

# 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 chloralase) 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

**Table 1** Tracheal, bronchial, and lung stretch receptor subtypes in cats identified by Widdicombe

	Slowly adapting receptors	Rapidly adapting receptors <sup>a</sup>	Intermediate receptors
<i>Stretch receptors responsive to whole lung inflation</i>			
Adaptation index	<70	≥70	
Response to lung deflation	Not activated	Activated	
Pressure/volume threshold	Low	Moderate	
Tracheal/bronchial inflation	Not activated	Activated	
Tracheal/bronchial deflation	Not activated	Activated	
Termination sites	Peripheral airways/lung	Trachea/carina/ mainstem bronchi	
<i>Stretch receptors responsive to tracheal/bronchial inflation and deflation<sup>a</sup></i>			
Pressure/volume threshold	Low	Not assessed	High
Active at eupnea	Yes	No	No
Termination site	Bronchi	Trachea/carina	Trachea/bronchi
Tracheal/bronchial mucosal probing	Unresponsive	Activated	Activated
Sulfur dioxide inhalation	11% sensitized	15% sensitized	80% sensitized
Powder inhalation	Not activated	Activated	Not activated
Response to topical anesthesia	Insensitive	Sensitive	Moderately sensitive
Response to repetitive stimulation	Sustained	Sustained	Decrementing

<sup>a</sup>Rapidly adapting receptors as defined by whole lung inflation correspond to the tracheal/bronchial stretch receptors described in the lower portion of the table. Many of the attributes listed (e.g., activated, not activated, low, high) are generalized, not uniformly expressed in each subtype. See the text for further details

of 40 or less. Amongst all fibers classified as *slowly adapting receptors* (SARs; adaptation index of less than 70), just 19% responded to lung deflation. The majority of SARs could be activated by mechanically probing the lung but not by tracheal/bronchial distension, suggesting a peripheral lung termination. About 80% of *rapidly adapting receptors* (RARs; defined by an adaptation index 70 or more) responded to lung deflation. Vagal cooling poorly differentiated the subtypes, while distension/volume thresholds were positively correlated with adaptation index.

Using catheters that allowed partition of the airways into pulmonary and tracheal/mainstem bronchial segments, each region subject to selective distension, and the trachea and bronchi accessible to mechanical probing, Widdicombe subsequently localized the terminals of RARs (as defined by whole lung inflation). In contrast to SARs, RARs terminated in the trachea and bronchi, not in the lung. When only the trachea and bronchi were distended, a highly heterogeneous group of afferent nerves was identified. The physiological properties of 166 such stretch receptors innervating the trachea and bronchi (thus differentiating this study from those of Adrian and of Knowlton and Larrabee (Adrian 1933; Knowlton and Larrabee 1946) were then characterized. Three subtypes were identified. Half of the tracheal and bronchial stretch receptors (82/166) gave a regular discharge in response to modest lung inflations and deflations. Adaptation indices amongst this group of stretch receptors

varied widely, with about half of those fully characterized having adaptation indices to tracheal/bronchial inflation of 0–50%. Receptor discharge amongst these tracheal/bronchial SARs increased or decreased incrementally as the tracheal pressure was altered. Most (approximately 90%) SARs in Widdicombe's analysis of the tracheal/bronchial stretch receptors terminated in the mainstem bronchi. Tracheal/bronchial SARs were unaffected by topically applied procaine, just partially inhibited by ether vapor, and only modestly responsive to mechanical stimulation of the airway mucosa.

The two additional subtypes of tracheal and bronchial stretch receptors were described as RARs (46 of 166 fibers) and intermediate receptors (38 of 166). The tracheal and bronchial RARs produced a burst of activity only during the dynamic phases of either inflation or deflation of the trachea/bronchi, all having an adaptation index of 100%. The RARs were more responsive to airway deflation than inflation. The majority (approximately 90%) of tracheal/bronchial RARs terminated in the trachea or carina. Topically applied procaine and ether vapor prevented RAR discharge but had little effect on the other tracheal/bronchial stretch receptors. RARs were also more responsive to dust/powder inhalation and to punctate mechanical stimulation of the airway mucosa than the other airway stretch receptor subtypes. As the name suggests, the intermediate receptors had characteristics of both RARs and SARs, but with one significant difference being a progressive diminution of responsiveness to repeated airway inflations/deflations. The ability of sulfur dioxide to *sensitize* the majority (80%) of intermediate receptors to airway distension or collapse relative to its inability to sensitize tracheal/bronchial RARs (15%) or SARs (11%) to airway pressure changes also differentiated this subtype from the other tracheal/bronchial stretch receptors. Intermediate receptors were distributed throughout the trachea, carina, and bronchi and had inflation pressure thresholds for activation nearly 10 times that of the tracheal/bronchial or pulmonary SARs.

Because the tracheal/bronchial RARs identified by Widdicombe were most responsive to negative luminal pressures, their inflation pressure thresholds were not evaluated. It is also unclear whether tracheal/bronchial RARs and intermediate receptors would have been activated by whole lung inflation unless very high intratracheal pressures were sustained (see later).

Taken together and using responsiveness to whole lung and then tracheal/bronchial inflation and deflation for differentiation, Widdicombe described at least four subtypes of airway and lung stretch receptors in his initial studies: pulmonary SARs, tracheal/bronchial SARs (which adapt rapidly to whole lung inflation), tracheal/bronchial RARs, and intermediate receptors, with characteristics of both the tracheal/bronchial RARs and SARs (Table 1). In subsequent studies, Widdicombe and colleagues (Mills et al. 1969, 1970; Sellick and Widdicombe 1969, 1971; Widdicombe et al. 1962) described another subtype of stretch receptor, the lung irritant receptors, also known as the intrapulmonary RARs, which are described in a subsequent section. Only the pulmonary and tracheal/bronchial SARs and the intrapulmonary RARs (lung irritant receptors) are thought to have any activity at eupnea (owing to their low pressure thresholds). On the basis of the characteristics of the subtypes described above and parallel studies of the stimuli initiating cough,

Widdicombe concluded that tracheal/bronchial RARs and intermediate receptors regulate the coughing initiated by mechanical and chemical (sulfur dioxide) stimulation, respectively. These conclusions have not been refuted in the more than 50 years that have passed since their original publication.

