Published in final edited form as:

Lung. 2008 ; 186(Suppl 1): S23–S28. doi:10.1007/s00408-007-9054-6.

The cough reflex in animals: Relevance to human cough research

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Abstract

All mammalian species studied cough or display some similar respiratory reflex upon aerosol challenge with tussigenic stimuli such as citric acid or capsaicin. Animals cough to the same stimuli that evoke coughing in humans, and therapeutic agents that display antitussive effects in human studies also prevent coughing in animals. The many invasive procedures and complementary in vitro studies possible in animals but readily reproduced in human subjects, along with the proven predictive value of cough studies in animals provides the rationale for animal modeling of human cough. The advantages and disadvantages of studying cough in animals are discussed.

Keywords

capsaicin; bradykinin; nucleus of the solitary tract; vagus

The cough reflex protects the airways and lungs from airborne and inhaled pathogens, allergens, aspirate and other irritants (figure 1). Humans that have a compromised cough reflex due to neuromuscular disorders or stroke are highly susceptible to pulmonary infections and aspiration (1-6). It would seem reasonable to expect that most or perhaps all mammalian species would have a similar respiratory reflex subserving the same role in lung defense. Indeed, although direct evidence for their protective role in animals has not been published, every mammalian species studied to date displays a cough reflex or some similar forceful expiratory reflex evoked by airway irritation (7-13) (figure 2). Given the similar physiologic patterning of these respiratory efforts and that the same stimuli that evoke coughing in humans also evoke coughing in animals, studying cough in animals is likely to provide insight into the physiology and pathophysiology of cough in humans. Rather than compare, contrast and critique the various animal models used to study cough, this review will discuss the rationale behind animal modeling of human cough, the advantages of studying cough in animals and the several disadvantages of studying this and other respiratory reflexes in animals.

Why study cough in animals?

Human physiology and consciousness is probably sufficiently unique amongst vertebrates that human pathophysiology is also likely to be distinct from that in other species. It would follow logically from the above assertion that animal models of human disease and/or pathophysiology are imperfect, and thus, whenever possible, research related to these diseases should be carried out using humans. But the symptoms and causes of human diseases including those diseases associated with cough are regulated by cells, organ systems and reflex pathways that have remained remarkably unchanged amongst animal species. Coughing, for example can be evoked in all species studied by mechanically stimulating the airways mucosa or by inhalation of acidic saline or capsaicin (7-9,14-16). The latter 2 stimuli acts on the ion channel and receptor TRPV1, which is preferentially localized to distinct subsets of nociceptive sensory

nerves innervating somatic and visceral tissues and encoded by a gene that shows upwards of 80% homology across species (17-21). The biophysical and pharmacological properties of TRPV1 are similar if not identical in different mammalian species. Thus, using animals to identify stimuli that do and do not evoke coughing and to evaluate the efficacy of putative antitussives has had good predictive value for the results of human studies (Tables 1 and 2).

The predictive value of animal studies of cough is nevertheless insufficient justification for animal experimentation relating to cough. Rather, the primary advantages of studying cough in animals are the many interventions, treatments and conditions under which and/or following which cough can be studied in animals that are simply not feasible in human subjects (7,9, 10,11,16,22-28). This allows experimenters precise control over the induction of cough and the conditions under which cough is evoked, and thus better insight into the physiology and pharmacology of cough. These physiological studies can be extended to in vitro settings, allowing for even more refined (reduced) approaches to studying the synaptic, cellular and molecular interactions and processes relevant to this respiratory reflex (23-25,27,28). With this experimental flexibility, new insights into the physiology and pharmacology of cough are routinely recorded and incorporated into our working models of the physiology and pathophysiology of cough. Such studies may reveal previously unrecognized causes of cough and perhaps new treatments or at least a rational basis for evaluating new treatments. Given the consensus that new, specific and effective treatments for cough remains a critically important, valued and yet unmet need in clinical practice and the advantages to studying cough in animals detailed above provides the rationale for continued study of the cough reflex in animals.

