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Afferent nerves regulating the cough reflex: Mechanisms and Mediators of Cough in Disease

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Abstract

Bronchopulmonary C-fibers and acid-sensitive, capsaicin-insensitive mechanoreceptors innervating the larynx, trachea and large bronchi regulate the cough reflex. These vagal afferent nerves may interact centrally with sensory input arising from afferent nerves innervating the intrapulmonary airways or even extrapulmonary afferents such as those innervating the nasal mucosa and esophagus to produce chronic cough or enhanced cough responsiveness. The mechanisms of cough initiation in health and in disease are briefly described.

Keywords

capsaicin; vagal; bradykinin; NMDA

The cough reflex protects the airways and lungs from aspiration, inhaled irritants, particulates and pathogens and clears the air spaces of accumulated secretions. Studies in animals provide conclusive evidence that cough is initiated by activation of vagal afferent nerves. Precisely which afferent nerve subtypes regulate cough has been debated and reviewed elsewhere [1]. In this review, we describe the stimuli that initiate cough and the mechanisms by which these stimuli activate airway sensory nerves. These data are related to the known physiological properties of bronchopulmonary afferent nerve subtypes. The review concludes with a discussion of the potential interactions between afferent nerve subtypes and the possible mechanisms of altered cough reflexes in disease.

Chemical and Mechanical Stimuli That Initiate Coughing

Multiple chemical and mechanical stimuli have been shown to initiate coughing in human subjects and in animals [1-4]. Several of these stimuli, including capsaicin, citric acid, hypertonic saline and low chloride buffers/ solutions, are often used to evoke cough experimentally. Other stimuli known to initiate coughing in animals and in human subjects include particulate/ dust, mechanical/ vibratory stimulation of the airway mucosa larynx or chest wall, chemical irritants such as resiniferetoxin, cinnamaldehyde and allylisothiocyanate (AITC), and the autacoids bradykinin, anandamide and prostaglandin E2 (PGE2). Although

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seemingly varied in origin and chemical composition, many of these stimuli share common modes of action. For example, acids/ protons, capsaicin, resiniferetoxin and anandamide all act in part or entirely by activation of the ion channel/ receptor TRPV1 [3,5-12]. Bradykinin and PGE2 may also act in part through TRPV1 activation [13-16]. Cinnamaldehyde, AITC, and several other known respiratory irritants (e.g. cigarette smoke, toluene diisocyanate) activate the ion channel TRPA1 [17-19]. Knowing the specific ion channels and receptors for the stimuli that initiate cough is important, as this information can be used to identify which afferent nerves express these ion channels and receptors. This information can then be used to identify possible mechanisms for coughing in disease but may also suggest therapeutic approaches to restore normal cough function and sensitivity (Table 1).

The stimuli that do not initiate coughing are equally helpful when attempting to identify the specific vagal afferent nerve subtypes that regulate this reflex (Table 2). These stimuli may also suggest a great complexity underlying the cough associated with disease. Consider, for example, three of the most common causes of chronic cough:

1. Asthma
2. Gastroesophageal reflux disease (GERD)
3. Upper airway inflammatory diseases (e.g. allergic rhinitis, sinusitis)

These conditions are often found simultaneously in patients with chronic cough [20,21]. While none of these disorders are adequately described by a single presenting symptom, it is generally agreed that reversible airways obstruction, acidic refluxate in the esophagus and inflammation of the upper airways are characteristics of asthma, GERD and upper airway diseases, respectively. Remarkably, however, bronchospasm, acid in the esophagus and upper airway challenges with a variety of inflammatory mediators are consistently ineffective at initiating cough in animals or human subjects [1,22-24]. The inability of these stimuli to initiate cough is not because they fail to activate sensory nerves. Histamine, capsaicin, allergen and bradykinin all initiate sneezing and reflex-dependent mucus secretion when delivered selectively to the upper airways, while the bronchoconstrictors histamine, substance P and even methacholine evoke reflex dependent changes in autonomic tone in the airways, changes in breathing pattern and respiratory sensations such as chest tightness and dyspnea [1,22,25,26]. Esophageal acidification is known to evoke reflex bronchospsam in animals and in human subjects but has rarely if ever been reported to initiate coughing [26-31]. Observations such as these argue against the afferent nerves responding to these stimuli as the primary initiators of cough in disease. This implies the involvement of other afferent nerves and afferent nerve subtype interactions in disease. Defining precisely how these afferent nerves interact to produce the coughing observed in diseases such as asthma and GERD are likely be critical to the development of better therapeutic strategies for the treatment of chronic cough.