In several places throughout the text of these papers, Widdicombe used the term “cough receptor” to describe the vagal afferent nerves that were activated by stimuli that initiated cough (Widdicombe 1954a,c). Used sparingly by Widdicombe and other physiologists since, the term has nevertheless achieved some degree of acceptance in the clinical literature but with little regard for what specific afferent nerves are being described (Barry et al. 1997; Chang et al. 1996; Fujimura et al. 1992, 1993; Malik et al. 1978). There are several arguments against using this term to describe an airway afferent nerve subtype. For starters, the term is nonsensical, and read literally may conjure images of one’s hands, or perhaps handkerchief, amongst the more refined. Second, it is nonspecific, and might prompt grouping of afferent nerve subtypes that can all initiate coughing upon activation but otherwise share no other physiological attributes. The term is also limiting, implying that these afferents may subserve no other reflex functions, and also implying a somewhat circular approach to characterization. Yet for better or worse, it seems, cough researchers are stuck with the term “cough receptor.” If so, then *cough receptor* should refer only to afferent nerves with attributes similar to those of the tracheal/bronchial RARs and intermediate receptors identified by Widdicombe, and should not be used to describe any other afferent nerve subtypes implicated in cough (e.g., C-fibers, intrapulmonary RARs) but possessing their own unique physiological characteristics.

### **3 Identification of the Afferent Nerves Regulating Cough in Anesthetized Guinea Pigs**

Guinea pigs have become the most frequently used species in studies of cough despite the fact that up until the past decade or so very little information about the physiological properties of their airway and lung afferent nerves had been published. Most cough studies in guinea pigs have been carried out in conscious animals, arguably the most clinically relevant approach for pharmacological analysis but providing limited physiological insight (Belvisi and Bolser 2002; Canning 2008; Karlsson and Fuller 1999; Lewis et al. 2007). Still, there are many advantages to the guinea pig for cough research. Guinea pigs can be used in both conscious and anesthetized models of cough, largely infeasible in cats and dogs (because it is difficult to study conscious cough in these species), or in human subjects and nonhuman primates (because the desirable, invasive aspects of cough studies done in anesthetized animals are generally not possible in humans or nonhuman primates). Guinea pigs are also small enough (as are rabbits, cats, and the rodents rats and mice; guinea pigs may not be rodents; D’Erchia et al. 1996) such that stereotaxic methods for studying central processes relevant to cough can be employed, as well as tracing and in

vitro electrophysiological studies. Guinea pigs also cough to the same stimuli (e.g., capsaicin, bradykinin, acid, punctate mechanical stimuli) that initiate coughing in human subjects, while there is some controversy as to whether mice or rats cough (Belvisi and Bolser 2002; Kamei et al. 1993; Ohi et al. 2004; Tatar et al. 1996, 1997). Studies from the laboratories of Advenier, Belvisi, Bolser, Chung, Fujimura, Kamei, Karlsson, McLeod, Morice, Sekizawa, Tatar and colleagues, and others have defined the pharmacology and pathophysiology of cough in guinea pigs (Bolser et al. 1991, 1994, 1997; Daoui et al. 1998; El-Hashim and Amine 2005; Forsberg et al. 1988; Fox et al. 1996; Gatti et al. 2006; Girard et al. 1995; Hara et al. 2008; Jia et al. 2002; Kamei and Takahashi 2006; Kamei et al. 2005; Karlsson et al. 1991a,b; Laloo et al. 1995; Laude et al. 1993; Leung et al. 2007; Lewis et al. 2007; Liu et al. 2001; McLeod et al. 2001; O'Connell et al. 1994; Pinto et al. 1995; Plevkova et al. 2004; Tatar et al. 1996, 1997; Trevisani et al. 2004; Xiang et al. 2002). These advantages and the careful electrophysiological analyses by Bergren (Bergren 1997, 2001; Bergren et al. 1984; Bergren and Kincaid 1984; Bergren and Myers 1984; Bergren and Sampson 1982), Fox (Fox et al. 1993, 1995), Joad (Bonham et al. 1995, 1996; Joad et al. 1997, 2004; Mutoh et al. 1999), Tsubone (Sano et al. 1992; Tsubone et al. 1991), Undem (Canning et al. 2004; Chuaychoo et al. 2005, 2006; Kollarik and Undem 2002; Lee et al. 2005; McAlexander et al. 1999; McAlexander and Undem 2000; Riccio et al. 1996; Ricco et al. 1996; Undem et al. 2004), and colleagues have made it feasible to identify the afferent nerves regulating cough in guinea pigs.

Working from the pre-existing knowledge base about laryngeal, tracheal, and bronchial afferent nerves in guinea pigs, Canning et al. (2004) established a model in anesthetized guinea pigs whereby cough could be evoked electrically, mechanically, or by acid applied topically to the laryngeal and tracheal mucosa. Capsaicin or bradykinin applied topically to the tracheal mucosa of these anesthetized guinea pigs did not evoke coughing. It was also observed that cutting the recurrent laryngeal nerves prevented cough evoked from the rostral trachea and larynx, while cutting the superior laryngeal nerves was without effect. A subsequent analysis of the responsiveness and projections of the various afferent nerve subtypes innervating the trachea and larynx was compared with the results of these cough studies. Responsiveness to mechanical and acid stimulation did not reliably differentiate the afferents that regulate cough, nor did recurrent laryngeal nerve transections. Thus, all three known tracheal/laryngeal afferent nerve subtypes project axons to the trachea and larynx via the recurrent laryngeal nerves, and all subtypes, albeit with varying sensitivities, are responsive to acidic and mechanical stimuli (Kollarik and Undem 2002; Ricco et al. 1996; Undem et al. 2004). But the inability of capsaicin or bradykinin to acutely initiate coughing when applied topically to the tracheal and laryngeal mucosa of anesthetized guinea pigs strongly implicated the capsaicin-insensitive afferent nerves arising from the nodose ganglia (Myers et al. 2002; Ricco et al. 1996). Conversely, the inability of the superior laryngeal nerves to sustain a cough reflex following recurrent laryngeal nerve transection argued against afferent nerves arising from the jugular ganglia, given that very few nodose ganglia neurons project to the airways via the superior laryngeal nerves, while about half

