Sensory Nerves and Airway Irritability

B.J. Canning and D. Spina

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Abstract  The lung, like many other organs, is innervated by a variety of sensory nerves and by nerves of the parasympathetic and sympathetic nervous systems that regulate the function of cells within the respiratory tract. Activation of sensory nerves by both mechanical and chemical stimuli elicits a number of defensive reflexes, including cough, altered breathing pattern, and altered autonomic drive, which are important for normal lung homeostasis. However, diseases that afflict the lung are associated with altered reflexes, resulting in a variety of symptoms, including increased cough, dyspnea, airways obstruction, and bronchial hyperresponsiveness. This review summarizes the current knowledge concerning the physiological role of different sensory nerve subtypes that innervate the lung, the factors which lead to their activation, and pharmacological approaches that have been used to interrogate the function of these nerves. This information may potentially facilitate the identification of novel drug targets for the treatment of respiratory disorders such as cough, asthma, and chronic obstructive pulmonary disease.

Keywords  Rapidly adapting receptors, C-fibers, Cough receptor, Cough, Parasympathetic nervous system, Sympathetic nervous system, Cough, Bronchoconstriction, Mucus secretion, Bronchial hyperresponsiveness

1 Introduction

The primary function of the lung is gas exchange. The airways serve as a conduit for moving inspired air to the gas-exchanging regions of the lungs, and for expiration of CO\textsubscript{2}. Airway and lung reflexes optimize lung capacity for gas exchange in response to a continually changing demand. Airway reflexes also serve to preserve airway patency. These reflexes can become aberrant, however, and may worsen the symptoms of diseases such as asthma and chronic obstructive pulmonary disease (COPD). Multiple afferent nerve subtypes regulate these homeostatic and defensive reflexes, each subtype with unique physiological, anatomical, and pharmacological attributes. The properties of airway afferent nerve subtypes will be reviewed, as will their role in regulating bronchopulmonary reflexes and bronchial responsiveness.

2 Airway and Lung Afferent Nerve Subtypes

Airway afferent nerve subtypes have been defined by their chemical and physical sensitivity, adaptation to mechanical stimulation, origin, myelination, conduction velocity, neurochemistry, basal activity, reflexes associated with their activation, and sites of termination in the airways, lungs, and brain stem. These various approaches to characterizing airway afferent nerves are hampered by their lack of specificity. But when used in combination, patterns of physiological and
pharmacological attributes have emerged to help define at least four distinct subtypes of airway afferent nerves (Canning et al. 2006b).

### 2.1 Slowly Adapting Receptors

Slowly adapting receptors (SARs) are the prototypical airway mechanoreceptors. The mechanical forces produced during breathing are the primary stimulus for SAR activation, with SAR activity increasing during inspiration and peaking prior to expiration (Miserocchi and Sant’Ambrogio 1974; Ho et al. 2001; Schelegle and Green 2001). SARs regulate the Hering-Breuer reflex, which terminates inspiration and initiates expiration when the lungs are adequately inflated (Schelegle and Green 2001). SARs thus play a primary role in regulating respiratory rate.

SARs can be differentiated from rapidly adapting receptors (RARs) in some species on the basis of action potential conduction velocity, and in most species by their modest adaptation to sustained lung inflation (Fig. 1). SARs may be differentially distributed in the airways of commonly studied mammalian species (Schelegle and Green 2001). In cats, guinea pigs, and rats, few SARs but many RAR-like receptors and C-fibers can be found in the extrapulmonary airways. In dogs, SARs may also be localized to the extrapulmonary airways (Miserocchi and Sant’Ambrogio 1974; Sant’Ambrogio et al. 1988). SARs also differ from RARs with respect to the reflexes they precipitate (see later). Subtypes of SARs have been described (Miserocchi and Sant’Ambrogio 1974; Schelegle and Green 2001).

SARs are generally unresponsive to chemical stimuli. With the exception of the small population of SARs terminating in airway smooth muscle, this also includes an insensitivity to stimuli that initiate bronchospasm, pulmonary edema, pulmonary vascular congestion, or any stimulus that decreases lung compliance. The ion channels regulating the mechanical sensitivity of SARs are also poorly defined. Gadolinium (20 mM applied repeatedly for 30 min to SAR receptive fields) slightly (10–40%) reduced rabbit bronchial SAR discharge to different levels of inflation pressures (Ma et al. 2004). Other drugs reported to modify SAR discharge include the voltage-sensitive K⁺-channel blocker 4-aminopyridine, the voltage-sensitive Na⁺-channel opener veratradine, the Na⁺–K⁺–2Cl⁻/Cl⁻ transporter inhibitor furosemide, sulfur dioxide, and the Na⁺–K⁺–ATPase inhibitor ouabain (Davies et al. 1978; Matsumoto et al. 1998, 1999, 2000, 2005, 2006; Sudo et al. 2000; Guardiola et al. 2007).

An additional and unique physiological and pharmacological property of SARs is their sensitivity to alveolar CO₂ concentrations (Coleridge et al. 1978; Fisher and Sant’Ambrogio 1982; Green et al. 1986). As alveolar CO₂ increases, SAR activity decreases. This contrasts sharply with bronchopulmonary C-fibers, which may be activated or at least sensitized by elevated alveolar CO₂ and/or decreases in extracellular pH (Delpierre et al. 1981; Lin et al. 2005). The inhibitory effect of CO₂ on SARs contributes in part to the hyperpnea associated with hypercapnea. The actions of CO₂ on SAR excitability may occur secondary to effects on nerve
terminal pH as evidenced by the preventive effect of the carbonic anhydrase inhibitor acetazolamide during CO₂ challenges (Ravi 1985; Matsumoto 1996; Hempleman et al. 2000). The expression of a carbonic anhydrase isozyme in SARs has not been systematically evaluated.

### 2.2 Rapidly Adapting Receptors

The term “rapidly adapting receptor” (RAR) describes a subtype of airway and lung stretch receptor that are activated during the dynamic phase of lung inflation, but unlike SARs become quiescent during static lung inflation (Knowlton and Larrabee 1946; Widdicombe 1954a). Often inappropriately, airway afferents that rapidly adapt to any stimulus are grouped into a broad and heterogeneous class, all of which are called “RARs.” This has proven misleading (Canning and Chou...
In this review, the term “RAR” refers to those intrapulmonary stretch receptors that rapidly adapt to sustained lung inflation (Fig. 1).

RARs are considerably less active than SARs during eupnea but more active than C-fibers. RARs are also 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 (Mills et al. 1970; Armstrong and Luck 1974; Bergren 1997; Ho et al. 2001; Canning et al. 2004; Canning and Chou 2009).

RARs are generally more responsive to chemical stimuli than SARs, prompting use of the term “irritant receptor” to describe this airway afferent nerve subtype. What has been less clear, however, is whether the ability of these chemical stimuli to activate RARs is through a direct action or secondary to a mechanical effect evoked in the lung. As mentioned above, RARs are exquisitely sensitive to decreases in lung compliance (Jonzon et al. 1986; Yu et al. 1987, 1989). Accordingly, bronchoconstrictors such as serotonin, methacholine, histamine, and substance P and many other stimuli that initiate bronchospasm likely activate RARs at least partly through their effects on lung mechanics (Mills et al. 1970; Mohammed et al. 1993; Bergren 1997; Canning et al. 2004; Chou et al. 2008). Similar mechanisms may underlie the ability of pulmonary embolism and pulmonary vascular congestion to activate RARs (Mills et al. 1969; Sellick and Widdicombe 1969; Ravi and Kappagoda 1992; Bonham et al. 1996) (Fig. 2). But there are several reports suggesting a direct effect of autacoids such as ATP, histamine, and serotonin

Fig. 2 Responsiveness to histamine and capsaicin differentiates RARs from C-fibers. (Reproduced from Canning and Chou 2009 and summarizes results published elsewhere)
on RARs (Vidruk et al. 1977; Dixon et al. 1979; Matsumoto and Shimizu 1989; Canning et al. 2004). Unlike SARs and C-fibers, however, RARs are largely unaffected by changes in alveolar CO$_2$ concentrations (Sampson and Vidruk 1975; Ravi 1985).

