



Peripheral neural circuitry in cough

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Cough is a reflex that serves to protect the airways. Excessive or chronic coughing is a major health issue that is poorly controlled by current therapeutics. Significant effort has been made to understand the mechanisms underlying the cough reflex. The focus of this review is the evidence supporting the role of specific airway sensory nerve (afferent) populations in the initiation and modulation of the cough reflex in health and disease.

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Introduction

Cough is an airway reflex in guinea pigs and larger mammals that serves to expel unwanted matter from the airways. Stimuli induce cough by activating afferent (sensory) nerves innervating the airways. These signals are transmitted centrally via the vagus nerve, where they synapse with networks in the brainstem (e.g. nucleus tractus solitarius (nTS)). Such networks coordinate the activation of motor output (e.g. phrenic, intercostal and recurrent laryngeal nerves (RLN)) and the ultimate expression of cough. The focus of this review will be the afferent nerves involved in cough: their characterization, activation and function.

Key to the understanding of afferents involved in cough is the use of specific stimuli to evoke cough experimentally. In anesthetized animals cough is evoked by mechanical stimulation (i.e. punctate) of the larynx, trachea and main bronchi [1,2]. This cough rapidly adapts to continued pressure, although repeated stimulation will evoke further coughs. Application of water and citric acid to these airways also evokes cough in anesthetized animals [3–5]. Interestingly, cough can be evoked by many other stimuli in conscious animals (but not in anesthetized animals). Thus inhalation of irritants such as bradykinin, capsaicin,

cinnamaldehyde and acrolein evokes cough [1,6–10,11[•]], as can bronchoconstricting agents [12–14]. Regardless of which receptors are involved, afferent activation depends on the gating of membrane ion channels at the airway afferent terminal. This leads to nerve depolarization (graded potential), which triggers the activation of voltage-gated sodium channels (Na_v) and the initiation of action potentials, that conduct towards the brainstem [15,16[•]].

Afferent innervation of the larynx, trachea, bronchi and intrapulmonary airways is largely supplied by the vagus nerve and its branches (e.g. RLN and superior laryngeal nerve (SLN)). The vagal ganglia comprises of the nodose and jugular ganglia, whose afferent neurons arise from distinct embryological sources (placodes and neural crest, respectively) [17]. Such differences manifest themselves in differential protein expression and functionality [18,19]. Airway afferents are not homogenous and numerous subtypes have been determined (Figure 1). Details of these subtypes can be found elsewhere [5,15,20,21], here we will focus on two important groups: the nodose Aδ fibers innervating the extrapulmonary airways and the vagal C fibers innervating throughout the airways. Both groups can be considered ‘nociceptive’ — afferents that do not respond to eupneic breathing and other ‘normal’ events, but which respond specifically to stimuli that can be considered noxious (or potentially noxious) [22].

Nodose Aδ fiber activation

Highly arborized nerve terminals are found innervating the smooth muscle layer of the extrapulmonary airways [2,23]. These are the peripheral terminals of myelinated afferents originating exclusively from the nodose ganglion. Electrophysiological recordings indicate conduction velocities of approximately 5 m/s (Aδ fibers) [24,25]. These afferents are exquisitely sensitive to punctate mechanical force, but not stretch. Acidic solutions, hypotonic and hypertonic solutions also activate extrapulmonary nodose Aδ fiber terminals [24,26]. Responses to continued punctate force or acidic solutions rapidly cease (adaptation) [27]. Aδ fibers in healthy animals are completely insensitive to bradykinin and capsaicin (selective agonist of transient receptor potential vanilloid 1 (TRPV1)) [1,24], due to a lack of TRPV1 expression [28^{••}] (Figure 2).

Nodose Aδ fibers innervating the trachea and larynx are carried by the RLN branch of the vagus [24]. Bilateral transection of the RLN interrupts Aδ fiber signaling [2,24] and cough evoked in anesthetized guinea pigs by stimulation of the trachea [1,2,29]. SLN transection

had no effect on A δ fiber signaling/cough. Recently, a more specific approach has indicated the contribution of nodose A δ fibers to cough [30^{••}]. Nav1.7, a vagal voltage-gated sodium channel, has been shown to be critical for action potential discharge in vagal afferents innervating the airways [31]. Using *in vivo* adeno-associated virus (AAV) delivery specifically to nodose neurons (jugular was not transfected) of shRNA targeted against Nav1.7, the overall electrical activity of nodose afferents was significantly reduced (jugular afferents were not reduced) [30^{••}]. In these studies punctate stimulation (under anesthesia) of the trachea evoked 11 ± 3 coughs in control guinea pigs but only 2 ± 1 coughs in nodose Nav1.7 knockdown guinea pigs (Figure 3). Breathing rates were not different between the groups.