The advantages of studying cough in animals

The cough reflex follows a fairly simple reflex arc. Chemical or mechanical irritants primarily in the larynx, trachea and large bronchi activate vagal sensory nerves that form action potentials that conduct up the vagus nerves to the brain. When the action potential invades the central terminals of these sensory nerves in the brainstem (primarily in the nucleus of the solitary tract; nTS), synaptic vesicles release their neurotransmitters onto nTS relay neurons in varying quantities depending on the frequency of action potential formation (impulses/ sec), the duration of activation and the number of sensory neurons activated. These transmitters (e.g. glutamate, substance P) act postsynaptically on nTS relay neurons, that in turn form action potentials and encode information projected elsewhere in the brainstem, resulting in respiratory reflexes. If the specificity and intensity of the afferent nerve activation is sufficient, the peculiarities of the cough reflex (enhanced inspiratory effort, closed glottis and respiratory muscle contraction during the compressive phase of the cough, opened glottis and sustained respiratory muscle contraction during the expulsive phase) are transmitted through the motor nerves innervating the diaphragm and related respiratory muscles (15,29,30). Each aspect of this reflex arc can be studied at the systems, synaptic, cellular and molecular level in animals using physiologic, pharmacologic, immunohistochemical and molecular techniques that are not readily duplicated in human studies.

Insights derived from multiple experimental approaches in animals reveal potential causes of cough and multiple physiologic and pharmacologic concepts that may lead to novel and rational therapeutic approaches to treating cough. Gastroesophageal reflux disease (GERD), for example, is a common cause of chronic cough in human subjects (31,32). It has not been firmly established why GERD precipitates coughing, but it is thought to occur secondary to aspiration/ microaspiration and direct activation of the airway nerves regulating cough, or alternatively, following effects on esophageal afferent nerves that in turn modulate cough centrally (15,33, 34). Studies in awake and anesthetized animals confirm that acid challenge to the tracheal or laryngeal mucosa or inhalation of acidic aerosols readily evokes coughing in animals (12-16,

25,26). Electrophysiological studies have identified the afferent nerve subtypes innervating the larynx, trachea and bronchi that are responsive to acid, and have identified the ion channels (TRPV1, acid sensing ion channels) that may regulate the excitability of these sensory nerves (35,36). Insights from these electrophysiological analyses have led to the development of potent and selective inhibitors of these ion channels, and studies in whole animals confirm their ability to prevent coughing initiated by acidification of the airways (16,37,38). With respect to the notion that esophageal afferent nerve activation might modulate coughing, we've shown that acid or capsaicin challenge to the esophagus does not induce coughing, but increases the sensitivity of the airways to tussive stimuli (unpublished observations). This sensitization of the cough reflex occurs centrally and is analogous to the process of central sensitization that is known to be fundamental to the onset of chronic pain (39). We've reported a similar interaction between airway afferent nerve subtypes, suggesting such synergistic effects amongst afferent nerves may be one rational therapeutic target for treating cough (15,26,39).

Therapeutic targets at the sensory nerve terminals have also been described in studies carried out in animals. Allergen and a number of autacoids associated with airways inflammation have been shown to sensitize sensory nerve terminals to subsequent activation and to exacerbate experimentally induced coughing in animals (12-15,40-47). These autacoids may be targeted in subsets of patients, as in cough variant asthma (48-50). Studies of cough in anesthetized animals and in vitro electrophysiological and immunohistochemical analyses have also identified a number of regulatory ion channels and pumps that may be targeted therapeutically to reduce coughing, including an isozyme of the sodium pump (15), Ca^{++} -activated Cl^- channels (16,51-53), and perhaps TTX-insensitive Na^+ channels (54,55).

Recent studies in animals might also encourage further study of the CNS as it relates to human cough. As mentioned above, our studies of airway and esophageal afferent nerve interactions highlights the importance of the central nervous system in regulating sensitivity to tussive stimuli. Other studies of the altered cough reflex following cigarette smoke exposure and studies in guinea pigs, cats and dogs reveal other central mechanisms by which cough can be enhanced or inhibited (26,56-58). More recent studies in guinea pigs describe a conceptual basis for new antitussive therapies for treating cough. In these studies, cough was evoked experimentally by electrically stimulating the tracheal mucosa. When the stimulation intensity and stimulation frequency were suprathreshold, cough could be reliably evoked. Interestingly, however, the stimulation frequency required for induction of cough (≥ 8 Hz) and the stimulus duration required (3-10 seconds) were quite high (55). The implications of these results are that centrally acting therapeutics that simply reduce but not necessary abolish synaptic efficacy in the CNS may greatly reduce coughing. Consistent with this notion, we have shown that NMDA- type glutamate receptor selective antagonists can nearly abolish coughing in anesthetized guinea pigs while having little or no effect on basal respiratory rate and other respiratory reflexes (15).