As with SARs, the ion channels regulating RAR activation secondary to mechanical stimulation are poorly defined. Gadolinium (20 mM applied repeatedly for 30 min to RAR receptive fields) is reported to have a profound effect on RAR excitation by lung inflation and pulmonary vascular congestion (Ma et al. 2004). Given the distinctive accommodative responses of RARs to sustained lung inflation, it seems possible that they express a unique set of ion channels that may be amenable to selective pharmacological modulation. This may prove useful in developing more selective drugs for treating respiratory disorders.

### 2.3 C-Fibers

With their defining physiological attribute of an axonal conduction velocity of 1 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; Ricco et al. 1996; Lee and Pisarri 2001; 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 (Figs. 1, 2), 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 (Mohammed et al. 1993; Bergren 1997; 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; Ricco et al. 1996; Lee and Pisarri 2001).

Subtypes of bronchopulmonary C-fibers have been described. The Coleridges defined C-fiber subtypes in dogs by their responsiveness to stimulants administered via the pulmonary or bronchial circulation (Coleridge and Coleridge 1984). More recently, Undem (Kollarik et al. 2003; Undem et al. 2004) described bronchopul-
monary C-fiber subtypes in both guinea pigs and mice. In guinea pigs, C-fiber subtypes are differentiated on the basis of their ganglionic origin (nodose vs. jugular ganglia) and, by extension, their embryological origin, their sites of peripheral termination (extrapulmonary and intrapulmonary vs. exclusively intrapulmonary), expression of neurokinins, and responsiveness to adenosine, serotonin 5-HT₃, and ATP receptor agonists (Undem et al. 2004; Chuaychoo et al. 2005, 2006). These subtypes are known to have opposing effects on both cough and respiration, but both subtypes may initiate reflex bronchospasm upon activation (Canning et al. 2006a, b; Chou et al. 2008; Reynolds et al. 2008) (Fig. 3). C-fibers arising from dorsal root ganglia also innervate the airways (Martling 1987; Kummer et al. 1992; Dinh et al. 2004; Oh et al. 2006; Kwong et al. 2008b). Their physiological properties and reflex actions have been only partially described.

C-fibers are found throughout the airways and lungs of all species. In guinea pigs, the jugular-type C-fibers have been localized to both intrapulmonary and extrapulmonary airways, while the nodose-type C-fibers are found predominantly in the peripheral airways and lungs (Undem et al. 2004). 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 (McDonald et al. 1988; Baluk et al. 1992; Kummer et al. 1992; Hunter and Undem 1999; 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; Yamamoto et al. 1998; Lamb and Sparrow 2002; Watanabe et al. 2006). C-fiber terminals can also be found in the airway microvasculature and airway smooth muscle layer, and comprise at least a portion of Paintal’s J-receptors, suggesting peripheral/interstitial lung terminations (Paintal 1973; McDonald et al. 1988; Baluk et al. 1992).

A myelinated (based on an axonal conduction velocity of 5 ms\(^{-1}\)) afferent nerve subtype with many shared physiological and pharmacological attributes of jugular C-fibers has also been described in guinea pigs (Ricco et al. 1996). These afferents have their cell bodies in the jugular ganglia and are activated by acid, hypertonic saline, bradykinin, and capsaicin. Unlike jugular C-fibers, these capsaicin-sensitive A\(\delta\)-fibers terminate exclusively in the large airways (larynx, trachea, mainstem bronchi) and do not normally express the neuropeptide substance P (but can be labeled immunohistochemically for the structural protein neurofilament). TRPV1-positive, substance P-negative nerve terminals have been described in the airway epithelium of guinea pigs and may correspond to this afferent subtype (Watanabe et al. 2005, 2006). The existence of an A\(\delta\) afferent subpopulation expressing TRPV1 in other species and their reflex effects in any species upon activation are unknown.

In contrast to the indirect effects of autacoids and irritants thought to account for their activation of RARs, there is molecular, immunohistochemical, and electrophysiological evidence to suggest that many mediators associated with airway inflammation act directly on bronchopulmonary C-fibers. Stimuli known to activate airway and lung C-fibers include capsaicin and other TRPV1 receptor ligands, acid, cationic proteins, bradykinin, and other protease-activated receptor 1 (PAR1) agonists, adenosine, 5-HT\(_3\) receptor agonists, nicotine, ATP, prostanoids, and isoprostanes, and a variety of environmental irritants including acrolein, toluene diisocyanate, and ozone (Coleridge and Coleridge 1984; Lee and Pisarri 2001; Undem et al. 2004; Chuaychoo et al. 2005, 2006; Nassenstein et al. 2008; Taylor-Clark et al. 2008). Many of these stimuli work partly or entirely through gating of the ion channels TRPV1 and TRPA1. PCR analyses confirm the expression of TRPV1 and TRPA1, but also adenosine A\(_1\), adenosine A\(_2\), PAR1, and multiple subunits of nicotinic receptors in bronchopulmonary C-fibers (Chuaychoo et al. 2006; Gu et al. 2008; Kwong et al. 2008a, b; Nassenstein et al. 2008). The responsiveness to such a variety of inflammatory mediators and environmental toxins and the reflexes initiated upon the activation of C-fibers lends credence to the notion that bronchopulmonary C-fibers are analogous to the nociceptors innervating somatic tissues.

TRPV1-dependent signaling is not the same in all bronchopulmonary C-fibers and is at least suggestive of the differential expression of a ligand-transporting system in some C-fibers or perhaps unique gating mechanisms for TRPV1 in the various bronchopulmonary C-fiber subtypes. Olvanil and anandamide are reasonably effective and potent activators of intrapulmonary C-fibers in rats and in guinea pigs, but are minimally effective at evoking tracheal/bronchial C-fiber action potential discharge or tachykinin release from the peripheral terminals of bronchial
and tracheal C-fibers (Tucker et al. 2001; Lin and Lee 2002; Kollarik and Undem 2004; Lee et al. 2005). This inability to activate bronchial C-fibers is overcome with sustained incubation times, suggesting an impaired access to the intracellular binding site of TRPV1. Conversely, cooling the terminals of pulmonary C-fibers rendered them considerably less responsive to olvanil and anandamide, but equally responsive to capsaicin. These data may predict the expression of an anandamide-transporting system in pulmonary C-fibers that is absent in bronchial and tracheal C-fibers (Ligresti et al. 2004). To date, however, no protein subserving this transporting function has been identified (Glaser et al. 2005). It is thus interesting that activation of TRPV1 has been shown to promote the movement of extraordinarily large molecules from the extracellular to the intracellular space through the open TRPV1 channel (Meyers et al. 2003; Binshtok et al. 2007). The Hill coefficient for TRPV1 activation is significantly different from unity, suggestive of cooperative binding properties (Szallasi 1994; Welch et al. 2000; Undem and Kollarik 2002). It seems possible that threshold TRPV1 activation resulting in transient channel opening promotes additional agonist influx and further receptor activation. Perhaps some subtle modification of TRPV1 channel gating in C-fiber subtypes determines the ability of anandamide and olvanil to move through the open TRPV1 channel.

In addition to the autacoids listed above that activate bronchopulmonary C-fibers, many other mediators can sensitize them to subsequent activation. These include histamine via H1 receptors, cysteinyi leukotrienes via cysLT1 receptors, epinephrine via β3 receptors, and prostaglandin EP and TP receptor agonists (Karla et al. 1992; Lee and Morton 1993, 1995; McAlexander et al. 1998; Xiang et al. 2002; Gu et al. 2007). Prostaglandins also likely account for the sensitizing effects of protease-activated receptor 2 (PAR2) agonists on bronchopulmonary C-fibers (Gatti et al. 2006). Some mechanistic studies of these sensitizing effects have been carried out in patch-clamp analyses. Other unique characteristics regulating airway C-fiber activation include sensitivity to changes in extracellular Cl⁻ and Ca²⁺ concentrations, changes in airway surface liquid osmolarity, TRPV1-independent activation by acid (perhaps involving acid-sensing ion channels), and activation/sensitization by CO₂ (Delpierre et al. 1981; Pisarri et al. 1992; Fox et al. 1995; Pedersen et al. 1998; Kollarik and Undem 2002; Undem et al. 2003; Lin et al. 2005; Gu and Lee 2006).