of the jugular ganglia neurons innervating the larynx and rostral trachea project to these airways via the superior laryngeal nerves. The evidence described above combined with the inability of capsaicin desensitization (which renders jugular ganglia neurons unresponsive to any stimuli) to prevent electrical-, mechanical-, or acid-induced coughing led to the conclusion that the capsaicin-insensitive nodose ganglia neurons innervating the trachea and larynx were both sufficient and necessary for initiating the cough reflex in anesthetized guinea pigs (Canning et al. 2004).

The nodose ganglia neurons innervating the larynx, trachea, and mainstem bronchi of guinea pigs had in previous studies by Undem and colleagues been called RARs on the basis of their response to punctate mechanical stimuli (McAlexander et al. 1999; Myers et al. 2002). To better define these afferent nerves regulating cough, we compared their physiological properties with those of intrapulmonary receptors innervating the guinea pig airways and lungs. Using a whole lung preparation, we identified intrapulmonary afferent nerve subtypes that adapted either rapidly or slowly to distending pressures applied to the trachea. Like the tracheal afferent nerves regulating cough, both stretch receptor subtypes innervating the intrapulmonary airways and lung had cell bodies in the nodose ganglia. But in contrast to the tracheal/bronchial cough receptors, which have axonal conduction velocities of approximately  $5 \text{ ms}^{-1}$ , the intrapulmonary stretch receptors have axon conduction velocities of approximately  $16 \text{ ms}^{-1}$ . Other differences, including responsiveness to distending pressures, airway smooth muscle contraction, and ATP receptor activation, led to the conclusion that the afferent nerves regulating cough evoked from the trachea and larynx are distinct from the well-defined RARs, SARs, and C-fibers of the airways and lungs (Canning et al. 2004).

The afferent nerves regulating cough in guinea pigs are similar to those described by Widdicombe in the cat (Widdicombe 1954a). Differences may, however, exist. Widdicombe's studies leave it unclear whether all of the fibers responding to tracheal/bronchial pressure changes and comprising three tracheal/bronchial subtypes would have been identified as RARs in whole lung inflation studies (Widdicombe 1954a). In the guinea pig, cough receptors are unresponsive to changes in luminal pressure (Canning et al. 2004). In fact, the cough receptors described in cats were activated by selective tracheal/bronchial distension or collapse, stimuli that reportedly caused cough in this species, whereas the guinea pig cough receptors were insensitive to airway pressure changes, even highly unphysiological distending and collapsing pressures, and these pressure changes also failed to cause cough in guinea pigs. This may simply reflect the physical/structural differences in cat and guinea pig airways. It is also possible, however, that the apparent species difference is nonexistent. Thus, of the eight RARs (as identified by whole lung inflation) characterized by Widdicombe using both whole lung and tracheal/bronchial lung inflation and prompting his conclusion that lung RARs were in fact tracheal/bronchial stretch receptors, all eight were described as SAR-type tracheal/bronchial stretch receptors (Widdicombe 1954a). The tracheal/bronchial SARs are essentially identical in sites of termination (bronchi) and function to the intrapulmonary RARs described by Widdicombe in subsequent studies (Mills et al. 1969, 1970; Sellick and Widdicombe 1969, 1971). They are also the only



tracheal/bronchial stretch receptor subtype *not* implicated in cough in cats by this investigator, and they represent only about half of the stretch receptors activated by tracheal bronchial luminal pressure changes. Also, while Widdicombe stated in the text that changes in tracheal/bronchial luminal pressures evoked coughing, the data presented in support of this assertion are not convincing (Widdicombe 1954c). As the reader can test, forceful expiratory and inspiratory efforts against a closed glottis can generate very large positive and negative airway pressures and sensations, and yet does not evoke coughing (Davies et al. 1984; Green and Kaufman 1990; Rao et al. 1981). In fact, Widdicombe argued against the notion that luminal pressure changes were a relevant stimulus for initiating cough, given the high pressure thresholds for the tracheal/bronchial RARs and intermediate receptors (Widdicombe 1954a, 1954c).

Widdicombe's studies in anesthetized cats (Widdicombe 1954a, 1954c) and our studies in anesthetized guinea pigs (Canning et al. 2004) concluded that the afferent nerves that regulate cough were myelinated (on the basis of axonal conduction velocities or sensitivity to vagal cooling). It has not been established whether the axons of cat cough receptors are also relatively slowly conducting (approximately  $5\text{ ms}^{-1}$ ), as in guinea pigs. It is also unclear whether the cough receptors in cats are insensitive to smooth-muscle contraction, as are guinea pig cough receptors, in contrast to the intrapulmonary RARs in all species (see later).

Through the combination of electrophysiological studies with intravital labeling methods, retrograde neuronal tracing, organotypic cultures, and immunohistochemistry, the peripheral terminals of cough receptors in the guinea pig trachea and bronchus have been identified (Canning et al. 2006b). Terminating between the epithelium and smooth-muscle layers of the airways mucosa, the cough receptors assume a circumferential position in the extracellular matrix. Branching is extensive at the terminals, with axons projecting from longitudinal nerve bundles through the smooth-muscle layer. Similar structures have been described in the airway mucosa of other species but their identity as cough receptors is unclear (De Proost et al. 2007; Gaylor 1934; Larsell 1921, 1922; Yamamoto et al. 1995; Yu 2005). Immunohistochemistry confirms the selective expression of subtypes of  $\text{Na}^+-\text{K}^+-\text{ATPase}$  and  $\text{Na}^+-\text{K}^+-2\text{Cl}^-$  transporter in guinea pig cough receptors (Canning et al. 2006b; Mazzone and McGovern 2006). More recently, Tetrodotoxin-insensitive  $\text{Na}^+$  channels have been localized to these cough receptors (Kwong et al. 2008). Pharmacological analyses suggest that these regulators of ion flux and gradients, as well as  $\text{Cl}^-$  channels and voltage-sensitive  $\text{K}^+$  channels may be critical to the regulation of cough receptor responsiveness to chemical (acid) and punctate mechanical stimuli (Canning 2007; Canning et al. 2006a; Fox et al. 1995; Mazzone and McGovern 2006; McAlexander and Undem 2000). No other stimuli thus far studied, including a variety of autacoids and neurotransmitters and ion channel modulators, alter cough receptor excitability or the ability of acid or mechanical stimuli to initiate coughing in guinea pigs.

