



Cough and gastroesophageal reflux: Insights from animal models

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ABSTRACT

Chronic cough in gastroesophageal reflux disease (GERD) has been attributed to irritation of the esophagus and/or upper airways by reflux of gastric content. Animal models have provided insight into both of these putative mechanisms. In patients with chronic cough and GERD, stimuli associated with reflux in the esophagus sensitize the cough reflex. This sensitization can be reproduced in the guinea pig and is most likely mediated by the esophageal afferent nerve fibers carried by the vagus nerves. Studies in animals have identified several subtypes of vagal esophageal C-fibers that may subserve this function. The putative nociceptive vagal C-fibers in the guinea pig esophagus are stimulated by acid and express the TRPV1 and TRPA1 receptors that confer responsiveness to disparate noxious stimuli. Acute and/or chronic irritation of the upper airways by reflux may contribute to cough by stimulation and/or sensitization of the airway afferent nerves. Studies in animals have identified airway nerves that likely initiate cough due to aspirated reflux; have characterized their pharmacology; and have provided insight into changes of their sensitivity. Studies in animal models have also described the neurophysiology of reflexes that protect the airways from reflux. In conclusion, animal models provide mechanistic insight into the modulation of cough from the esophagus and the pharmacology of neural pathways mediating cough in GERD.

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Modeling cough in animals has inherent advantages and limitations (reviewed in [1]). The major advantage of animal models is the amenability to mechanistic manipulations. Thus animal models are the source of important information that cannot be readily obtained in humans. The major disadvantage of studying cough in animals is that animal models rarely completely mimic all aspects of a human disorder. Nonetheless, useful extrapolations regarding the pathogenesis of cough can be made from animal models with appropriate caution. In this review we focus on the insights made from animal models regarding the neurophysiology and pharmacology of neural pathways mediating cough associated with GERD. Animal models have also provided invaluable information about the pathogenesis of GERD, however, the discussion of this extensive research area is beyond the scope of the current review.

1. Putative mechanisms of cough in gastroesophageal reflux disease

Based on data from human studies, two major mechanisms of cough in GERD have been proposed: cough mediated by the activation of the afferent nerves in the esophagus and cough as a result

of acute or chronic (micro-) aspiration of the refluxed content into the airways [2,3]. Studies in animal models have identified and characterized the neural pathways for each of these two putative mechanisms.

It has been suggested that activation of the vagal sensory nerves in the esophagus triggers cough in patients with GERD and chronic cough [4]. A strong temporal association between the reflux episodes and cough would argue that cough is directly triggered from the esophagus. Unfortunately, the reported association between reflux and cough is variable among the studies (depending also on patient selection and methods for detection of cough and reflux, see for example [5–9]). Cough is occasionally encountered during prolonged infusion of acid into the esophagus [4], but this finding is inconsistent across the studies [10,11]. Thus, based on the available evidence it is difficult to unequivocally conclude that cough is directly initiated from the esophagus in patients with chronic cough and GERD.

More circumstantial evidence supports the hypothesis that activation of afferent nerves in the esophagus leads to sensitization of the cough reflex (i.e. cough reflex hypersensitivity) in patients with chronic cough and GERD. Increased cough reflex sensitivity is a regular finding in patients with gastroesophageal reflux [12,13]. Increased cough reflex sensitivity is thought to contribute to chronic coughing because the endogenous and environmental

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stimuli are more effective in triggering cough. Additional support for the role of the cough reflex hypersensitivity in the pathogenesis of cough comes from reports that the cough reflex sensitivity decreases with effective treatment of gastroesophageal reflux [13–16].

While the mechanisms of cough reflex hypersensitivity in humans are incompletely understood, the data from clinical studies indicate that the hypersensitivity is at least in part caused by the stimulation of distal esophagus. Infusion of acid into the distal esophagus of patients with GERD and chronic cough induced the cough reflex hypersensitivity (documented as lowered cough threshold to inhaled capsaicin) [11]. The increase in the cough reflex sensitivity developed within 15 min (the earliest time point evaluated). Similar rapid (within 10 min) sensitization of cough reflex by infusion of acid into the esophagus was also demonstrated in patients with asthma [17]. The relatively rapid change in cough sensitivity is best explained by assuming a neurally-mediated process. Indeed, the effects of acid infusion on cough are inhibited by esophageal instillation of the local anesthetic lignocaine [4].

Regardless of whether the cough reflex is only sensitized or also directly triggered from the esophagus, the data from human studies predict an afferent neural pathway mediating the effects of esophageal stimuli on the cough reflex. Since the afferent pathways of the cough reflex have been so far convincingly demonstrated only in the vagus nerves, the simplest hypothesis predicts a vagal pathway from the esophagus that sensitizes the cough reflex. Although it cannot be excluded that the esophageal inputs sensitizing cough are also carried by other than vagal afferent pathways (i.e. spinal or other cranial nerves), this alternative remains speculative in the absence of supporting evidence. It should be also noted that a subgroup of patients with chronic cough due to gastroesophageal reflux do not present with heartburn and chest pain. A likely interpretation of this finding is that the pathways mediating the effects on cough (presumably vagal pathways) are different from the pathways mediating heartburn and pain (spinal pathways).