2.4 Cough Receptors

C-fiber-selective stimulants that readily initiate coughing in awake human subjects and in awake guinea pigs have consistently failed to initiate cough in anesthetized cats, dogs, or guinea pigs. On the basis of the studies of Widdicombe (1954a, b) published in 1954 and the results of vagal cooling studies in cats and dogs by Tatar et al. (1988, 1994), it had become almost dogma that cough is initiated by activation of RARs. But many well-known and even selective stimuli for RARs, including a variety of bronchoconstrictors, negative airway luminal pressures, or inspiratory
efforts against a closed glottis, have been consistently ineffective at evoking cough in either awake or anesthetized animals or humans. Recent studies carried out in guinea pigs and a reappraisal of Widdicombe’s studies in cats suggest that a vagal afferent nerve subtype distinct from both C-fibers and RARs plays an essential role in regulating the cough reflex in anesthetized guinea pigs and cats and likely in any species that has a well-defined cough reflex. These afferents have thus been called “cough receptors” (Canning et al. 2004, 2006a, b; Canning and Chou 2009).

Cough receptors are differentiated from C-fibers and RARs in guinea pigs by conduction velocity. With a conduction velocity of approximately 5 ms\(^{-1}\), these afferents conduct action potentials considerably faster than C-fibers (1 ms\(^{-1}\) or less) but considerably slower than either RARs or SARs (more than 20 ms\(^{-1}\)). Cough receptors are also differentiated from C-fibers and RARs by mechanical sensitivity, being exquisitely sensitive to punctate mechanical stimulation (5–10 times more sensitive than C-fibers) but utterly insensitive to changes in airway luminal pressure or airway smooth muscle contraction, both of which activate RARs. Also unlike C-fibers, the cough receptors are insensitive to capsaicin and bradykinin (Fig. 4). Cough receptors are activated by acid but entirely through TRPV1-independent mechanisms (Canning et al. 2004, 2006a, b).

By 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. 2006a, b). Terminating between the epithelium and smooth muscle layers of the airways mucosa, the cough receptors assume a

![Fig. 4](image)

**Fig. 4** Electrophysiological characteristics of the extrapulmonary vagal afferent nerves regulating cough of guinea pigs. Cough receptors and C-fibers are both activated by punctate mechanical stimulation and by acid, but the cough receptors are insensitive to capsaicin. Capsaicin and other C-fiber-selective stimulants initiate coughing in awake animals and in awake human subjects, but have consistently failed to initiate coughing in anesthetized animals. In anesthetized guinea pigs, topical acid challenge of the tracheal mucosa initiates coughing, while topical capsaicin challenge does not evoke coughing. Rather, capsaicin challenge in anesthetized guinea pigs evokes respiratory slowing and, occasionally, a profound apnea followed by gasping and a gradual recovery of a normal respiratory pattern. (Reproduced with permission from Canning et al. 2004)
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 (Larsell 1921, 1922; Gaylor 1934; Yamamoto et al. 1995; Yu 2005; De Proost et al. 2007). Immunohistochemistry confirms the selective expression of subtypes of Na\(^+\)–K\(^+\)–ATPase and Na\(^+\)–K\(^+\)–2Cl\(^-\)/C\(_0\) transporter in guinea pig cough receptors (Canning et al. 2006a, b; Mazzone and McGovern 2006, 2008). More recently, tetrodotoxin-insensitive Na\(^+\) channels have been localized to these cough receptors (Kwong et al. 2008a, b). Pharmacological analyses suggest that these regulators of ion flux and gradients, as well as Cl\(^-\) channels and voltage-sensitive K\(^+\) channels, may be critical to the regulation of cough receptor responsiveness to chemical (acid) and punctate mechanical stimuli (Fox et al. 1995; McAlexander and Undem 2000; Canning et al. 2006a, b; Mazzone and McGovern 2006; Canning 2007). 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.

3 Autonomic Reflexes

3.1 Parasympathetic Nerve Regulation of Airway and Vascular Smooth Muscle and Mucus Secretion

Parasympathetic nerves play a primary role in regulating airway smooth muscle tone and glandular secretion in the airways and also regulate pulmonary and bronchial vascular tone (Canning 2006; Wine 2007). There are two anatomically, physiologically, and pharmacologically distinct parasympathetic pathways projecting to the airways with opposing effects on airway smooth muscle but synergistic effects on airway mucus secretion. Parasympathetic-cholinergic nerves initiate airway smooth muscle contraction, pulmonary vascular dilatation, and mucus secretion upon activation, with acetylcholine acting in each target tissue via muscarinic M3 receptors. Parasympathetic noncholinergic nerves also innervate the airways of most species, including humans. Noncholinergic parasympathetic nerves utilize the peptide transmitter vasoactive intestinal peptide and related peptides (pituitary adenylate cyclase activating peptide, peptide histidine isoleucine, peptide histidine methionine) as well as the gaseous transmitter nitric oxide (formed from arginine by the neuronal isoform of nitric oxide synthase). Upon activation, noncholinergic parasympathetic nerves evoke bronchodilatation, airway vascular dilatation, and mucus secretion. Coincident activation of cholinergic and noncholinergic parasympathetic nerves may have synergistic effects on airway glandular secretion (Choi et al. 2007; Wine 2007).
Airway and lung afferent nerve activation initiates myriad patterns of airway parasympathetic nerve responses (Canning 2006). At eupnea, basal parasympathetic tone appears to be necessarily dependent upon the ongoing activity of airway vagal afferent nerves, either RARs or C-fibers (Jammes and Mei 1979; Kesler and Canning 1999). With challenge, activation of bronchopulmonary C-fibers or RARs increases airway cholinergic and noncholinergic parasympathetic nerve activity (Fig. 5). Activation of intrapulmonary stretch receptors (SARs) by lung

**Fig. 5** Reflex-evoked, airway parasympathetic nerve-dependent regulation of airway smooth muscle tone in guinea pigs in situ. (a) The C-fiber-selective stimulant bradykinin evokes reflex bronchospasm largely independent of any direct effects on airway smooth muscle. Histamine-evoked reflex bronchospasm occurs secondary to its direct effects on airway smooth muscle, which in turn activates intrapulmonary RARs. Evidence for the selective effects of bradykinin and histamine on C-fibers and RARs, respectively, is apparent from the marked inhibition of bradykinin-evoked reflex bronchospasm by intravenous or intracerebroventricular administration of neurokinin receptor antagonists, which are without effect on histamine-evoked reflexes. Neurokinins are selectively expressed by C-fibers in guinea pigs. (b) When RARs and C-fibers are activated simultaneously, marked synergism is apparent. This synergistic effect of RAR and C-fiber activation on airway parasympathetic tone may result from central convergence in the nucleus of the solitary tract of these afferent nerve subtypes. (c, d) The mean data for reflex bronchospasm and whole-lung-inflation pressures evoked by histamine, bradykinin, or the combination of histamine and bradykinin. (Reproduced with permission from Canning et al. 2001 and Mazzone and Canning 2002a, b)
inflation or during the hyperpnea associated with exercise induces a withdrawal of parasympathetic cholinergic nerve activity and bronchodilatation, but has no effect on parasympathetic noncholinergic nerves.

Reflex regulation of airway parasympathetic nerves by vagal afferents may not be entirely unidirectional. Secondary to the end-organ effects precipitated by parasympathetic nerve stimulation (e.g., mucus secretion, bronchospasm), action potential patterning in airway mechanoreceptors may change dramatically (Coleridge et al. 1982; Richardson et al. 1984). This is especially true under conditions in which tidal volumes are held constant (e.g., mechanical ventilation). An increase in parasympathetic cholinergic tone will decrease airway volume and deadspace, resulting in an increase in end-inspiratory pressure with mechanical ventilation and an increase in alveolar stretch under any mode of static volume ventilation. The increase in alveolar distension will favor an increase in SAR activation and a resulting withdrawal of cholinergic tone. In this way, airway afferent and efferent nerves may work in concert to establish a set point for airway parasympathetic tone (Fisher and Sant’Ambrogio 1982; Richardson et al. 1984; Matsumoto 1996). Perhaps in COPD, with alveolar destruction and increases in lung compliance, SAR activation may be diminished, prompting the elevation in airway cholinergic tone observed in this disease (Gross et al. 1989; Canning 2006).