Afferent nerves regulating the cough reflex

Coughing can be partitioned into at least four phases.

The initial phase comprises the encoding of action potentials by the afferent nerves directly responding to the tussive stimulus, and the subsequent reconfiguration of the respiratory motor drive within the brainstem. This initial phase immediately precedes any change in respiratory muscle activity.

The second phase is the enhanced inspiratory effort that accompanies cough.

The expiratory phase of cough has 2 components:

1. an initial compressive phase when expiration is initiated against a restricted or occluded upper airway
2. the expulsive phase, when the upper airways are dilated, allowing forceful expiration and the high airflow velocities that facilitate airway clearance

Depending on the stimulus and social situation, the number and forcefulness of the resulting coughs can vary substantially. Given this complexity and the multiple elements involved (lower and upper airways, respiratory muscles, brain stem), it is apparent that multiple afferent nerve subtypes act in concert to regulate the sensitivity, forcefulness and repetitions of coughs in response to all tussive stimuli. The discussion below focuses only on those afferents involved in the initial encoding phase of cough (Figure 1).

C-fibers

Bronchopulmonary C-fibers are identified physiologically by their action potential conduction velocity, which falls in the "C" range (≤1 m/ sec) of the compound action potential. C-fibers comprise the majority of afferent nerves innervating the airways and lungs, terminating in the mucosa and submucosa of the nose, pharynx, larynx, trachea, bronchi and throughout the lungs. C-fibers project to the airways from the jugular and nodose ganglia of the vagus nerves, and from thoracic dorsal root ganglia [1,32-34].

Bronchopulmonary C-fibers are activated by capsaicin, bradykinin (Figure 2), protons, nicotine and the TRPA1 agonists cinnamaldehyde and AITC. C-fibers are selectively desensitized by high dose capsaicin treatment, which also prevents coughing evoked by citric acid [35]. In guinea pigs, C-fibers utilize the peptide neurotransmitters substance P and neurokinin A, which act primarily via neurokinin$_1$ (NK_1), NK_2 and NK_3 receptors. Neurokinin receptor antagonists prevent coughing evoked in guinea pigs by capsaicin and citric acid [36-39]. These results and observations provide conclusive evidence that C-fiber activation initiates coughing.

Despite the overwhelming evidence that C-fiber activation can initiate coughing, the role of C-fibers in cough remains controversial. Much of the controversy arises from the inability of C-fiber selective stimuli to initiate coughing in anesthetized animals [1,22,26,40,41]. It seems likely that anesthesia selectively inhibits C-fiber dependent coughing. But anesthesia does not readily explain the observation that C-fiber activation not only fails to initiate coughing in anesthetized animals, but also actively inhibits coughing evoked by activation of other afferent nerves subtypes [40,41]. We speculated that these opposing effects of C-fibers on cough might be attributable to the opposing actions of C-fiber subtypes. Studies carried out in guinea pigs using stimuli that are selective for vagal C-fiber subtypes suggest that C-fibers arising from the nodose ganglia can acutely inhibit coughing while activation of C-fibers arising from the jugular ganglia sensitize or initiate coughing [42,43]. Circumstantial evidence suggests that C-fiber subtypes in humans play similar opposing roles [2,44-46].