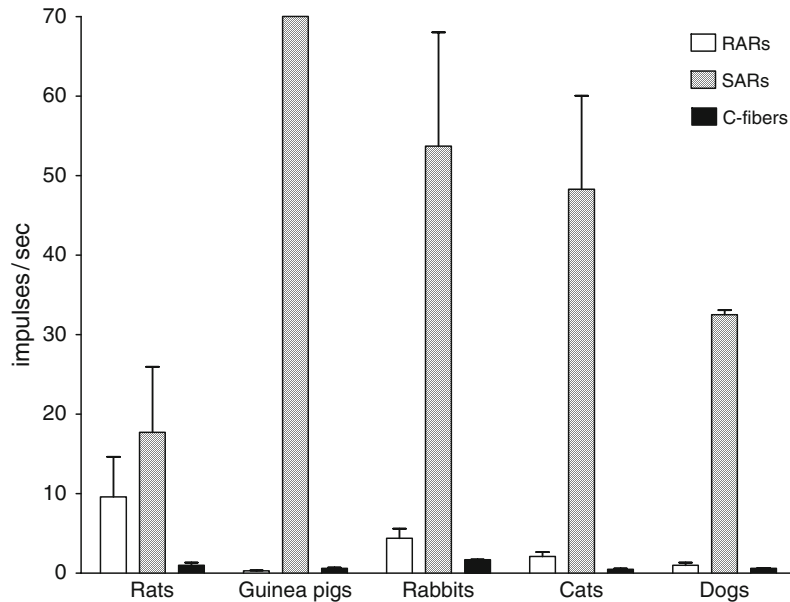


#### 4 Intrapulmonary Rapidly Adapting Receptors

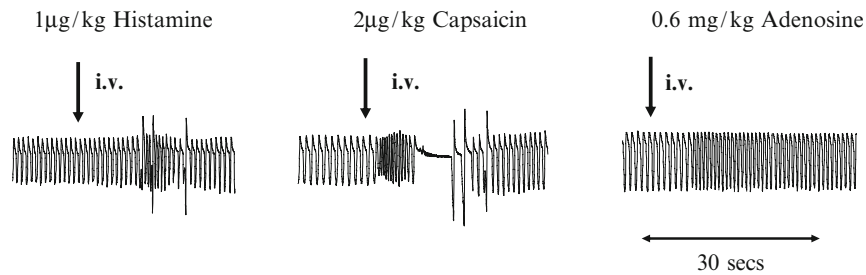
The term “rapidly adapting receptor” (RAR) was originally used to describe a subtype of airway and lung stretch receptor that is activated during the dynamic phase of lung inflation, but that unlike SARs becomes quiescent during static lung inflation (Knowlton and Larrabee 1946; Widdicombe 1954a). While elegant in clarity and as a means of differentiating the stereotypical responses of these subtypes of airway sensory nerves to this specific stimulus, the term “rapidly adapting” has also been the source of considerable confusion. Often, describing an afferent nerve as *rapidly adapting* or *slowly adapting* based on responsiveness to one stimulus fails to adequately describe the properties of the spectrum of afferent nerves captured by this term (Canning et al. 2004; Widdicombe 1954a; Yu 2000, 2005). Indeed, there are reports of rapidly adapting SARs (Bergren and Peterson 1993; Widdicombe 1954a; Yu 2000, 2005). Other studies have shown that RARs, as defined by their response to static lung inflation, may adapt very slowly to lung deflation, airway smooth muscle contraction, pulmonary embolism, and carbon dust inhalation (Armstrong and Luck 1974; Bergren 1997; Canning et al. 2004; Ho et al. 2001; Mills et al. 1969, 1970; Sellick and Widdicombe 1969, 1971; Widdicombe, 1954a). Still another problem is use of the term “rapidly adapting receptors” to describe subtypes of airway sensory nerves (extrapulmonary *irritant* receptors (cough receptors), intrapulmonary irritant receptors or RARs) that share few physiological or morphological properties (Canning et al. 2004; Sellick and Widdicombe 1969, 1971; Widdicombe 1954a). Thus, in this review article, the term “rapidly adapting receptor” refers only to those intrapulmonary stretch receptors that rapidly adapt to sustained lung inflation.

Intrapulmonary RARs in most species display some activity during the dynamic phase of inspiration. Basal activity in RARs varies widely within and amongst species (Fig. 1), which may reflect heterogeneity of this subtype but also in how these receptors are defined. In general, RARs are considerably less active than SARs but more active than C-fibers during tidal breathing. Given their response to lung stretch/inflation, it is perhaps not surprising that RARs are activated (either directly or indirectly) by a variety of mechanical stimuli in the lung, including airway smooth muscle contraction, pulmonary edema, decreased lung compliance, lung collapse, and negative airway luminal pressures. The responsiveness of RARs to airway smooth muscle contraction implies that RARs may be associated with airway smooth muscle. Direct evidence for such an association in the intrapulmonary airways is, however, lacking, as there are no morphological studies adequately identifying the peripheral terminals of RARs.