Reflexes regulating noncholinergic airway parasympathetic nerves have been studied in guinea pigs, cats, and human subjects (Szarek et al. 1986; Ichinose et al. 1987, 1988; Michoud et al. 1987; Inoue et al. 1989; Lammers et al. 1989; Canning et al. 2001; Kesler et al. 2002; Mazzone and Canning 2002a). Unlike cholinergic contractions of the airway smooth muscle, which reach a near maximum within 30 s and can reverse at the same rate, noncholinergic parasympathetic nerve mediated relaxations of airway smooth muscle are slow in both onset and reversal (Chesrown et al. 1980; Diamond and O’Donnell 1980; Irvin et al. 1982; Matsumoto et al. 1985; Lama et al. 1988; Canning and Undem 1993; Canning et al. 2001; Kesler et al. 2002; Mazzone and Canning 2002a, b). Perhaps noncholinergic parasympathetic nerves function to restore or maintain airway patency during or at the conclusion of defensive reflexes (Coburn and Tomita 1973; Canning et al. 2006a). Consistent with this hypothesis, noncholinergic parasympathetic nerve activation is only modestly effective at preventing bronchospasm mediated reflexively or by direct actions on smooth muscle, but can gradually reverse an evoked contraction and modulate sustained cholinergic tone at eupnea (Aizawa et al. 1982, 1997, 1999; Bai et al. 1986; Szarek et al. 1986; Clerici et al. 1989; Miura et al. 1990; Inoue et al. 1991; Matsumoto et al. 1999; Canning et al. 2001; Kesler et al. 2002).

### 3.2 Reflex Regulation of Airway Sympathetic Nerves

Sympathetic nerves innervate the airways and lungs of all species. In most species, including humans, sympathetic-adrenergic innervation of intrapulmonary airway smooth muscle is limited or nonexistent (Canning 2006). In all species, sympathetic
aderenergic nerves have been found innervating the airway vascular smooth muscle. Until recently, however, no study has directly addressed the reflex mechanisms controlling airway sympathetic nerve activity. We recently studied reflex regulation of airway sympathetic nerves innervating the trachealis of guinea pigs (Oh et al. 2006). The vagus nerves were cut bilaterally to limit the influence of airway parasympathetic nerves on smooth muscle tone. With the trachealis precontracted with histamine, capsaicin inhalation evoked a marked relaxation of the trachealis that was prevented by sympathetic denervation of the trachealis, propranolol, or dorsal rhizotomy (T1-T4). Retrograde tracing and electrophysiological analyses identified a population of capsaicin-sensitive spinal afferent nerves innervating the intrapulmonary airways and lungs. The majority of these spinal afferent nerves expressed substance P. Not surprisingly, then, neurokinin receptor antagonists prevented the reflex-mediated relaxations evoked by capsaicin inhalation.

Interestingly, we found that the sympathetic reflexes evoked in the airways by capsaicin inhalation occurred without any coincident cardiovascular responses (Oh et al. 2006). This adds further evidence against historical notions regarding sympathetic nerve function in homeostatic and defensive settings (Morrison 2001; Janig and Habler 2003). We also observed that stimulating the central cut ends of the vagus nerves evoked propranolol-sensitive relaxations of the trachealis (Oh et al. 2006). Vagal afferents are known to regulate sympathetic outflow to multiple organs, including the airways (Barman and Gebber 1976; Bachoo and Polosa 1987; Habler et al. 1994; Huang et al. 2000).

3.3 The Axon Reflex

In rats and in guinea pigs, bronchopulmonary C-fiber activation can also initiate an axon reflex, characterized by the peripheral release of neuropeptides that produce a variety of end-organ effects within the airways and lungs, including bronchospasm, mucus secretion, vascular engorgement, inflammatory cell recruitment, and plasma extravasation (Barnes 1986, 2001; Canning et al. 2006a, b). The prominent role of the axon reflex in the response to a variety of experimental challenges in rats and guinea pigs prompted a nearly two decade effort to address the hypothesis that respiratory disorders such as asthma and COPD were due in part to an axon reflex. This notion did not live up to its promise in rats and guinea pigs when evaluated in the human airways, in large part owing to the relative paucity of neuropeptide-containing afferent nerve terminals in the airways and lungs of humans (Hislop et al. 1990; Howarth et al. 1995; Chanez et al. 1998; Lamb and Sparrow 2002). It is nevertheless possible that axonal reflexes regulate human airway function, but through the actions of transmitters (e.g., ATP, glutamate) other than substance P, neurokinin A, and CGRP.

The most effective stimulants of the axon reflex work through the gating of the ion channel TRPV1. Capsaicin, for example, evokes a profound C-fiber discharge
and an axon reflex, all of which are abolished when TRPV1 gating is prevented. By contrast, bradykinin, which acts only partially through TRPV1 gating on bronchopulmonary C-fibers, evokes little if any axon reflex (Mizrahi et al. 1982; Bramley et al. 1990; Schlemper and Calixto 2002). Other stimuli evoking an axon reflex include hypertonic saline, cold, dry air, PAR2 agonists, nicotine, immunosuppressants (cyclosporin A, FK 506), and TRPA1 receptor activation (Lundberg et al. 1983; Umeno et al. 1990; Mapp et al. 1991; Harrison et al. 1998; Pedersen et al. 1998; Yoshihara et al. 1998; Carr et al. 2000; Ricciardolo et al. 2000; Andresen and Saugstad 2008; Taylor-Clark et al. 2008).

A variety of stimuli have also been reported to inhibit the axon reflex through effects on the airway C-fiber terminal, including $\alpha_2$ adrenoceptor agonists, $\beta_2$ adrenoceptor agonists, $\mu$-opioid receptor agonists, GABA$_B$ receptor agonists, nociceptin, neurotensin, galanin, serotonin (via 5-HT$_1$ receptors), prostaglandin E$_1$, adenosine, phosphodiesterase type 4 inhibitors, neuropeptide Y, vasoactive intestinal peptide/pituitary adenylate cyclase activating peptide, dopaminergic $D_2$ receptor agonists, bradykinin channel openers, and histamine H$_3$ receptor agonists (Grundstrom et al. 1984; Belvisi et al. 1988, 1989; Giuliani et al. 1989; Kamikawa 1989; Matran et al. 1989; Aikawa et al. 1990; Stretton 1991; Verleden et al. 1993; Takahashi et al. 1994; Undem et al. 1994; Spina et al. 1995; Fox et al. 1997; Fischer et al. 1998; Shah et al. 1998; Birrell et al. 2002). It is tempting to speculate that the ability of these agents to inhibit the action-potential-independent axon reflex predicts a peripheral site of action of these drugs on bronchopulmonary C-fiber activation. This seems unlikely. Thus, prostaglandin E and adenosine both inhibit the axon reflex but activate and/or sensitize C-fibers to action potential formation (Kamikawa and Shimo 1989; Aikawa et al. 1990; Hong et al. 1998; Ho et al. 2000). The PAR2 agonist initiates an axon reflex but fails to initiate action potentials on airway C-fibers (Carr et al. 2000). Removal of extracellular Ca$^{2+}$ reduces neuropeptide release from capsaicin-sensitive nerves, but enhances airway C-fiber excitability (Hua et al. 1992; Undem et al. 2003). Together, the data argue for an almost complete dissociation of the axon reflex from C-fiber action potential formation.

4 Respiratory Reflexes

4.1 Respiratory Pattern Changes and Respiratory Sensations

Changes in respiratory pattern attributable to airway afferent nerve activation have been studied extensively in animals (Fig. 3). Respiratory sensations such as dyspnea are less amenable to study in animals, but have been studied in human subjects. The classic triad of the pulmonary chemoreflex includes bradycardia and apnea followed by rapid shallow breathing (Green and Jackman 1984; Lee et al. 1995). Both the apnea and the rapid shallow breathing depend upon pulmonary C-fiber activation (Green and Jackman 1984). Apnea/respiratory slowing can also be evoked by
C-fiber activation in the extrapulmonary airways of anesthetized animals (Palecek et al. 1989; Chou et al. 2008). In both animals and humans, activation of intrapulmonary C-fibers and RARs can initiate tachypnea (Mills et al. 1969; Green and Jackman 1984; Chou et al. 2008). In humans, the increase in respiratory rate evoked by pulmonary C-fiber activation with adenosine is accompanied by a sensation of dyspnea (Burki et al. 2005). Dyspnea and “breathlessness” can be reduced by airway or vagus nerve anesthesia or transection (Winning et al. 1985; Davies et al. 1987b; Taguchi et al. 1991). Prostaglandin E₂ worsens the sensation of dyspnea (Taguchi et al. 1992). Bradykinin, a selective stimulant for airway C-fibers, reproduces the sensation of “sore throat” associated with upper respiratory tract infections (Proud and Kaplan 1988). Enhanced breaths (or sighs) become more frequent as airway lung compliance decreases. These have been attributed to the activation of RARs and may serve to open closed airways during tidal breathing at rest or during bronchospasm (Matsumoto et al. 1998; Dybas et al. 2006).

