily or subconsciously manipulated with or without concomitant sensory stimulation (Davenport et al., 2002; Mazzone et al., 2011a). Thus, individuals can voluntarily cough, suppress urge-related cough and even have their urge-to-cough sensation and cough motor response manipulated through placebo interventions, distractions or alterations to cognitive states (e.g., anxiety) (Davenport and Vovk, 2009; Leech et al., 2012; von Leupoldt et al., 2013). There may be a need to acknowledge that the emphasis on motor events that are employed to define cough do not encompass additional attributes of the human experience of airway clearance that are likely to have a bearing on the expression of cough in health and disease. The more elaborated experience could be thought of as a complex multifaceted respiratory response with sensory, motor, affective and cognitive dimensions (Fig. 1). Indeed, adopting such a viewpoint may help with the understanding of problematic cough in disease, which all too often is simply labeled as a change in cough reflex threshold sensitivity without recognition of the other dimensions of the experience that may also play a role.

2.2. The urge-to-cough

The urge-to-cough, a higher brain-dependent sensory experience related to irritation of the airways, constitutes an important component of coughing and several studies have reported urge-to-cough measures alongside urge-related cough responses evoked by airway stimulation as indices of cough sensitivity thresholds. Arguably less is known about the phenomenology of the urge-to-cough compared to actual coughing, perhaps because studies are confined to human subjects, who can articulate the nature of the sensation. Recently, capsaicin inhalation has been used to model the urge-to-cough in the laboratory setting (Davenport et al., 2002; Mazzone et al., 2007) and the lowest dose to reliably elicit a report of an urge-to-cough without a preceding motor cough event has been dubbed the urge-to-cough threshold (C_u) (Dicpinigaitis et al., 2012). Whether this experimental model accurately reflects the endogenous urge-to-cough present in respiratory diseases is not clear. Surprisingly there have been no studies explicitly evaluating the phenomenology of urge-to-cough in disease and only a few reports documenting urge-to-cough measures collected in patients in the absence of challenge testing. Nevertheless studies employing urge-to-cough induced by inhaled capsaicin have provided some