Rapidly Adapting Receptors

Rapidly adapting receptors (RARs) are mechanoreceptors that respond to the dynamic physical forces associated with lung inflation and deflation. RARs are also activated by punctate mechanical stimuli and airway smooth muscle contraction [32,47-49]. The seminal work of Widdicombe has been interpreted as evidence that RARs play an essential role in the initiation of cough [47,50]. A critical reassessment of Widdicombe's studies suggests otherwise [51].

Central to the thesis that RARs play a role in the initiation of cough in anesthetized animals has been the inability of C-fiber selective stimuli to initiate cough, and the sensitivity of the cough reflex to vagal cooling temperatures that target myelinated afferent nerves such as RARs [41,47,50]. Slowly adapting receptors (SARs), the stretch receptors that regulate the Hering

Breuer reflex, are not implicated in the initiation of cough [1,47,50,51], and with C-fiber-selective stimuli failing to evoke cough and nearly all airway sensory nerve classification schemes limited to 3 types (C-fibers, RARs and SARs), RARs have been implicated largely by default [1,32,48-51]. But there is overwhelming evidence against a role for RARs in cough. Hyperventilation and maximal inspiratory efforts against a closed glottis, for example, are very effective at activating RARs and consistently ineffective at initiating cough [1,51]. Bronchoconstrictors such as histamine, neurokinin A, the cysteinyl-leukotrienes and even methacholine are also effective stimulants of RARs but rarely if ever initiate coughing [1,22, 49,51,52].

The imprecise semantics often used in describing airway afferent nerve subtypes likely contributes to the misconception that RARs regulate coughing. The term RAR is used to describe a variety of afferent nerve subtypes that differ substantially in peripheral termination sites, sensitivity to mechanical stimuli and in the reflexes initiated upon their activation. The term ‘rapidly adapting’, when used as a means of differentiating airway afferent nerve subtypes, should refer only to the response of afferent nerves to sustained lung inflation. Indeed, RARs adapt only modestly to smooth muscle contraction/ bronchoconstriction or lung deflation [1, 51]. By contrast, most bronchopulmonary afferent nerves adapt rapidly to punctate mechanical stimuli. Studies in guinea pigs and a reappraisal of Widdicombe’s work carried out in cats suggests that vagal afferent nerves that are distinct from RARs but possessing RAR-like characteristics likely regulate the coughing studied in anesthetized animals [49,51].

Cough Receptors

Coughing can be initiated in anesthetized animals by mechanically probing the laryngeal, tracheal or bronchial mucosa or by acid applied topically to the mucosa of these airways [22, 36,49-52]. C-fiber selective stimuli (e.g. capsaicin and bradykinin) consistently fail to initiate coughing, as does sustained lung inflation (which activates SARs) or the bronchoconstrictors histamine, neurokinin A and methacholine. Sustained or dynamic increases or decreases in intraluminal pressure in an isolated segment of the extrathoracic trachea also fails to initiate coughing, while acid applied topically to this tracheal segment readily initiates cough. Electrophysiological analyses combined with these physiological studies of cough suggest that a vagal afferent nerve subtype distinct from RARs, SARs and C-fibers plays an essential role in the initiation of cough [22,26,49,51].

The “cough receptors” are myelinated as evidenced by their action potential conduction velocity (~5 m/ sec) and terminate almost exclusively in the larynx, trachea and extrapulmonary bronchi. These afferents are insensitive to airway smooth muscle contraction or changes in intraluminal pressure, but are exquisitely sensitive to punctate mechanical stimuli. The cough receptors are also activated by acid and by the voltage-gated K+ channel blocker 4-aminopyridine [22,49].

Cough receptors terminate peripherally in the submucosa of the laryngeal, tracheal and bronchial mucosa [22,49,53,54]. The terminations of these afferents nerves branch extensively in a circumferential arbor, adhered the subepithelial matrix and largely uncoupled to the underlying smooth muscle. Their structure and sites of termination give the appearance of a spider adhered to its web, sensing mechanical stimuli transduced through the intricate structure of the extracellular matrix. Their sites of termination and sensitivity to acid and to punctate mechanical stimuli render the cough receptors ideally suited to protect the airways from aspiration and to facilitate clearance of accumulated secretions.