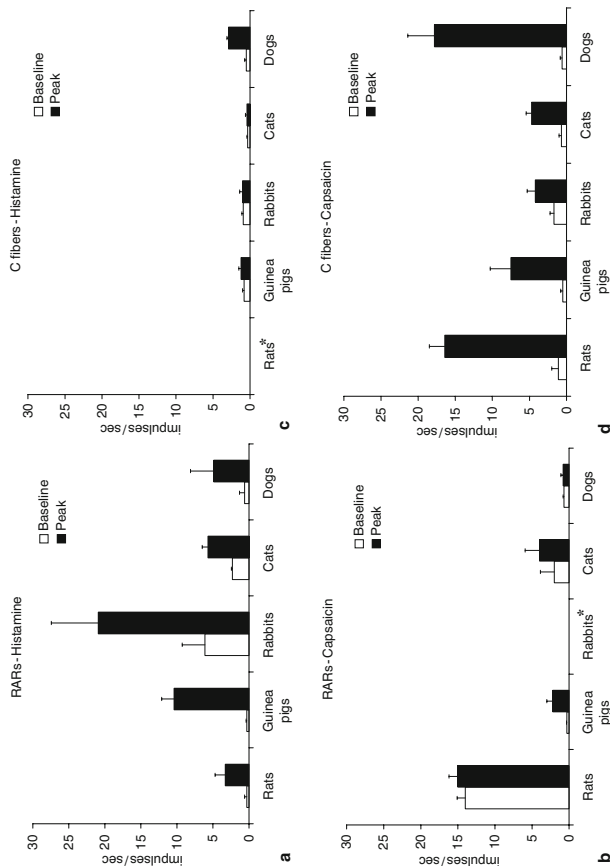
Intrapulmonary RAR activation initiates bronchospasm and mucus secretion via parasympathetic reflexes and tachypnea, characterized by decreased postexpiratory/preinspiratory pause (Canning et al. 2001; Haxhiu et al. 1997, 2000; Mills et al. 1969; Raj et al. 1995; Widdicombe et al. 1962; Yu et al. 1989) (Fig. 2). But intrapulmonary RAR activation does not initiate coughing. Intrapulmonary RAR stimulants, including lung deflation/collapse, pulmonary embolism, decreased lung compliance, and airway smooth muscle contraction, are highly ineffective at initiating cough in either conscious or anesthetized animals or humans (Canning et al.



**Fig. 1** Basal activity of rapidly adapting receptors (RARs), slowly adapting receptors (SARs), and C-fibers during tidal breathing in various species (Adcock et al. 2003; Armstrong and Luck 1974; Bergren 1997, 2001; Bergren and Peterson 1993; Bonham et al. 1995; Coleridge and Coleridge 1977, 1984; Coleridge et al. 1965, 1983; Davies et al. 1996; Delpierre et al. 1981; Green et al. 1986; Gu et al. 2003; Gu and Lee 2002; Hargreaves et al. 1993; Ho et al. 2001; Jonzon et al. 1986; Karlsson et al. 1993; Kaufman et al. 1980; Kunz et al. 1976; Lee and Morton 1993; Lin and Lee 2002; Matsumoto 1997; Matsumoto et al. 1990; Mills et al. 1970; Mohammed et al. 1993; Paintal 1969; Sellick and Widdicombe 1971; Vidruk et al. 1977; Yu et al. 1987, 1987, 1991)

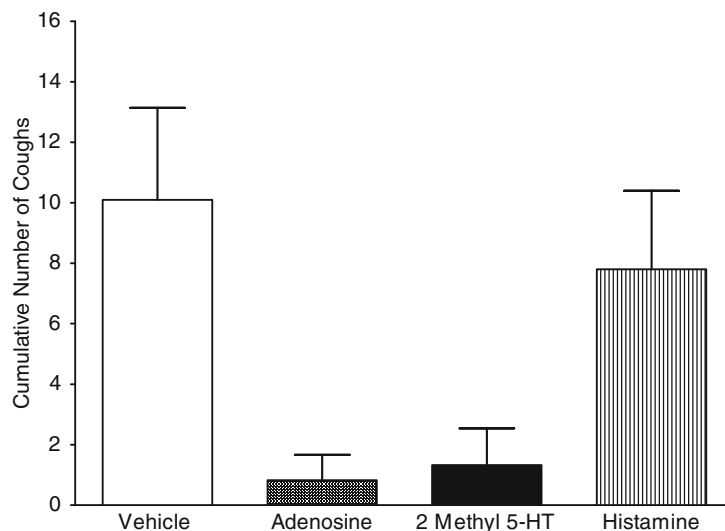


**Fig. 2** Representative traces illustrating the respiratory reflex effects initiated in anesthetized guinea pigs by activation of RARs by intravenous histamine and C-fibers by intravenously administered capsaicin and adenosine. Adenosine acts selectively on C-fibers arising from the nodose ganglia in guinea pigs, whereas capsaicin activates all bronchopulmonary C-fibers in this species. Note that none of these challenges initiate coughing and the distinct differences in reflex effects initiated by the nonselective C-fiber stimulant capsaicin, which evokes both apnea and tachypnea, and the nodose C-fiber-selective stimulant adenosine, which evokes only tachypnea. In these same animals, mechanically probing the laryngeal, tracheal, or bronchial mucosa, or acid applied topically to the mucosa readily evokes coughing. These studies illustrate the distinct reflex effects initiated by RAR and C-fiber subtypes and facilitates differentiation of the afferent nerves regulating cough from other afferent nerve subtypes in the airways



**Fig. 3 a-d** Mean data illustrating the responsiveness of airway and lung RARs and C-fibers in various species to histamine and capsaicin challenges. Open bars depict mean  $\pm$  standard error of the mean (SEM) basal activity during tidal breathing. Filled bars depict mean  $\pm$  SEM peak activity following challenge with either capsaicin or histamine. Where multiple studies have evaluated the actions of histamine or capsaicin on a specific afferent nerve subtype in a single species, the average of the results in these studies is presented (Adcock et al. 2003; Armstrong and Luck 1974; Bergren 1997, 2001; Bergren and Peterson 1993; Coleridge and Coleridge 1977, 1984; Coleridge et al. 1965; Delpiere et al. 1981; Ho et al. 2001; Lee and Morton 1993; Lin and Lee 2002; Mills et al. 1970; Mohammed et al. 1993; Paintal 1969; Sellick and Widdicombe 1971; Vidruk et al. 1977). Both stimuli were administered either intravascularly (bronchial artery or right atrial injection) or by inhalation at various doses and in animals that were either freely breathing or paralyzed and ventilated, with or without open chest. Despite these different experimental conditions, a clear pattern of selectivity for capsaicin (C-fibers) and histamine (RARs) is apparent. Comparable selectivity for C-fibers has been reported for bradykinin and 5-HT<sub>3</sub> receptor selective agonists, while stimuli that like histamine evoke bronchospasm, such as substance P, methacholine, and efferent vagus nerve stimulation, have been found to be relatively selective for RARs \*not previously studied