For good reason, much of the focus on respiratory sensations in disease has been directed to the activation of pulmonary C-fibers. But a role for SARs in respiratory sensations should not be discounted. The accumulation of CO₂ in the alveoli would limit SAR discharge, delaying inspiratory termination and thus prompting hypopnea. In COPD, with alveolar destruction, the lung stretch associated with a normal tidal volume may have limited stretching effects in the peripheral airways and thus may limit SAR discharge, prompting a compensatory increase in end expiratory lung volume or an enhanced sensation of air hunger despite normal or near-normal blood gases. The Na⁺–K⁺–2Cl⁻ transport inhibitor furosemide is reported to diminish air hunger sensation during breath hold, perhaps owing to an inhibition of RAR discharge but an enhancement of SAR discharge (Nishino 2000; Sudo et al. 2000).

4.2 Cough

The cough reflex is initiated by activation of the cough receptors and by activation of a C-fiber subtype innervating the large airways (Canning and Chou 2009). The role of C-fibers in cough has been the subject of considerable debate. 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 (Forsberg et al. 1988; Laude et al. 1993; Karlsson and Fuller 1999; Jia et al. 2002; Trevisani et al. 2004; Dicpinigaitis 2007). These stimuli work entirely or partly through TRPV1, and immunohistochemical and single-cell PCR confirms expression of TRPV1 in airway C-fibers (Myers et al. 2002; Groneberg et al. 2004; Watanabe et al. 2006; Kwong et al. 2008a, b). Prior capsaicin desensitization prevents citric acid induced coughing in awake guinea pigs, as does pretreatment with TRPV1 receptor antagonists (Forsberg et al. 1988; Bolser et al. 1991; Laloo et al. 1995; Trevisani et al. 2004; Gatti et al. 2006; Leung et al. 2007). Taken together, these and other observations
argue strongly for a role of bronchopulmonary C-fibers in cough (Canning et al. 2006a, b). But C-fiber-selective stimuli have consistently failed to evoke coughing in anesthetized animals (Tatar et al. 1988; Karlsson et al. 1993; Tatar et al. 1994; Canning et al. 2004, 2006a, b). 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 do not evoke cough in anesthetized animals (Coleridge and Coleridge 1984; Tatar et al. 1988; Canning et al. 2006a, b).

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. But 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 have recently addressed the hypothesis 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\textsubscript{3} receptor agonists (Undem et al. 2004; Chuaychoo et al. 2005, 2006). 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 (Mazzone et al. 2005; Canning et al. 2006a, b). 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. 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 bradykinin, capsaicin, or phenyl diguanide (a 5-HT\textsubscript{3} receptor agonist) does not induce cough but can inhibit cough (Tatar et al. 1988, 1994; Karlsson et al. 1993). In rabbits, a species in which cough can be evoked by citric acid aerosol inhalation (consistent with a TRPV1- and C-fiber-dependent mechanism; Tatar et al. 1997, Adcock et al. 2003), it has also been reported that sulfur dioxide inhalation is acutely inhibitory for cough (Hanacek et al. 1984). Sulfur dioxide is known to activate lung C-fibers (Ho et al. 2001).
Adcock et al. (2003) 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. Humans readily cough to capsaicin and bradykinin challenge, but are refractory to serotonin and adenosine challenge (Stone et al. 1993; Burki et al. 2005) while intravenous capsaicin infusion is only minimally effective at evoking cough (Winning et al. 1986). There is also a report of serotonin-mediated inhibition of cough in human subjects (Stone et al. 1993). A comparable inability of intravenously capsaicin to evoke coughing has been reported in studies using conscious nonhuman primates (Deep et al. 2001).

5 CNS Pharmacology and Central Interactions Between Airway Afferent Nerve Subtypes

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 the nucleus of the solitary tract (nTS), particularly in the commissural and medial subnuclei (Davies and Kubin 1986; Kalia and Richter 1988; Bonham and Joad 1991; Ezure et al. 1991; Kubin et al. 1991; Lipski et al. 1991; Otake et al. 1992; Mazzone and Canning 2002a, b; Kubin et al. 2006). SARs terminate primarily ipsilateral to their vagal origin, rostral to obex in the lateral and interstitial subnuclei (Kalia and Richter 1985; Davies et al. 1987a,b; Bonham and McCrimmon 1990; Ezure et al. 2002; Kubin et al. 2006). No attempt at differentiating termination sites of RAR, SAR, or C-fiber subtypes has been described. In addition to the studies of SAR, RAR, and bronchopulmonary C-fiber termination sites, some work has been done to identify the nTS subnuclei regulating the cough reflex (Gestreau et al. 1997; Ohi et al. 2005; Jakus et al. 2008).

Electrophysiological and functional studies show evidence for bronchopulmonary afferent nerve convergence in the CNS (Takagi et al. 1995; Paton 1998; Silva-Carvalho et al. 1998). Coincident activation of airway afferent nerve subtypes can have synergistic effects on airway reflexes, including reflex bronchospasm and cough (Mazzone and Canning 2002a, b; Mazzone et al. 2005) (Fig. 5). Such synergistic interactions may explain the association between extrapulmonary disorders (e.g., gastroesophageal reflux disease, allergic rhinitis) and cough.

Several studies have characterized the pharmacology of the primary central synapses for airway vagal afferent nerves and have revealed a prominent role for glutamate acting via non-NMDA receptors (Bonham et al. 1993; Vardhan et al.
Notably, however, NMDA receptor activation plays an essential role in the initiation of cough, explaining in part the ability of the antitussive agent dextromethorphan to prevent coughing in animals and in human subjects (Canning et al. 2004, 2006a, b; Mutolo et al. 2007). Other agents shown to act centrally in nTS to regulate airway vagal reflexes include μ-opioid receptor agonists (codeine, DAMGO), GABA_B receptor agonists, sigma agonists, and TRPV1 receptor agonists (Mazzone and Geraghty 1999; Mazzone et al. 2005; Ohi et al. 2005, 2007; Mutolo et al. 2007, 2008). Serotonin (5-HT) receptor antagonists have also been shown to act centrally to modulate airway reflexes, but their site of action has not been determined (Bootle et al. 1996).

The tachykinins substance P and neurokinin A have been localized to airway afferent neurons, and tachykinin receptor antagonists have been shown to reduce or abolish coughing evoked in guinea pigs, dogs, rabbits, cats, and pigs (Advenier and Emonds-Alt 1996; Bolser et al. 1997; Moreaux et al. 2000; House et al. 2004; Mutolo et al. 2008). Capsaicin microinjection in nTS evokes respiratory reflexes in rats that are abolished by neurokinin receptor antagonists, while coughing evoked in rabbits and sensitization of cough induced in guinea pigs is markedly inhibited or abolished by nTS microinjection of neurokinin receptor antagonists (Mazzone and Geraghty 1999; Mazzone et al. 2005; Mutolo et al. 2008). A central site of action for neurokinin receptor antagonists in cough in cats and in guinea pigs has also been suggested (Bolser et al. 1997). Reflex bronchospasm evoked by laryngeal capsaicin and by intravenous bradykinin in guinea pigs is also prevented by centrally acting neurokinin receptor antagonists (Canning et al. 2001; Mazzone and Canning 2002a, b) (Fig. 5). Neurokinin-1 receptor antagonists are also used clinically to treat emesis, a vagal reflex in humans that has many similarities to the cough reflex (Hornby 2001; Warr 2006). It seems likely then that neurokinins released from the central terminals of airway afferent nerves may also modulate airway reflexes in humans and in other species. It is thus interesting and confusing that in electrophysiological recordings of nTS neurons receiving synaptic input from airway afferent nerves, little evidence for an excitatory effect of neurokinins in otherwise healthy animals has been reported. Indeed, in one study, exogenously administered substance P was found to act presynaptically to depress synaptic transmission in nTS (Sekizawa et al. 2003). Many of these studies involved recording from unidentified synapses or the synapses of RARs or SARs, which are unlikely to express substance P under normal conditions. But even in recordings in C-fiber relay neurons, synaptic transmission has been explained entirely by the actions of glutamate (Wilson et al. 1996; Mutoh et al. 2000). This suggests that under the experimental conditions used for the electrophysiological recordings done to date, solitary tract stimulation is subthreshold in intensity, frequency, or duration for tachykinin release, the neurons selected for recording (i.e., neurons receiving monosynaptic input) are typically devoid of direct tachykinin input, or the process of tissue harvest and slice preparation effectively silences neurokinin-mediated effects in nTS.
6 Airway Sensory Nerves and Bronchial Hyperresponsiveness

6.1 Defining Characteristics of Bronchial Hyperresponsiveness

A number of clinical features distinguish asthmatic subjects from other respiratory diseases and may be considered characteristic of this phenotype (Avital et al. 1995). These include an exacerbation of disease following exposure to β-adrenoceptor antagonists (Bond et al. 2007), an impairment in the ability to bronchodilate following deep inspiration (Slats et al. 2007), and their bronchoconstrictor sensitivity to a wide range of innocuous stimuli (Cockcroft and Davis 2006; Van Schoor et al. 2002).