Physiological and pharmacological studies have identified several mechanisms regulating cough receptor excitability [22,49,54,55]. The cough receptors are insensitive to capsaicin and bradykinin and not surprisingly, therefore, do not express the capsaicin receptor TRPV1. Acid

activates the cough receptors, perhaps through gating of Acid-Sensing Ion Channels (ASICs). Other regulatory mechanisms identified on the peripheral terminals of the cough receptors include unique isozymes of Na+-K+-ATPase and the Na+-K+-2Cl- transporter as well as voltage-gated sodium and chloride channels. Centrally, the cough receptors utilize glutamate acting via NMDA and nonNMDA receptors to initiate coughing [1,56].

Afferent Nerve Interactions in Cough and Mechanisms of Cough in Disease

There is considerable evidence for vagal afferent nerve convergence onto subpopulations of relay neurons in the nucleus of the solitary tract (nTS). Such convergence may account for the imprecise nature of visceral reflexes, whereby vagal afferent nerve activation in one organ reflexively initiates changes in autonomic outflow to other organs [57-59]. Similar interactions likely regulate the cough reflex and may explain the extrapulmonary origins of cough in some patients.

Studies carried out in guinea pigs suggest that bronchopulmonary C-fibers and cough receptors may act synergistically to regulate coughing [43]. As discussed previously, C-fiber activation is consistently ineffective at initiating cough in anesthetized animals. But C-fiber activation coincident with cough receptor stimulation produces a heightened sensitivity to tussive challenge (Figure 3). This sensitizing effect of C-fiber activation is similar to the central sensitization attributed to somatic C-fibers in models of pain [60]. Like central sensitization in somatic tissues, neurokinin receptor antagonists prevent the sensitizing effects of bronchopulmonary C-fiber activation in cough.

Vagal afferent nerve interactions may account for the coughing attributed to gastroesophageal reflux disease. Refluxate or acid in the esophagus are very ineffective at initiating cough in animals or in human subjects and refluxate rarely reaches the airways or even the pharynx. But acid or capsaicin infusion into the esophageal lumen markedly enhances airway sensitivity to tussive stimuli [61,62]. This sensitizing effect of acid or capsaicin in the esophagus on subsequently evoked cough suggests that in patients presenting with GERD cough, in addition to the sensitizing refluxate in the esophagus, some tussive stimuli or condition within the airways ultimately initiates coughing. Evidence for airway inflammation in GERD has been presented [63-66]. A similar sensitizing effect on cough may also account for the coughing associated with upper airways diseases [67].

Synopsis

The cough reflex is initiated by activation of bronchopulmonary C-fibers and the mechanically-sensitive cough receptors. Stimuli initiating cough through activation of one or both of these vagal afferent nerves include capsaicin, acid, bradykinin, cinnamaldehyde, cigarette smoke and non-isotonic aerosols. Multiple ion channels and cell surface receptors regulating the response to these tussive stimuli have been identified. The cough receptors and C-fibers may interact centrally to produce a heightened sensitivity to challenge. Interactions of afferent pathways innervating the esophagus and upper airways may contribute to the heightened cough sensitivity in chronic diseases such as GERD, asthma and upper airways disorders.