2. Vagal afferent pathways from the esophagus and cough reflex

The afferent nerves in the esophagus responsible for modulation of the cough reflex are predicted to respond to stimuli associated with reflux. A number of clinical studies have shown that acid is an important mediator of cough in GERD (reviewed in [2,3]). In addition to acid, other chemicals in the refluxed fluid such as components of bile and pepsin have been implicated in the activation of esophageal nerves in GERD [2,18]. Another stimuli likely relevant for gastroesophageal reflux are the mechanical stimuli [18]. While mechanical stimuli are present in the esophagus during its normal activity, the abnormal mechanical pattern associated with reflux or sustained esophageal contractions [19] may provide an adequate stimulus for modulation of cough. The effects of weakly acidic (pH > 4) reflux have been, at least in part, attributed to its volume (i.e. mechanical effects) and the association of cough with weakly acidic reflux has been reported in several studies [8,20–22], reviewed in [23]. Thus the afferent pathways modulating the cough reflex are likely responsive to chemical stimuli including acid and to mechanical stimulation.

A complex picture of the vagal afferent innervation of the esophagus has emerged from anatomical and neurophysiological studies in various species [24]. A number of thorough anatomical studies have characterized neural structures in the esophagus; however, with few exceptions it is still difficult to assign a morphological correlate to a functionally characterized afferent nerve. We will therefore base our discussion on the functional

neurophysiological studies and refer to histological data whenever possible. In general the afferent nerves in the esophagus fit into two broad categories: (1) afferent nerves sensitive to low intensity mechanical stimuli - low threshold mechanosensors and (2) afferent nerves discriminately responsive to noxious stimuli - nociceptors. In this discussion, we use the term nociceptive to describe the capacity of an afferent nerve to respond to noxious stimuli.

2.1. Vagal nociceptive C-fiber subtypes in the esophagus

Vagal nociceptive afferent nerves in the esophagus have been defined based on their discriminative responsiveness to noxious mechanical stimuli and their sensitivity to noxious chemical stimuli [25,26]. Vast majority of the vagal nociceptive nerves in the guinea pig esophagus conduct action potentials in the C-fiber range (<1 m/s). The vagal nociceptive afferent nerves described in the guinea pig [25,26] are likely analogous to mucosal-tension receptors described in the ferret [27] and a subset of vagal afferent nerves described in the rat [28]. Vagal nociceptive C-fibers express the TRPV1 receptor, which is activated by acid and certain lipid mediators [25,26]. Vagal C-fibers are also activated and/or sensitized by a wide range of the endogenous mediators associated with inflammation such as bradykinin (B₂ receptor) [29], adenosine (A₁ and possibly A_{2A} receptor, unpublished data), purines (P2X receptors for ATP) [30], histamine (H₁ receptor) [31] and serotonin (5-HT₃ receptor) [25]. We have recently investigated the activation of the vagal esophageal C-fibers via the TRPA1 receptor (Fig. 1). As discussed elsewhere in this issue, TRPA1 confers the afferent nerve sensitivity to a number of endogenous molecules associated with inflammation and tissue damage [62]. We found that TRPA1 agonists induce robust activation of the vagal esophageal C-fibers (Fig. 1), an observation consistent with the findings of a recently-published study [29].

Given their capacity to detect noxious stimuli and their vagal origin, vagal nociceptive C-fibers appear to be the most likely candidates for mediating the effects of reflux on cough. The sensitization of the cough reflex by esophageal acid demonstrated in patients with GERD and cough can be reproduced in the guinea pig model [B] Canning, personal communication). Similar observations were made in the guinea pig after infusion of the TRPV1 receptor agonist capsaicin into the esophagus. The cough sensitization is mimicked by the activation of central terminals of vagal nerves evoked by injection of capsaicin into the appropriate areas of the brainstem [32]. These data also support the notion that sensitization of the cough reflex from the esophagus is mediated by the vagal afferent capsaicin-sensitive C-fibers innervating the esophagus.

Some studies in the lung and esophagus have demonstrated that there are at least two subtypes of vagal nociceptive C-fibers. Vagal C-fiber subtypes are determined by their embryonic origin and distinguished by certain activation properties and anatomical distribution [25,26,30,33,34]. In most species the neurons of the neural crest-derived nociceptive subtype reside in the vagal jugular ganglion, while the neurons of the placodes-derived subtype reside in the vagal nodose ganglion [35]. In the guinea pig both vagal afferent subtypes project into the esophagus [25,26]. It is currently unknown which vagal C-fiber subtype in the esophagus mediates the cough reflex sensitization, but available evidence suggests a role for the jugular nociceptive subtype. First, the jugular C-fiber subtype is more likely to express neurokinins implicated in the central sensitization of the cough reflex [26,36]. Second, the circumstantial evidence indicates that afferent nerve terminals of the jugular nerve fibers are likely located in the esophageal mucosa and submucosa close to esophageal lumen [28,36]. Finally, in the

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