It is well established that asthmatic subjects are invariably more responsive to a range of stimuli, as expressed by an increase in provocative concentration that induces a 20% fall in forced expiratory volume in 1 s termed “bronchial hyperresponsiveness” (BHR). However, not only is there an increase in the sensitivity of the airways to a stimulus, but there is also an increase in the maximum degree of airway narrowing for a given dose of agonist (Fig. 6). The importance of understanding the underlying mechanism contributing toward BHR is confirmed by a study showing that treating the underlying hyperresponsiveness leads to a better improvement in asthma symptoms (Sont et al. 1999). A number of mechanisms have been proposed to account for why asthmatic subjects are invariably more responsive to the external environment. These include an alteration in airway geometry due to an increase in airway smooth muscle thickness that would lead to a greater degree of airway narrowing for a given dose of agonist and/or perturbations in myosin-actin function resulting in a loss in the ability of smooth muscle to dilate in response to deep inspiration, thereby leading to enhanced bronchoconstrictor responses (An et al. 2007; Gil and Lauzon 2007); the release of cytokines and growth factors from epithelial cells which stimulate mesenchymal cells and promote structural changes in the airways leading to airway remodeling, airway inflammation, and BHR (Holgate 2007); and recruitment and activation of dendritic cells, T lymphocytes, and eosinophils whose cell-derived products trigger a cascade of events within the lung leading to epithelial cell damage, increased smooth muscle contractility, and airway remodeling (Beier et al. 2007; Hammad and Lambrecht 2007; Jacobsen et al. 2007; Kallinich et al. 2007; Lloyd and Robinson 2007; Rosenberg et al. 2007). These mechanisms are all thought to contribute toward BHR in asthma, are likely to be interrelated, and contribute to the overall expression of BHR. However, there is also good evidence for the contribution of airway sensory nerves in this phenomenon (Spina and Page 2002) that might be likened to allodynia and/or hyperalgesia, which are characteristic of pain syndromes (Carr and Undem 2003; Undem et al. 2002).
It is common for clinicians to use stimuli such as methacholine and histamine to induce bronchoconstriction because these agents are relatively convenient to use. However, although there is a separation in airways responsiveness to these agents between asthmatic subjects and healthy individuals, there is a considerable degree of overlap and it has been suggested that these agents may not be sensitive indicators of the asthma phenotype (Avital et al. 1995; O'Connor et al. 1999). In contrast, asthmatic subjects invariably respond to a wide range of physiological stimuli that are otherwise refractory in healthy subjects. An understanding of the mechanisms by which these stimuli induce bronchoconstriction suggests that sensitization of afferent pathways may underlie this phenomenon.

6.2 Bronchial Hyperresponsiveness and Sensory Nerves

It is common for clinicians to use stimuli such as methacholine and histamine to induce bronchoconstriction because these agents are relatively convenient to use. However, although there is a separation in airways responsiveness to these agents between asthmatic subjects and healthy individuals, there is a considerable degree of overlap and it has been suggested that these agents may not be sensitive indicators of the asthma phenotype (Avital et al. 1995; O’Connor et al. 1999). In contrast, asthmatic subjects invariably bronchoconstrict in response to the indirect-acting stimuli described earlier, which provoke little if any response in otherwise healthy individuals or in subjects with other respiratory diseases (Avital et al. 1995; Van Schoor et al. 2000).

Asthmatic subjects bronchoconstrict in response to a number of physiological stimuli such as exercise, distilled water, cold air, and hypertonic saline which are otherwise refractory in healthy subjects. Similarly, acidification, pollutants such as sulfur dioxide, and chemical substances, including adenosine, bradykinin, and neuropeptides, evoke bronchoconstriction in asthma but have little if any effect in

![Fig. 6 Bronchial hyperresponsiveness (BHR) in asthma. It is convenient to measure changes in forced expiratory volume in 1 s (FEV₁) to increasing doses of methacholine. In asthma, there is an increase in sensitivity (leftward position of the dose–response curve) often measured in terms of PC20 (dotted line) and reactivity (increase in slope) and in severe cases of the disease an inability to define the maximum degree value for airway narrowing compared with healthy subjects. However, BHR as measured by changes in FEV₁ to increasing doses of methacholine may not be a sensitive indicator of the asthma phenotype (see the text). An increase in BHR can occur during exacerbation of disease as observed naturally during the pollen season, in the case of an allergic asthmatic, or following the deliberate exposure to a relevant antigen (arrow). However, asthmatic subjects are invariably responsive to a wide range of physiological stimuli that are otherwise refractory in healthy subjects. An understanding of the mechanisms by which these stimuli induce bronchoconstriction suggests that sensitization of afferent pathways may underlie this phenomenon.](image)
nondiseased individuals. These agents are commonly referred to as “indirect-acting stimuli,” since they do not appear to mediate bronchoconstriction by direct activation of airway smooth muscle. They are thought to elicit bronchospasm by activating a number of different cell types, including mast cells, vascular smooth muscle cells, and vascular endothelial cells, and/or airway nerves (Spina and Page 1996, 2002; Van Schoor et al. 2000). A number of studies which measured the generation of action potentials from individual afferent nerves using well-established electrophysiological techniques have shown that stimuli including sulfur dioxide, acidification, distilled water, bradykinin, neuropeptides, and adenosine can activate C-fiber and Aδ-fibers in vivo (Table 1). It is therefore of interest that asthmatic subjects are sensitive to such stimuli, whereas healthy subjects are invariably unresponsive to these agents (Van Schoor et al. 2000).

This suggests that the mechanisms by which these stimuli provoke bronchoconstriction are upregulated in asthma and characteristic of this phenotype. Furthermore, airways inflammation appears to be correlated better with BHR to indirect stimuli such as adenosine (van den Berge et al. 2001), bradykinin (Polosa et al. 1998; Roisman et al. 1996), and hypertonic saline (Sont et al. 1993) than it is to more direct acting stimuli such as methacholine. Similarly, during an exacerbation of BHR following the deliberate exposure of an asthmatic subject to an environmental allergen (e.g., house dust mite) there is a preferential increase in BHR to an indirect-acting stimulus such as bradykinin compared with methacholine (Berman et al. 1995).

On the other hand, a number of pharmacological drugs used to treat asthma, including nedocromil sodium and ipratropium bromide, suppress airways responsiveness to these indirect-acting stimuli, suggesting the likely involvement of neural reflexes (Van Schoor et al. 2000). Furthermore, it is now recognized that glucocorticosteroids preferentially suppress BHR to adenosine (Ketchell et al. 2002; van den Berge et al. 2001) and bradykinin (Reynolds et al. 2002) compared with methacholine.

It is also noted that there is often a wide variability in airway sensitivity to spasmogens in subjects with mild asthma and there is little or very poor correlation between airway sensitivity to indirect-acting bronchoconstrictor agents such as adenosine and sensitivity to direct-acting stimuli such as methacholine. Also, BHR to an indirect-acting stimulus is greater during an exacerbation of asthma and lower following anti-inflammatory treatment compared with BHR to methacholine, which directly activates airway smooth muscle (O’Connor et al. 1999; Van Schoor et al. 2000). This apparent lack of correlation between bronchoconstrictor potency of these different types of stimuli suggest that alteration in the thickness of the airway wall (i.e., airway remodeling) alone cannot account for these discrepancies. If airway remodeling were responsible, then there would be a better correlation between bronchoconstrictor potency of indirect-acting and direct-acting stimuli. Furthermore, inflammatory insults to the airway wall would cause a similar change in BHR to these different agents and, finally, there would be no preferential effect of drug treatment on BHR to different stimuli.