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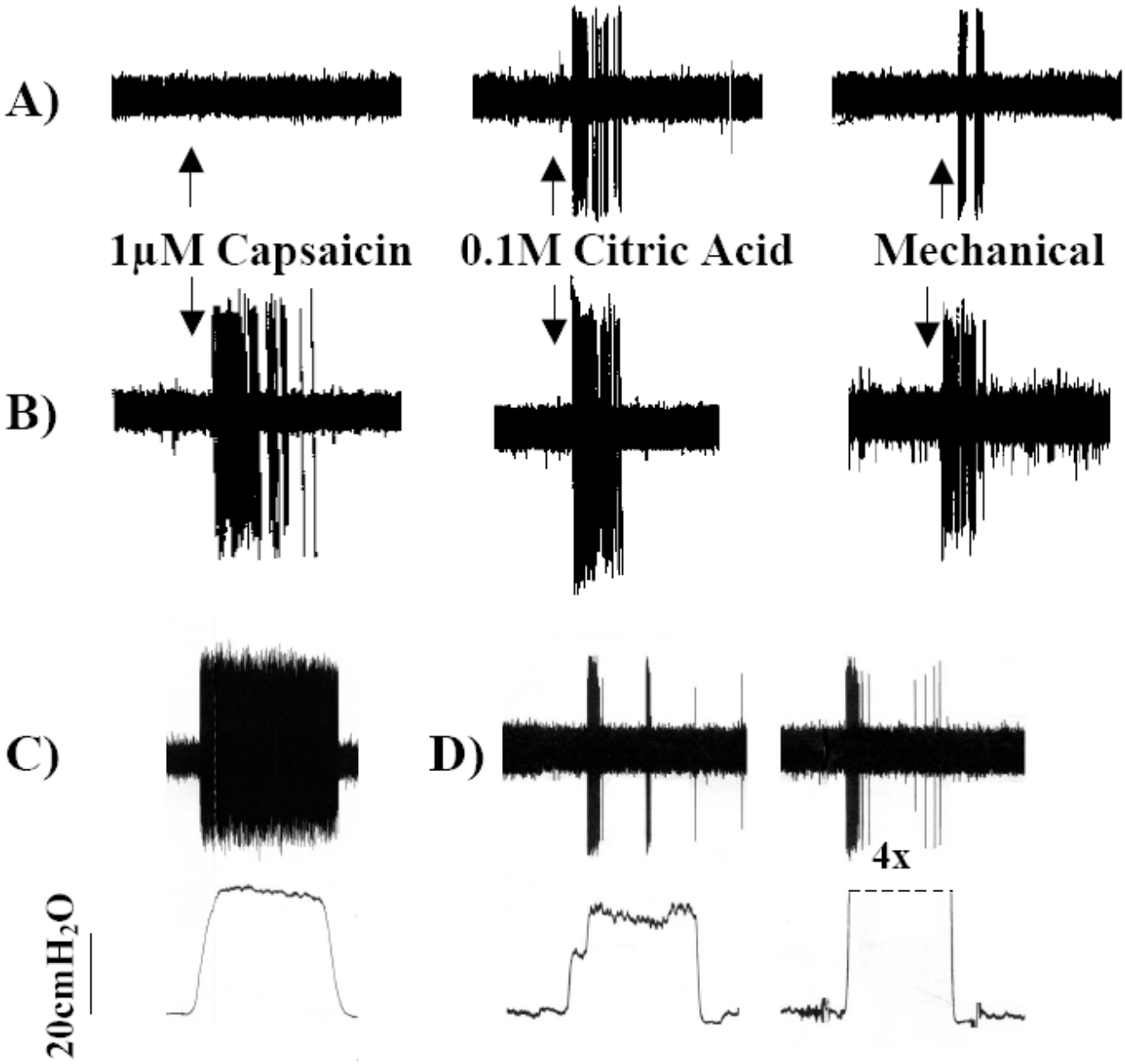

Figure 1.

Representative extracellular recordings from the vagal afferent nerve subtypes innervating the airways and lungs. **A**) The cough receptors innervate the larynx, trachea and mainstem bronchi. They are insensitive to capsaicin, airway smooth muscle contraction (not shown) and distending or collapsing airway luminal pressures (not shown) but are activated by punctate mechanical stimulation and acid. When activated, these afferent nerves initiate coughing. **B**) Bronchopulmonary C-fibers terminate throughout the airways and lungs. C-fibers are less sensitive to mechanical stimulation than other airway afferent nerves but are activated by chemical stimuli such as capsaicin, bradykinin, acid and adenosine. When activated, C-fibers initiate coughing, changes in respiratory pattern and autonomic reflexes (e.g. airway smooth muscle contraction, mucus secretion. C-fiber subtypes have been described. **C**) Slowly adapting receptors are active during the dynamic and static phases of lung inflation. Slowly

