Cough Sensors. I. Physiological and Pharmacological Properties of the Afferent Nerves Regulating Cough

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Abstract The afferent nerves regulating cough have been reasonably well defined. The selective effects of general anesthesia on C-fiber-dependent cough and the opposing effects of C-fiber subtypes in cough have led to some uncertainty about their regulation of this defensive reflex. But a role for C-fibers in cough seems almost certain, given the unique pharmacological properties of these unmyelinated vagal afferent nerves and the ability of many C-fiber-selective stimulants to evoke cough. The role of myelinated laryngeal, tracheal, and bronchial afferent nerve subtypes that can be activated by punctate mechanical stimuli, inhaled particulates, accumulated secretions, and acid has also been demonstrated. These “cough receptors” are distinct from the slowly and rapidly adapting intrapulmonary stretch receptors responding to lung inflation. Indeed, intrapulmonary rapidly and slowly adapting receptors and pulmonary C-fibers may play no role or a nonessential role in cough, or might even actively inhibit cough upon activation. A critical review of the studies of the afferent nerve subtypes most often implicated in cough is provided.

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1 Introduction

Cough is a defensive reflex initiated primarily from the larynx, trachea, and large bronchi. Stimuli initiating cough include punctate mechanical stimuli, accumulated secretions, aspirate, particulate (e.g., powder, dust), capsaicin, bradykinin, and interventions that alter the pH or tonicity of airway surface liquid. Although afferents throughout the upper and lower airways and sensory nerves innervating the mediastinum, respiratory muscles, and chest wall all likely contribute to the encoding of cough thresholds and intensity, vagal afferent nerves innervating the large extrapulmonary and intrapulmonary airways are the primary regulators of cough. The physiological properties of airway vagal afferent nerves have been described in detail elsewhere (Canning et al. 2006). In this review, a description of the known physiological, morphological, and pharmacological properties of the vagal afferent nerve subtypes primarily implicated in cough is provided, as well as a summary of the important contributions of Widdicombe.

2 Widdicombe’s Studies of Cough and Description of the “Cough Receptors”

The landmark studies by Widdicombe published in 1954 and cited in subsequent papers nearly 1,000 times since remain the best characterization of the afferent nerves regulating cough (Widdicombe 1954a,b,c). Three attributes of those studies account for their importance and lasting impact on the field. First, the methods for maintaining and monitoring respiration and respiratory reflexes while isolating the trachea and bronchi for selective afferent stimulation were highly novel and have served as the model for many subsequent studies of airway neural control. Second, the combination of respiratory reflex measurements with parallel single and/or multifiber afferent nerve recordings as well as phrenic nerve recordings in some preparations provided unmatched insight into the cause and effect of airway neural control. Finally, the rigor with which the studies were carried out – comparing different anesthetics (pentobarbital and chloralose) with decerebrate preparations, the care with which the afferents were described (see Table 1), the identification of afferent nerve termination sites, the first-ever comparison of pulmonary stretch receptors with tracheal/bronchial stretch receptors, and the differentiation of nearly 300 units into four subtypes – have greatly influenced subsequent studies of airway neural control. Notably, these studies formed the basis of Widdicombe’s graduate thesis (Widdicombe 2001). Because this work has been so influential and affirmed repeatedly in the years following, a summary of the key findings serves well as an introduction to this review.

Focusing initially on afferents stimulated by lung inflation in cats, Widdicombe described two mechanically sensitive afferent nerve subtypes. The majority of the afferents identified by lung inflation were slowly adapting, with adaptation indices