Together, the findings of clinical studies support the notion that inflammatory insults to the lung might increase the activity of neuronal pathways, thereby
Table 1 Electrophysiological evidence for activation of afferent nerves in vivo by substances that elicit bronchoconstriction in asthmatic subjects

| Stimulus        | RARs               | C-fibers                   | References                                                                 |
|-----------------|--------------------|----------------------------|-----------------------------------------------------------------------------|
| Sulfur dioxide  | Cat, rabbit        | Dog, rat                   | Widdicombe (1954a, b), Boushey et al. (1974), Ho et al. (2001), Matsumoto et al. (1997), Roberts et al. (1982) |
| Distilled water | Dog                | Dog, guinea pig            | Fox et al. (1995), Pisarri et al. (1992)                                    |
| Bradykinin      | Guinea pig         | Guinea pig, Mouse          | Bergren (1997), Fox et al. (1993), Ricco et al. (1996)                       |
|                 |                    |                            | Kollarik and Undem (2004)                                                  |
| Neuropeptides   | Rabbit             | Rabbit, guinea pig         | Bergren (2006), Bonham et al. (1996), Prabhakar et al. (1987)                |
| Capsaicin       | Cat, guinea pig    | Cat, dog, guinea pig, rat, mouse | Armstrong and Luck (1974), Bergren (1997)                                   |
|                 |                    |                            | Mohammed et al. (1993), Morikawa et al. (1997)                              |
|                 |                    |                            | Coleridge and Coleridge (1977), Dixon et al. (1980), Fox et al. (1993), Ho et al. (2001), Jackson et al. (1989), Kollarik and Undem (2004), Ricco et al. (1996) |
| Adenosine       |                    | Rat, guinea pig            | Chuaychoo et al. (2006), Hong et al. (1998), Kwong et al. (1998)             |
| Endotoxin       | Rat                | Rat                        | Lai et al. (2005), Ruan et al. (2005)                                       |

RARs rapidly adapting receptors
resulting in heightened sensitivity of the lungs to these indirect-acting stimuli. Furthermore, one cannot view BHR as a nonspecific phenomenon, that is to say, that asthmatics are hyperresponsive to all stimuli, but rather it is increasingly apparent that BHR is more heterogeneous than is widely appreciated (O’Connor et al. 1999) and sensory nerves might be a common pathway through which BHR is manifested in respiratory diseases such as asthma.

6.3 TRPV1 and Bronchial Hyperresponsiveness

Transient receptor potential (TRP) channels are protein sensors for the perception of pain, taste, hearing, and smell and comprise at least six subfamilies (Nilius et al. 2007). One member of this superfamily (TRPV1) is predominantly localized to small-diameter afferent neurons in dorsal and vagal sensory ganglia (Szallasi and Blumberg 1999) and activation by capsaicin gives rise to feelings of warmth, heat, and pain. The cloning and expression of TRPV1 has increased our understanding of the role of this protein in neurogenic pain, but also with migraine, cough, irritable bladder disease, and gastrointestinal inflammation (Cortright et al. 2007; Geppetti and Trevisani 2004; Jia and Lee 2007; Kollarik et al. 2007; Liddle 2007; Ma and Quirion 2007; Okajima and Harada 2006; Storr 2007). The role of these proteins in contributing to BHR has been investigated in a number of experimental models. It has long been recognized that capsaicin selectively activates a subpopulation of afferent nerves, the neuropeptide containing C-fibers. However, it is now well established that capsaicin may also target a subset of airway Aδ-fibers whose cell nuclei reside within the jugular but not nodose ganglion (Myers et al. 2002). The activation of both of these nerve types can lead to a number of physiological changes within the airways, including reflex bronchoconstriction, release of sensory neuropeptides, edema, cough, and submucosal gland secretion (De Swert and Joos 2006).

Chronic treatment with capsaicin in various animal species leads to an impairment of somatosensory function as a consequence of depletion of sensory neuropeptide content, downregulation of TRPV1 receptor expression, and/or destruction and loss of sensory nerves (Watanabe et al. 2005, 2006). A consequence of chronic treatment with capsaicin upon neural function in the lung is an attenuation of BHR induced by a range of stimuli (Table 2). Thus, BHR induced by exposing nonallergic animals to lipid mediators, including platelet-activating factor and 15-hydroperoxyeicosatetraenoic acid, is attenuated. A similar observation was noted when BHR was elicited following exposure of nonallergic animals to lipopolysaccharide, ozone, citric acid, parainfluenza-3 virus, and poly(l-lysine) or exposure of allergic animals to inhaled antigens (Table 2). It has been concluded that the peripheral release of sensory neuropeptides per se was responsible for inducing BHR because depletion of sensory neuropeptides within the airways was a natural consequence of chronic treatment with capsaicin. Indeed a variety of animal experimental data have provided a wealth of information concerning the potential role of tachykinins
Table 2  Studies demonstrating a role for sensory nerves in bronchial hyperresponsiveness (BHR)

| Stimulus\(^a\) | Spasmogen | Species         | Effect of chronic capsaicin treatment on BHR | Effect of chronic capsaicin treatment on inflammatory cell recruitment | References                   |
|----------------|-----------|-----------------|---------------------------------------------|----------------------------------------------------------------|------------------------------|
| Antigen        | Acetylcholine | Guinea pig     | Inhibited                                  | No effect                                                   | Matsuse et al. (1991)         |
| Histamine      | Acetylcholine | Rabbit          | Inhibited                                  | No effect                                                   | Herd et al. (1995)            |
| Histamine      | Acetylcholine | Rabbit          | Inhibited                                  | No effect                                                   | Riccio et al. (1993)\(^f\)   |
| Serotonin      | Serotonin   | Rat (BNxWi/Fu)  | Increased\(^e\)                            | Increased\(^e\)                                             | Ahlstedt et al. (1986)\(^f\) |
| TDI            | Acetylcholine | Guinea pig     | Inhibited                                  | Not measured                                                | Thompson et al. (1987)        |
| Acetylcholine  | Rabbit      | Inhibited      | Not measured                               |                                                             | Marek et al. (1996)           |
| SO\(_2\)       | Methacholine | Rat (Sprague-Dawley) | Augmented\(^c\)                           | Not measured                                                 | Long et al. (1997)\(^f\)     |
| LPS            | Histamine   | Guinea pig     | Inhibited                                  | Inhibited                                                   | Jarreau et al. (1994)         |
| Histamine      | Guinea pig  | Augmented\(^d\) | Not measured                               |                                                             | Loeffler et al. (1997)        |
| Ozone          | Histamine   | Guinea pig     | Inhibited                                  | Not measured                                                 | Tepper et al. (1993)          |
| Methacholine   | Guinea pig  | Inhibited      | Not measured                               |                                                             | Koto et al. (1995)            |
| EFS\(^b\)      | Acetylcholine | Guinea pig     | Inhibited                                  |                                                             | Jimba et al. (1995)\(^f\)   |
| Citric acid    | Acetylcholine | Guinea pig     | Inhibited                                  | Not measured                                                 | Vesely et al. (1999)\(^f\)   |
| Parainfluenza-3| Acetylcholine | Guinea pig     | Inhibited                                  | Not measured                                                 | Riedel et al. (1997)          |
| Cigarette smoke| Acetylcholine | Guinea pig     | Inhibited                                  | Not measured                                                 | Daffonchio et al. (1990)      |
| PAF            | Histamine   | Rabbit          | Inhibited                                  | Neutrophils inhibited; eosinophils not inhibited             | Spina et al. (1991)           |
| 15-HPETE       | Acetylcholine | Guinea pig     | Inhibited                                  | Not measured                                                 | Perretti and Manzini (1993)   |
|                | Histamine   | Rabbit          | Inhibited                                  | No effect                                                   | Riccio et al. (1997)          |

(continued)
Table 2 (continued)

| Stimulus  | Spasmogen | Species                          | Effect of chronic capsaicin treatment on BHR | Effect of chronic capsaicin treatment on inflammatory cell recruitment | References               |
|----------|-----------|----------------------------------|---------------------------------------------|-----------------------------------------------------------------------|---------------------------|
| Poly(L-lysine) | Methacholine | Rat (Sprague-Dawley) | Inhibited                          | Not determined                                                        | Coyle et al. (1994) |
|          |           | Nonallergic chronic rhinitis     | Nasal resistance inhibited; symptom scores reduced |                                                                 | Lacroix et al. (1991) |
|          |           | Allergic rhinitis                | Hyperosmolar response inhibited; symptom scores reduced |                                                                 | Sanico et al. (1999) |

15-HPETE 15-hydroperoxyeicosatetraenoic acid, LPS lipopolysaccharide, PAF platelet-activating factor, TDI toluene diisocyanate, EFS electrical field stimulation

*Stimulus denotes a substance used to induce bronchial hyperresponsiveness

*EFS and BHR was measured in vitro

Unlike in guinea pigs, rabbits, ferrets and humans, neurokinins released from capsaicin-sensitive nerves are bronchodilators in rats (and mice), which may explain in part the augmentation of bronchial responsiveness seen with capsaicin pretreatment in rats (Manzini 1992; Szarek et al. 1995)

*BHR augmented at 2 h but not at 1 and 3 h after LPS challenge

*Data not analyzed statistically

*Treatment of neonates with capsaicin but measurement of bronchial hyperresponsiveness and inflammation performed in adult animals
such as substance P, neurokinin A, and CGRP in altering both resident lung and inflammatory cells, thereby perpetuating the inflammatory process in the lung and contributing to this process and inducing BHR (De Swert and Joos 2006).