adapting receptor activation initiates respiratory slowing but does not initiate coughing. **D**) Rapidly adapting receptors are active during the dynamic phases of lung inflation and deflation and are activated by airway smooth muscle contraction/ bronchospasm and lung collapse/ negative airway luminal pressures. Rapidly adapting receptor activation initiates parasympathetic reflexes such as mucus secretion and airway smooth muscle contraction as well as tachypnea.

Figures are reproduced with permission from Canning et al., 2004 (49). Canning BJ, Mazzone SB, Meeker SN et al. Identification of the tracheal and laryngeal afferent neurones mediating cough in anaesthetized guinea-pigs. J Physiol 2004;557:543-58.

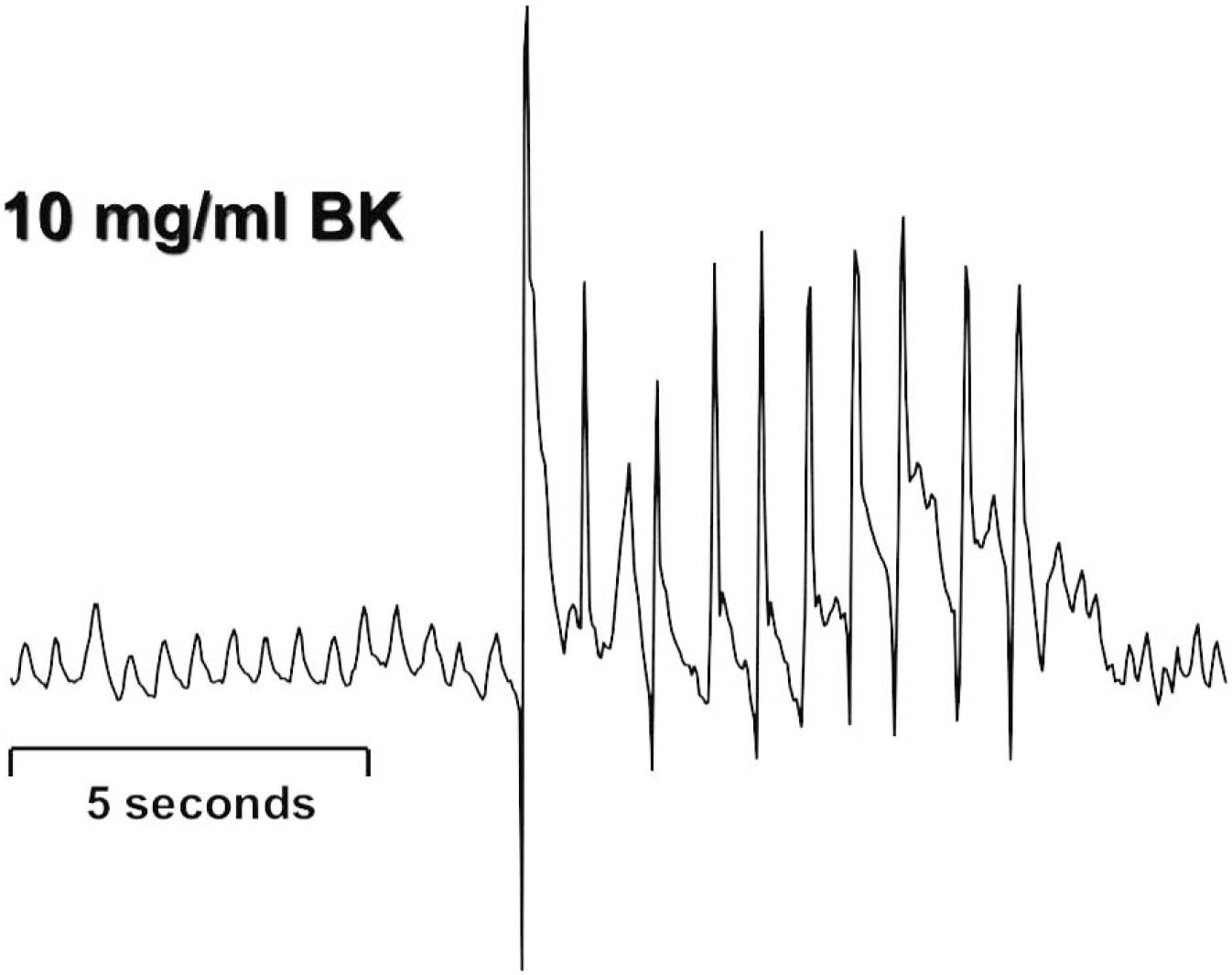

Figure 2.

A representative trace of coughing recorded from a guinea pig following exposure to an aerosol of bradykinin aerosol is shown. Many animal species cough in response to the same stimuli that initiate coughing in human subjects. This permits more mechanistic studies of the cough reflex and has led to the development of novel therapeutic strategies for the treatment of cough. The figure is reproduced with permission from Canning et al. (49). Canning BJ, Mazzone SB, Meeker SN et al. Identification of the tracheal and laryngeal afferent neurones mediating cough in anaesthetized guinea-pigs. J Physiol 2004;557:543-58.