2006b). Conversely, stimuli that do initiate coughing (e.g., capsaicin, bradykinin, acid) are either modestly effective or ineffective at activating RARs (Armstrong and Luck 1974; Bergren 1997; Coleridge and Coleridge 1984; Ho et al. 2001; Mohammed et al. 1993) (Fig. 3 a–d). It is unclear whether intrapulmonary RARs can even modulate the cough reflex. Pulmonary edema is a potent RAR (and pulmonary C-fiber) stimulant but fails to induce cough and may even inhibit cough acutely (Korpas et al. 1993; Polacek et al. 1986; Sellick and Widdicombe 1969). In humans, there is a poor correlation between lung function and responsiveness to tussive stimuli. Asthmatics, for example, may have a cough response to experimental challenge that is indistinguishable from that of normal subjects (Dicpinigaitis 2007). Similarly, acute pretreatment with bronchodilators or bronchoconstrictors has no effect on cough responsiveness despite profoundly and oppositely altering airway smooth muscle tone and likely RAR activity (Fujimura et al. 1992, 1993). The data in animals are less clear. There is a very poor correlation between the ability of stimuli to initiate coughing and bronchospasm. The bronchoconstrictor substance P is ineffective at inducing cough and without effect on cough evoked subsequently by citric acid (El-Hashim and Amine 2005). We have found similar results in anesthetized guinea pigs using histamine as a means of inducing bronchospasm (Fig. 4). By contrast, in dogs, histamine and allergen (both of which induce bronchospasm) fail to evoke coughing but greatly enhance coughing evoked subsequently by mechanical stimulation of the airways (House et al. 2004).



**Fig. 4** Selective activation of pulmonary C-fibers arising from the nodose ganglia with either adenosine or 2-methyl-5-hydroxytryptamine (a 5-HT<sub>3</sub> receptor selective agonist) markedly inhibits citric acid induced coughing in anesthetized guinea pigs, while intrapulmonary RAR activation by histamine is without effect. Citric acid (0.001–2 M) was applied topically to the tracheal mucosa in 100- $\mu$ L aliquots at 1-min intervals and in ascending concentrations. Each bar represents the mean  $\pm$  SEM cumulative number of coughs evoked by citric acid in five to six experiments

Problematic in interpreting these results, however, are the indirect consequences of bronchospasm on the airways that might influence subsequently evoked reflexes, including changes in respiratory pattern and blood gases and perhaps a coincidentally evoked reflex mucus secretion (Cohn et al. 1978; Coleridge et al. 1982; Green et al. 1986; Lin et al. 2005; Olgiati et al. 1981). Histamine may also modulate excitability or activate some airway C-fibers (Coleridge and Coleridge 1984; Lee and Morton 1993). Taken together, however, the data suggest more of a modulatory, nonessential role of intrapulmonary RARs in cough.

## 5 C-Fibers

Given their defining physiological attribute of an axonal conduction velocity of  $2\text{ ms}^{-1}$  or less, bronchopulmonary C-fibers are the most readily identifiable vagal afferent nerve subtype innervating the airways. C-fibers can be activated by several chemical and mechanical stimuli, with responses depending upon the stimulus and the C-fiber subtype studied (Coleridge and Coleridge 1984; Lee and Pisarri 2001; Ricco et al. 1996; Undem et al. 2004). The majority of C-fibers innervating the airways and lungs of all species are activated by the TRPV1 receptor agonist capsaicin, a predictable observation, given the known expression patterns of TRPV1 in afferent C-fibers throughout the body of most species (Caterina et al. 1997). But it is inappropriate to conclude from these data that responsiveness to capsaicin is the defining characteristic of airway C-fibers. C-fibers in dogs, rats, and mice that are not activated by lung capsaicin challenge have been described (Coleridge and Coleridge 1984; Ho et al. 2001; Kollarik et al. 2003). Moreover, perhaps secondary to the end organ effects associated with C-fiber activation (mucus secretion, vascular engorgement, airway smooth muscle contraction, altered respiratory pattern, and cough), other afferent nerve subtypes, especially intrapulmonary RARs, can be activated by capsaicin challenge (Bergren 1997; Mohammed et al. 1993; Morikawa et al. 1997). A lack of responsiveness to mechanical stimulation and basal activity may also fail to differentiate C-fibers from other subtypes of bronchopulmonary afferent nerves. While C-fibers are generally less responsive to mechanical stimulation, they can be activated by punctate mechanical stimulation or lung inflation, and can have basal activity comparable to that of some RARs (Coleridge and Coleridge 1984; Fox et al. 1993; Lee and Pisarri 2001; Ricco et al. 1996).

C-fibers are found throughout the airways and lungs of all species. The extensively branched terminals of C-fibers in guinea pig and rat tracheae can be immunohistochemically labeled for the neuropeptides calcitonin gene-related peptide (CGRP), substance P, and neurokinin A (Baluk et al. 1992; Hunter and Undem 1999; Kummer et al. 1992; McDonald et al. 1988; Yamamoto et al. 2007). Comparable structures can be found in the airways of other species and in the peripheral airways of guinea pigs (Dey et al. 1990; Lamb and Sparrow 2002; Watanabe et al. 2006; Yamamoto et al. 1998). C-fiber terminals can also be found in the airway microvasculature and airway smooth muscle layer, and comprise at least a portion

of Painsal's J-receptors, suggesting peripheral/interstitial lung terminations (Baluk et al. 1992; McDonald et al. 1988; Painsal 1973). To date, however, very little specific information about the intrapulmonary airway and lung terminations of C-fibers is available.