It is therefore surprising that neurokinin antagonists have thus far proved disappointing in clinical trials in asthma (De Swert and Joos 2006). However, the rationale for the development of tachykinin antagonists was based on the assumption that local release of tachykinins from C-fibers was sufficient to perpetuate the inflammatory response. One can only conclude that other mediators released within the airways contribute to the inflammatory process, or the possibility that capsaicin is selective for C-fiber afferents in the airways needs to be revised since TRPV1 may also be localized to non-C-fiber afferents, or is not necessarily colocalized with sensory neuropeptides (Guo et al. 1999; Myers et al. 2002; Tominaga et al. 1998; Watanabe et al. 2005, 2006), and, therefore, sensory-neuropeptide-independent mechanisms may also operate in the lung. Furthermore, most studies showing an importance for tachykinins in mediating BHR stem from studies conducted in the guinea pig, an animal rich in sensory neuropeptide innervation in the lung. In contrast, the rabbit is relatively resistant to the neuropeptide-depleting effects of capsaicin despite the inhibition of BHR induced by nonimmunological and immunological methods (Herd et al. 1995; Riccio et al. 1997) and, therefore, mechanisms other than neuropeptide depletion must account for this phenomenon, and the peripheral release of sensory neuropeptides is not obligatory for the development of BHR. This may be one reason why, thus far, selective neurokinin antagonists have proved disappointing in the treatment of asthma (Spina and Page 2002).

Studies using capsaicin have shown that the functional effect of neuropeptides on airway smooth muscle is species-dependent. Rabbit, monkey, and human airways contract weakly on exposure to capsaicin in vitro (Ellis et al. 1997; Spina et al. 1998), whereas guinea-pig airways are very sensitive (Grundstrom et al. 1981). These variable functional effects are superficially consistent with the differential localization of substance P and CGRP in the airways across species, as the occurrence of these neuropeptide-containing nerves in human and rabbit tends to be sparse (Hislop et al. 1990; Howarth et al. 1995; Laitinen et al. 1983; Lundberg et al. 1984), whereas neuropeptides are found widely throughout the airways of guinea pigs (Hua et al. 1985; Nohr and Weihe 1991; Saria et al. 1985).

Hyperalgesia induced by chemical and thermal stimuli is suppressed in TRPV1 knockout mice, suggesting that this protein is an important transducer of pain (Gunthorpe et al. 2002; Julius and Basbaum 2001). It is therefore of interest that chronic treatment with capsaicin in humans can lead to a suppression of alldynia and hyperalgesia induced by intradermal injection of capsaicin (Davis et al. 1995) and when applied topically to the nose, capsaicin reduces nasal hyperresponsiveness in allergic rhinitis patients (Sanico et al. 1999). A loss in TRPV1 signaling might help explain the loss in BHR observed in various experimental animal models (Spina and Page 2002).
6.4 TRPV1 Antagonist and Knockout Studies

If the activation of TRPV1 is important for the sensitization of primary afferent nerves in the lung, then it would seem reasonable to suggest that pharmacological antagonism of this protein might reduce BHR. Unfortunately, very few studies have specifically addressed this question in the context of BHR. In one study, BHR was induced in the guinea pig by acute challenge with platelet-activating factor, which was inhibited following pretreatment with ruthenium red, a nonselective TRP channel blocker (Perretti and Manzini 1993). Studies using TRPV1 antagonists may require an additional control to rule out any possible bronchorelaxant capabilities that may confound any potential effect on BHR (Skogvall et al. 2007).

The effect of TRPV1 antagonists on cellular recruitment has been investigated in a number of inflammatory models. The TRPV1 antagonist N-(4-chlorobenzyl)-N'-[(4-hydroxy-3-iodo-5-methoxybenzyl) thiourea had no effect on neutrophil recruitment induced by injection of complete Freund’s adjuvant into the hindpaw of mice (Tang et al. 2007). In contrast, capsazepine inhibited neutrophil recruitment to the lung induced by systemic administration of hydrogen sulfide donor (Bhatia et al. 2006) and inhibited neutrophil recruitment in a model of colitis (Kihara et al. 2003) and pancreatitis (Hutter et al. 2005). Differences in the severity of the inflammatory models utilized in these studies may account for the lack of general consensus concerning the role of TRPV1 in inflammatory cell recruitment; however, as indicated earlier, the findings of most chemical ablation studies using chronic treatment with capsaicin are consistent with the peripheral involvement of sensory neuropeptides in neutrophil recruitment to sites of inflammation (Table 2).

There has also been a paucity of studies utilizing TRPV1 gene deficient mice to study the role of this protein in BHR and inflammation. In one study, BHR in response to lipopolysaccharide challenge was significantly augmented in TRPV1 knockout mice, and highlighted the existence of an anti-inflammatory substance (e.g., somatostatin) released from TRPV1-positive cells, which could act in a negative-feedback mechanism to limit the inflammatory response (Helyes et al. 2007). However, these data are not consistent with those form chemical ablation studies showing that BHR to lipopolysaccharide is inhibited in the guinea pig (Jarreau et al. 1994). This discrepancy may be due to the two different methods employed to “impair” TRPV1 signaling. It could be envisaged that sensory nerves would be bombarded by multiple signals by a plethora of mediators released following the initial insult, resulting in the activation of various receptor proteins (e.g., bradykinin and NGF receptor, other TRPs) on primary afferent terminals. These signals would be processed at the level of the nTS, but would also require the activation of TRPV1 for a facilitated response (i.e., gain in function). However, the interpretation of these signals by the nTS would be lost following chemical ablation with capsaicin, owing to destruction of the peripheral terminations of C-fibers in the airway, but these would be retained in TRPV1 knockout mice with an intact afferent nervous system and therefore would still able to signal to the nTS. Alternatively, compensatory mechanisms during the development of TRPV1 knockout mice
might account for this anomaly. The implication is that impairment of sensory nerve function (e.g., via TRPV1 desensitization) may be required instead of TRPV1 antagonism to completely suppress BHR.

In terms of the inflammatory response, it appears that neutrophil recruitment in joint inflammation was either unaffected (Keeble et al. 2005) or augmented during inflammatory insults to the lung (Helyes et al. 2007) and gastrointestinal tract (Massa et al. 2006). Similarly, the amounts of TNF-\(\alpha\) released within the extracellular space at sites of inflammation were either increased (Clark et al. 2007) or unaffected (Keeble et al. 2005) by gene deletion of TRPV1 in different inflammatory models. Hence, these murine models have been inconclusive concerning the role of TRPV1 in mediating BHR and/or inflammation. The observation that activation of TRPV1 may stimulate the release of an anti-inflammatory substance in the mouse also makes it difficult to elucidate the role of TRPV1 in BHR and inflammation in this species (Helyes et al. 2007).

7 Conclusions

Airway sensory nerves play an essential role in regulating airway and lung defensive and homeostatic reflexes. The afferent nerve subtypes regulating these reflexes have unique physiological and pharmacological attributes that are amenable to selective therapeutic interventions. There is extensive evidence to suggest that airway sensory nerves are dysregulated in disease. Therapeutic strategies that target the excitability of airway sensory nerves at their central and peripheral terminations may provide symptom relief in conditions such as cough, asthma, and COPD.

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