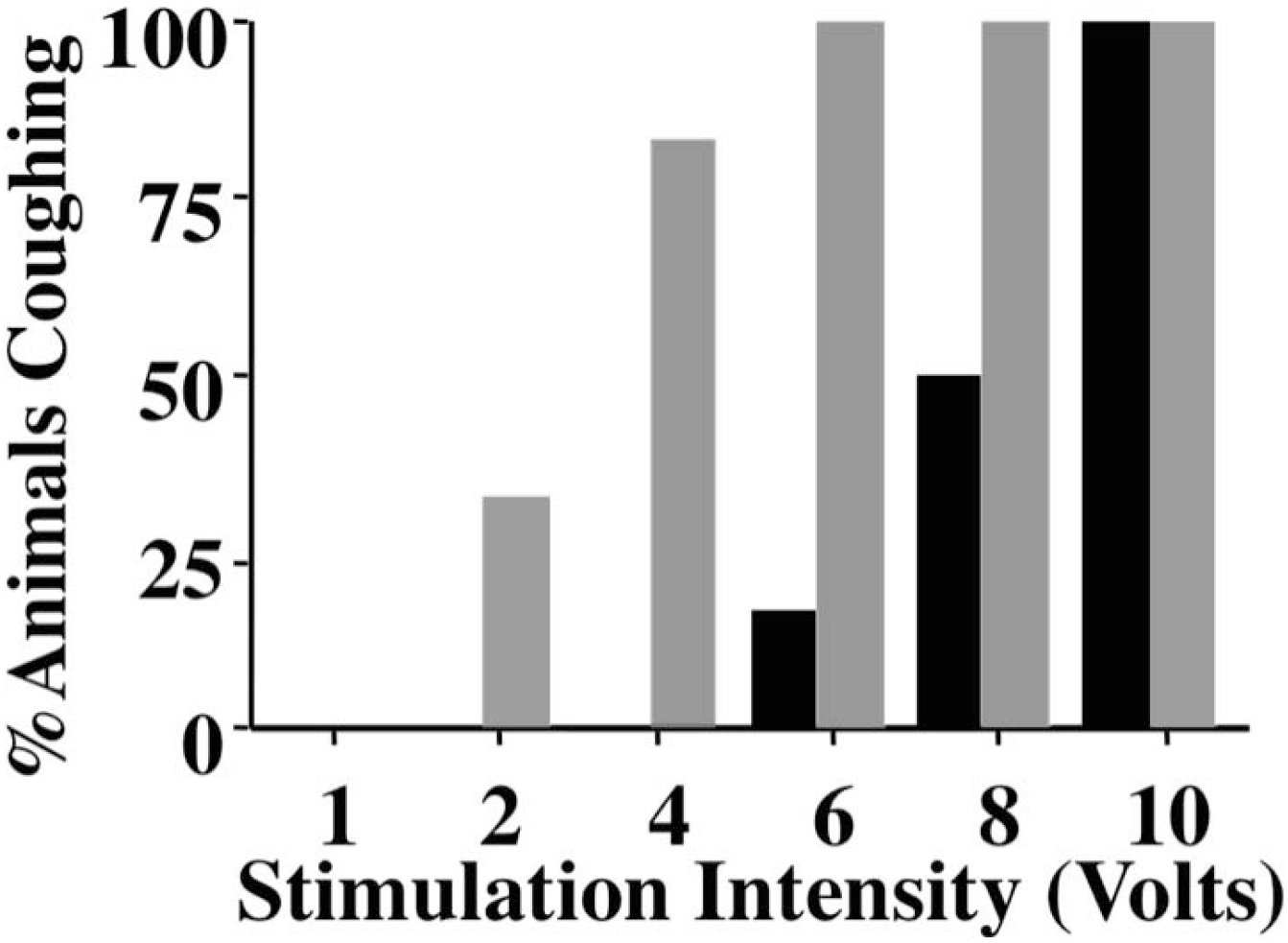

Figure 3.

Cough reflex sensitivity can be enhanced by coincident activation of airway afferent nerve subtypes. Coughing was evoked electrically from the tracheal mucosa of anesthetized guinea pigs. Optimal stimulation frequencies (16 Hz) and pulse duration were maintained during 10 second stimuli delivered at varying stimulation voltages. The percentage of animals coughing at various voltages was determined in animals inhaling saline (black bars) or the C-fiber stimulant bradykinin (1mg/ mL; grey bars).

This graph is reproduced with permission from Mazzone et al. (43).

Mazzone SB, Mori N, Canning BJ. Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. J Physiol 2005;569:559-73.

Table 1

Stimuli Initiating Cough: Mode of Action and Afferent Nerve Targets.

Stimulus	Mode of Action	Afferent nerves targeted
Capsaicin	TRPV1	C-fibers
Bradykinin	Bradykinin B2 receptors	C-fibers
Acid	TRPV1, Acid-Sensing Ion Channels	C-fibers, cough receptors
Particulates	Unknown	Cough receptors, C-fibers
TRPA1 agonists	TRPA1	C-fibers