The chemical stimuli most effective at activating bronchopulmonary C-fibers, including capsaicin, bradykinin, and acid, are similarly very effective at initiating cough in conscious human subjects and in conscious animals (Dicpinigaitis 2007; Forsberg et al. 1988; Jia et al. 2002; Karlsson and Fuller 1999; Laude et al. 1993; Trevisani et al. 2004). These stimuli work entirely or partly through TRPV1, and immunohistochemical and single-cell PCR confirms expression of TRPV1 in airway C-fibers (Groneberg et al. 2004; Kwong et al. 2008; Myers et al. 2002; Watanabe et al. 2006). Prior capsaicin desensitization prevents citric acid induced coughing in awake guinea pigs, as does pretreatment with TRPV1 receptor antagonists (Bolser et al. 1991; Forsberg et al. 1988; Gatti et al. 2006; Laloo et al. 1995; Leung et al. 2007; Trevisani et al. 2004). Taken together, these and other observations argue strongly for a role of bronchopulmonary C-fibers in cough (Canning et al. 2006b).

Some controversy about the role of C-fibers in cough has arisen from the utter inability of C-fiber-selective stimulants to evoke coughing in anesthetized animals (Canning et al. 2004, 2006a; Karlsson et al. 1993; Tatar et al. 1988, 1994) (Fig. 2). Anesthesia has no effect on coughing evoked by mechanical or acid stimulation of the airway mucosa and does not prevent C-fiber activation or other C-fiber-dependent reflexes, and yet capsaicin and bradykinin have been consistently ineffective at evoking cough in anesthetized animals (Canning et al. 2006a; Coleridge and Coleridge 1984; Tatar et al. 1988). But perhaps it should be expected that C-fiber-selective stimulants would fail to evoke coughing in anesthetized animals. Airway and lung C-fibers share many characteristics with somatosensory nociceptors, and it is the objective of general anesthesia to prevent the sensations and reflexes associated with nociceptor activation.

While the effects of anesthesia on nociceptor signaling may explain the inability of C-fiber-selective stimulants to evoke coughing in anesthetized animals, anesthesia cannot account for the known acute inhibitory effects C-fiber activation may have on cough in anesthetized animals, or the inability of some C-fiber stimuli to evoke coughing in conscious animals and in conscious human subjects (Tatar et al. 1988, 1994). We speculated that C-fiber subtypes might account for these opposing effects on cough. Subtypes have been described in several species (Coleridge and Coleridge 1984; Kollarik et al. 2003; Undem et al. 2004). In guinea pigs, airway vagal C-fiber subtypes can be differentiated by their ganglionic origin, distribution in the airways, and responsiveness to ATP, adenosine, and serotonin 5-HT<sub>3</sub> receptor agonists (Chuaychoo et al. 2005, 2006; Undem et al. 2004). The ability of C-fiber activation to evoke coughing in awake guinea pigs is reasonably well established, and we also reported a facilitating effect of C-fiber activation on cough (Canning et al. 2006b; Mazzone et al. 2005). In these latter studies, capsaicin or bradykinin applied topically to the tracheal mucosa greatly enhanced sensitivity to subsequent tussive stimuli. On the basis of the location of these bradykinin

and capsaicin challenges, C-fibers arising from the jugular ganglia likely promote coughing. By inference, then, we further speculated that nodose C-fiber activation might acutely inhibit coughing. Consistent with this hypothesis, we found that selective activation of nodose C-fibers with adenosine or 2-methyl-5-hydroxytryptamine did not evoke coughing but greatly reduced the ability of citric acid to evoke coughing in anesthetized animals (Fig. 4). Prior adenosine inhalation also inhibited capsaicin-induced coughing in conscious guinea pigs.

The results of studies carried out in other species are at least consistent with the notion that C-fiber subtypes may have opposing effects on cough. In anesthetized dogs and cats, C-fiber activation by either capsaicin or phenyldiguanide (a 5-HT<sub>3</sub> receptor agonist) can inhibit cough (Tatar et al. 1988, 1994). There is no published evidence that capsaicin, bradykinin, or citric acid can evoke coughing in awake dogs and cats, but if they cannot, these would be the only species studied that are known to cough but do not cough in response to these stimuli when awake. Similarly, in rats, a species in which we (and others) have been unable to evoke cough, it is unclear from the published literature whether the jugular type (which are insensitive to ATP, adenosine, and serotonin receptor activation), cough-promoting C-fibers that can be found in guinea pigs innervate the airways of rats, a species that may have little or no capacity to cough (Belvisi and Bolser 2002; Lee and Pisarri 2001; Ohi et al. 2004; Tatar et al. 1996, 1997). In rabbits, a species in which cough can be evoked by citric acid aerosol inhalation (at least suggestive of a TRPV1 and C-fiber-dependent mechanism; Adcock et al. 2003; Tatar et al. 1997), it has also been reported that acute sulfur dioxide inhalation is acutely inhibitory on cough (Hanacek et al. 1984). These data have been reasonably interpreted as evidence for a permissive effect of SARs in cough, given the peculiar sensitivity of rabbit SARs to sulfur dioxide inhalation. But sulfur dioxide is also known to activate lung C-fibers (Ho et al. 2001). Adcock and colleagues even speculated that the inhibitory effects of the compound RSD931 in cough induced in rabbits might be due to its ability to activate pulmonary C-fibers (Adcock et al. 2003). In humans, who cough readily in response to capsaicin and bradykinin challenge, serotonin and adenosine challenge may not cause coughing (Burki et al. 2005; Stone et al. 1993). There is also at least one report of serotonin-mediated inhibition of cough in human subjects (Stone et al. 1993). A comparable inability of intravenous capsaicin to evoke coughing has been reported in studies using conscious nonhuman primates (Deep et al. 2001).