The disadvantages of modeling altered cough reflexes in animals

There are several disadvantages to studying cough in animals. As mentioned previously, there are no perfect animal models of the human diseases most often associated with acute or chronic cough. Although existing models approximate these human conditions, the peculiarities of GERD and asthma and COPD and various respiratory tract infections are not reliably reproduced. Since coughing in humans during illness is spontaneous, it would be ideal to study animals that had developed spontaneous cough. But this is essentially never done, with coughing in animals typically studied in response to artificial delivery of a tussive stimulus. The physiology and pharmacology of spontaneous coughing and induced coughing is likely to be different (59). Another problem with modeling cough in animals is that just as there are peculiarities of human physiology, there are also peculiarities of animal physiology that can

negatively impact the predictive value of cough research. The profound role of tachykinins and the axon reflex in guinea pigs and rats and their limited role in humans is one example (15). The complete inability to study subjective endpoints such as urge to cough and dyspnea are also limitations to using animals. Finally, one of the primary reasons that animal experimentation allows for more invasive approaches is that many of these interventions can be carried out following anesthesia. The many benefits afforded by anesthesia and the interventions then possible are detailed above, but the detrimental effects of anesthesia on cough are not so obvious. Naturally, the reason animals are given anesthetic is to blunt or eliminate their response or sensitivity to noxious stimuli. Many of the stimuli used to evoke cough in conscious animals would evoke pain when administered to somatic tissues. These same stimuli fail to evoke pain when administered to somatic tissues following anesthesia and similarly do not evoke coughing in anesthetized animals (7,9,15,25). Thus, although it is possible to study the cough reflex in anesthetized animals, a complete and fully functional cough reflex and coughing pattern is never achieved except in awake animals. In the absence of anesthesia, many of the benefits of studying cough in animals are lost.

Conclusions

We still have a limited understanding of the causes of chronic cough. A consequence of this gap in our existing knowledge is that therapeutic approaches used for treating cough are minimally effective and nonspecific. Better therapies based on rational approaches are needed. There is no precedent for drug discovery based entirely or even largely on human experimentation, and animal models have been and will remain essential to our progress in understanding and treating this chronic, and often troublesome respiratory reflex.

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THE COUGH REFLEX ARC

Figure 1.

The neural pathways that regulate the cough reflex are depicted. Each component of this reflex arc functions similarly in all species including humans. Studies carried out in animals allow for more mechanistic experimentation at each site of regulation, allowing for a more complex, broader and comprehensive understanding of the neurogenesis of cough.

Figure 2.

Coughing and expiration reflexes (labeled with asterisks) in awake guinea pigs evoked by aerosol challenges with 10 mg/ mL bradykinin. Tracing depicts changes in pressure within a chamber containing the guinea pig and filled with a bradykinin aerosol. Expiratory efforts produce an upward deflection in the chamber pressure, reflecting an increase in chamber pressure. All animals and human subjects display a similar pattern of respiratory reflex when challenged with tussive stimuli such as acid, capsaicin and bradykinin. Figure reproduced with permission from Canning et al. 2004 (25).

Table 1**Stimuli Evoking Cough in Humans and Animals.**

Mechanical stimulation
mucus
foreign body
tumor
TRPV1 receptor activation
Capsaicin
Acid
Autacoids and second messengers (e.g. HETEs, bradykinin, adenosine)
Bradykinin
Asthma
Viral infections
ACE Inhibitor
Citric acid and Tartaric acid
Aspiration
Airway acidification in disease (as measured by exhaled breath condensate)
Low Chloride and/ or non-isosmotic aerosols
Aspiration
Fog

Subheadings identify stimuli that are known to reliably evoke cough experimentally in both humans and animals. Below each subheading are natural stimuli associated with coughing and/or diseases that precipitate cough and likely work through the identified mechanisms.

Table 2

Stimuli that do not reliably evoke cough in humans or animals.

Airways obstruction

methacholine

histamine

cysteinyl-leukotrienes

Lung inflation/ hyperinflation**Direct nasal stimulation**

Acidification of the esophagus

The stimuli listed are known to activate mechanically sensitive vagal afferent nerve subtypes innervating the airways or act in the nose or the esophagus, which when diseased are associated with coughing. That these stimuli do not evoke coughing in either humans or animals suggests that similar mechanisms and sensory nerves regulate coughing in all animals including humans.