Prostaglandin E2	Prostaglandin EP3 receptors	C-fibers
Nicotine	Nicotinic Receptors	C-fibers

Abbreviations: TRPV1: transient receptor potential vanilloid 1; TRPA1: transient receptor potential ankyrin 1

Table 2

Stimuli that do not initiate cough: Reflexes evoked, afferent nerves activated.

Stimulus	Reflexes evoked	Afferent nerves targeted
Bronchoconstriction *(1)*	mucus secretion, tachypnea	RARs
Esophageal acid	bronchospasm, mucus secretion	Esophageal nociceptors
Upper airway stimulation	Sneeze, mucus secretion	Trigeminal afferent nerves
Inc. airway luminal pressure	Respiratory slowing	SARs
Dec. airway luminal pressure	Tachypnea	RARs
Adenosine	Tachypnea, dyspnea	RARs, C-fibers
Pulmonary embolism	Tachypnea, dyspnea	RARs, C-fibers

(1) Bronchoconstrictors including histamine, methacholine, leukotriene D4, thromboxane A2 and neurokinin A fail to reliably evoke coughing in humans or in animals despite initiating reflex bronchospasm and mucus secretion, an increase in respiratory rate and dyspnea. Abbreviations: Inc.: Increase; Dec.: Decrease; RARs: Rapidly adapting receptors; SARs: slowly adapting receptors