The receptors responsible for A δ fiber activation have not been definitively determined. Acid activates both TRPV1 and a family of proteins termed the Acid-Sensing Ion Channels (ASIC) in sensory neurons. However, TRPV1 is not expressed in A δ fibers and selective TRPV1 inhibitors have no effect on acid-induced A δ fiber activation [26]. The mRNA for multiple ASICs have been found in nodose neurons [32^{*}], but specific studies in airway afferents are lacking. Numerous candidates have been proposed for mediating mechanical-induced sensory nerve activation including EnaC, TRPV4, TRPA1, and Piezo [15,33–36], but so far no definitive determinations have been made.

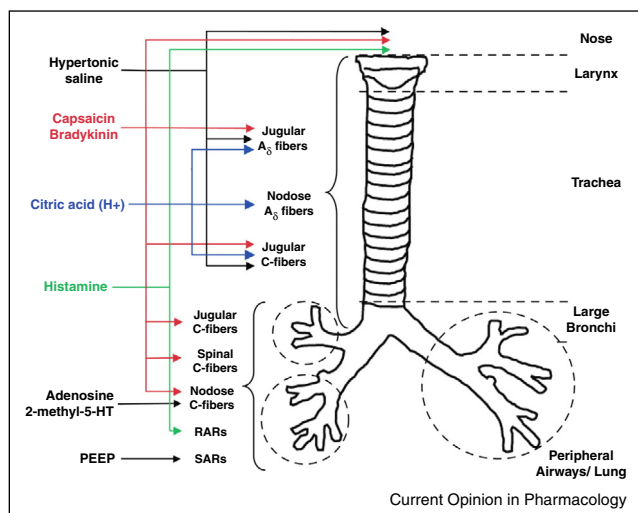
Characterizations of A δ fiber terminals and their nodose soma suggest that these neurons represent a biochemically distinct neuronal subset [24,37]. These neurons

express neurofilament, neuronal nitric oxide synthase and vGlut1 and vGlut2 (transport glutamate into excitatory vesicles) but do not express substance P, CGRP or somatostatin (nociceptor neuropeptides). Interestingly, these fibers express the α_3 subunit of the Na-K-ATPase pump, which is not found elsewhere within the trachea [2,37]. Ouabain, at concentrations that preferentially block α_3 subunit, inhibited the activation of tracheal A δ fibers and inhibited cough evoked by tracheal stimulation in anesthetized guinea pigs [2]. Ouabain had no effect on basal breathing rates or on citric acid-induced apneas, suggesting a selective inhibition of tracheal A δ fiber afferents.

Vagal C fiber activation

The vast majority of airway afferents are unmyelinated and conduct action potentials at 0.3–1.5 m/s (C fibers) [18,38,39]. C fibers terminate in unstructured endings throughout the mucosa and submucosa of the airways [2,23,40]. C fibers are polymodal sensors of noxious stimuli [18,41–43], due to their characteristic expression of specific receptors for noxious stimuli. The hallmark of C fiber nociceptive afferents is sensitivity to capsaicin due to the expression of TRPV1 in nociceptors [44]. Capsaicin activates airway C fibers [18,24,38,42,43] (Figure 2), and this is abolished by selective TRPV1 inhibitors and in TRPV1 $^{-/-}$ mice [45–47]. Capsaicin does not evoke cough in anesthetized animals, although it does evoke apnea [1,48–50]. In conscious animals capsaicin evokes cough (Figure 3) that is reduced by TRPV1 inhibitors [7,30^{••},51–53]. Similar data are observed in humans, where capsaicin produces cough bouts and urge-to-cough sensations [6,11^{*}].

Figure 1



The distribution and responsiveness of airway afferent subtypes in the guinea pig. RARs, rapidly adapting receptors; SARs, slowly adapting receptors.

Source: Taken from Ref. [5].

TRPV1 itself is a polymodal receptor that is activated by heat and extracellular acidity [44]. Airway C fibers are activated by acid, in a manner that is partially inhibited by TRPV1 inhibition/knockout [26,47]. Consistent with these findings, TRPV1 inhibitors reduce citric acid-induced cough in conscious guinea pigs [51,54,55]. The other mechanism(s) underlying acid-induced activation of airway C fibers is probably mediated by ASIC channels [32^{*},56].

TRP ankyrin 1 (TRPA1) is commonly co-expressed with TRPV1. TRPA1 is activated by a host of noxious stimuli including cinnamaldehyde, allyl isothiocyanate (AITC, pungent ingredient of wasabi), H₂O₂, ozone, cigarette smoke, dehydrated prostaglandins and products of lipid peroxidation and nitration [57–64]. This disparate group of substances all activate airway C fibers, in a manner that is abolished by inhibition or genetic knockout of TRPA1 [61,64,65]. Point mutation studies of TRPA1 suggest that a covalent modification of key intracellular cysteines by electrophilic moieties underlies much TRPA1s activation by these activators [66,67]. TRPA1 agonists evoke cough

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