## **6 Central Terminations and Pharmacology of Airway and Lung Afferent Nerves**

Studies of airway reflexes in response to stimuli known to be selective for the various airway afferent nerve subtypes largely substantiate the accepted classification schemes for afferent nerves. Implicit in the observation that afferent nerve subtypes subserve distinct reflex functions is that central termination sites of the



various afferent nerve subpopulations must diverge to some extent, allowing for reflex specificity. From the little published evidence available, this notion would seem to be substantiated. Most of the work on central terminations of airway sensory nerves has been carried out in cats and rats. Bronchopulmonary C-fibers and RARs terminate extensively and often bilaterally in nucleus tractus solitarius (nTS), particularly in the commissural and medial subnuclei (Bonham and Joad 1991; Davies and Kubin 1986; Ezure et al. 1991; Kalia and Richter 1988; Kubin et al. 1991, 2006; Lipski et al. 1991; Mazzone and Canning 2002; Otake et al. 1992). SARs terminate primarily ipsilateral to their vagal origin, rostral to obex in the lateral and interstitial subnuclei (Bonham and McCrimmon 1990; Davies et al. 1987; Ezure et al. 2002; Kalia and Richter 1985; Kubin et al. 2006). No attempt at differentiating termination sites of RAR, SAR, or C-fiber subtypes has been described.

With respect to the central terminations of the afferent nerve subtypes primarily implicated in cough (cough receptors, tracheal/bronchial C-fibers, as opposed to pulmonary C-fibers), very little specific information derived from physiological studies has been published. The complex multichannel recordings of Shannon and colleagues, and the anatomical results from c-fos and tracing studies provide some insight (Bolser et al. 2006; Gestreau et al. 1997; Jakus et al. 2008; Ohi et al. 2005; Shannon et al. 2004), but to date there have been no electrophysiological or functional studies definitively implicating specific nTS subnuclei as primary sites of cough receptor or tracheal/bronchial C-fiber termination. There are several potential explanations for this gap in our knowledge. For starters, while any brainstem recording in a freely breathing animal is problematic, it would be especially problematic in an animal that was coughing. Similarly, while it is somewhat complicated to deliver stimuli selectively to the airways while an animal is held in a stereotaxic frame, it would be even more difficult to deliver stimuli selectively to the larynx, trachea, and/or mainstem bronchi in such restrained animals. Even if an experimenter could devise a way in which stimuli could be isolated to these large airways and maintain viable recordings while the animals were coughing, the number of afferents targeted would represent only a fraction of those targeted in whole lung challenges (lung inflations or deflations, intravenous capsaicin) to search for nTS termination sites of intrapulmonary RARs, SARs, or C-fibers. In short, an experimenter would have to be both very lucky and very skilled to position an electrode near enough to the relay neurons of the very few afferent nerves targeted by a stimulus confined to the extrapulmonary airways.

As an alternative approach, we have employed a functional assay combined with stereotaxic microinjections to identify the location of the primary synapses of the tracheal afferent nerves regulating cough in guinea pigs (Canning et al. 2006b). What made this approach feasible was the ease with which we could transition from microinjection to subsequent cough challenges in guinea pigs, and the relatively small portion of the airway from which cough is evoked in our studies. We varied the concentration of glutamate receptor antagonists and the location of bilateral microinjection in an attempt to locate the nTS location likely corresponding to the cough receptor termination sites. Bilateral microinjections of a combination of the glutamate receptor antagonists CNQX (6-Cyano-7-nitroquinoxaline-2,3-dione)

and AP-5 (D-(-)-2-Amino-5-phosphonopentanoic acid) about 1 mm rostral from obex and 1 mm lateral from midline, near the medial and/or intermediate subnuclei of nTS, readily blocked cough at doses that were without effect when microinjected into adjacent nTS/brainstem locations (0.5–2 mm distal). Importantly, these same microinjections were without effect on basal respiratory rate (largely SAR dependent) or tachypnea evoked by either intravenous histamine (an intrapulmonary RAR-dependent reflex) or intravenous bradykinin (a bronchopulmonary C-fiber-dependent reflex). Subsequent anterograde and retrograde tracing experiments have confirmed a preponderance of cough receptor terminations in this discrete region of nTS.

Establishing this cough model and the stereotaxic locations relevant to cough will guide subsequent electrophysiological analyses. These methods also permit more thorough pharmacological analyses of the central regulation of cough. Initial studies have documented a prominent role of glutamate *N*-methyl-D-aspartate receptors in the regulation of cough. As has been reported by other investigators,  $\gamma$ -aminobutyric acid (inhibiting) and substance P (facilitating) were found to have opposing effects on cough (Bolser et al. 1994; Joad et al. 2004; Mazzone et al. 2005; Mutolo et al. 2007). Previous studies have implicated a role for neurokinins acting centrally in the regulation of cough and other C-fiber-dependent reflexes, even though neurokinins seem to have little or no direct role in RAR-, SAR-, or cough-receptor-dependent signaling in nTS (Bolser et al. 1997; Canning et al. 2001; Mazzone and Canning 2002; Mazzone et al. 2005).

## 7 Conclusions

Much of what we know about the afferent nerves regulating cough was established in the initial studies of Widdicombe. Unfortunately, these relatively firmly established notions relating to cough have been obscured by an imprecise nomenclature. The role of C-fibers in cough may be the most widely accepted notion, given their unique pharmacological properties and the ability of C-fiber-selective stimulants to initiate coughing in awake animals and human subjects. A role for the laryngeal/tracheal/bronchial mechanoreceptors activated by mechanical stimulation and acid has also been well established. What has not been so well established, however, is an appropriate name for these mechanoreceptors. While they rapidly adapt to a punctate mechanical stimulus, they share few other physiological characteristics with other afferent nerve subtypes called RARs. Cough receptors might be an appropriate name, but only if used to describe these nerves alone. Future studies of the afferent nerves regulating cough should fill gaps in our knowledge about the central pathways regulating cough, and potential targets for cough therapy at the nerve terminals and perhaps also at the central terminations of these vagal afferent nerves.

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