The Role of Vagal Afferent Nerves in Chronic Obstructive Pulmonary Disease

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Circumstantial evidence supports the hypothesis that the vagal nervous system is dysregulated in chronic obstructive pulmonary disease. This dysregulation can lead to an increased sensitivity of the cough reflex such that the coughing becomes, at times, "nonproductive" or inappropriate. Vagal dysregulation can also lead to an increase in the activity of the parasympathetic reflex control of the airways, which contributes to greater mucus secretion and bronchial smooth muscle contraction. Indirect evidence indicates that lung disease is accompanied by substantive changes to the entire reflex pathways, including enhanced activity of the primary afferent nerves, increases in synaptic efficacy at secondary nerves in the central nervous system, and changes in the autonomic nerve pathways. Drugs aimed at normalizing neuronal activity may, therefore, be beneficial in chronic obstructive pulmonary disease.

Keywords: bronchopulmonary C-fibers; nociceptors; stretch-sensitive mechanosensors; vagal dysregulation

An optimal therapeutic strategy in chronic obstructive pulmonary disease (COPD) targets airway obstruction and lung tissue destruction so the disease process can be slowed or reversed. The optimal strategy should include treatments aimed at improving symptoms and patients' quality of life (QOL). With a chronic disease such as COPD, achieving these goals may require a combination of therapies. Regarding symptoms and QOL, it is reasonable to assume that abnormal activity in bronchopulmonary vagal sensory nerves significantly contributes to the suffering caused by excessive coughing, bronchospasm, mucus secretion, and dyspnea. Drugs aimed at normalizing neuronal activity may, therefore, be beneficial in COPD. This article reviews the bronchopulmonary sensory nerves and discusses how they, in theory, may contribute to the pathophysiology of COPD.

CLASSIFICATION OF BRONCHOPULMONARY SENSORY NERVES

Categorizing sensory nerves in the respiratory tract can lead to as much confusion as clarity. This is because a sensory nerve "character" is a compilation of several disparate properties, such as conduction velocity, ganglionic origin, activation profile, anatomic location, and the reflexes that activation of the nerve engenders. This review segregates the afferent nerves in the respiratory tract into two general categories: the stretch-sensitive mechanosensors and the nociceptors. There are also myelinated vagal afferent nerve fibers that terminate within the epithelium near neural epithelial bodies, which may represent a subset of mechanosensors or a unique subset of nerves in the lungs. The neuroepithelial afferent nerves are not further discussed here, more because of a lack of functional information on these nerves than their lack of potential importance. For a review of neuroepithelial bodies and their afferent innervation, see Adriaensen and colleagues (1).

Stretch-Sensitive Mechanosensors

A stretch-sensitive mechanosensor is defined as an afferent nerve that responds to nonharmful distention of the lungs. Bronchopulmonary stretch-sensitive nerves have myelinated nerve fibers; that is, they are "A" fibers that conduct action potentials at a relatively high velocity. Most, if not all, of the stretch-sensitive nerves in the lungs are vagal afferent nerves.

The stretch-sensitive fibers can be subdivided based on their adaptation to sustained lung distention. There are those in which the response rapidly adapts to sustained lung distension (rapidly adapting receptors [RAR]) and those in which the response adapts slowly (slowly adapting receptors [SAR]). The RAR and SAR stretch mechanosensors can be activated during eupneic breathing by cyclic lung distention, which occurs during respiration. In most species, the majority of RAR and SAR fibers are situated in the intrapulmonary tissues. Little is known about the specific anatomic location of stretch receptors in the lungs. It is presumed that the sensory nerve structures in the smooth muscle layer long described by neuroanatomists correspond to SAR, whereas those in the mucosal layer are RAR (2).

Nociceptors

The concept and terminology of sensory nociceptors is derived from the early work of Sherrington (3) on sensory innervation of the dog skin. He writes, "There is considerable evidence that the skin is provided with a set of nerve endings whose specific office it is to be amenable to stimuli that do the skin injury, stimuli that in continuing to act would injure it still further." He describes, by inference, a subgroup of sensory nerves in which "the harmfulness is the characteristic of the stimuli by which they are provocable." He goes on to state, "For physiological reference therefore they are … preferably termed nocicipient." Later, in his classic treatise on the integrated nervous system, Sherrington (4) refers to these nocicipient nerves as nociceptive nerves.

It is an obvious advantage for the tissues to have a "sense" of their own injury. It is, therefore, not surprising that neurobiologists have described sensory nerves analogous to cutaneous nociceptors in virtually all organs of the body. Defining a sensory nerve type as nociceptive is somewhat ambiguous. For a nerve to fall under the category of nociceptors, one might reason that two criteria must be met. First, the nerves should be silent in healthy, noninjured, or nonpathologic tissue. Second, on activation they should evoke defensive reflexes. Based on these criteria, at least two types of nociceptors have been described in the respiratory tract. One type of nociceptor is situated in the larynx and large airways and, on punctiform mechanical stimulation (focused touch) of the mucosal surface, evokes a rapid cough reflex. The other type of nociceptive nerve is the bronchopulmonary C-fiber. In a healthy environment, neither the cough-evok-

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ing, touch-sensitive mechanosensors nor the bronchopulmonary C-fibers are activated during respiration.

Touch-sensitive cough fibers. In guinea pig airways, the nodose ganglia project a unique nociceptor to the larynx, trachea, and main bronchi (5, 6). These are A-fibers that conduct action potentials about three to five times faster than C-fibers but about three to five times slower than the stretch-sensitive RAR and SAR fibers. The nerves terminate in the submucosa just beneath the basement membrane. The terminals are exquisitely sensitive to a punctate mechanical "touch" stimulus applied to the mucosa. The nerves respond primarily to the dynamic phase of a ramp-and-hold mechanical stimulus applied to the mucosa, thus resembling a rapidly adapting response (7). Unlike RAR nerves, however, these fibers are relatively insensitive to smooth muscle constriction or stretch (longitudinal or circumferential). In addition to being activated by punctate mechanical stimuli, they are activated by acid in a rapidly adapting manner (8). Activation of these extrapulmonary touch-sensitive nociceptors causes a rapid cough reflex, even in an anesthetized animal (6). Afferent fibers of this type are absent (or nearly so) in rats and mice, two species that typically do not cough in response to mechanical probing of their large airways (B. Canning, personal communication).

Bronchopulmonary C-fibers. Most of the afferent nerve fibers innervating the respiratory tract are thin unmyelinated fibers (9). As a consequence, they conduct action potentials at a much slower rate than the stretch-sensitive mechanosensors. Based on their slow conduction velocity, they are termed C-fibers. Capsaicin, the active ingredient in hot peppers, is a prototypical C-fiber stimulus in the somatosensory system. With few exceptions, C-fibers in mammalian lungs are robustly activated by capsaicin (10). Capsaicin-sensitive C-fibers typically respond to noxious stimuli such as intense heat, cold, or harmful mechanical forces. Capsaicin-sensitive C-fibers are also sensitive to many autocoids released on tissue damage and inflammation. On activation, C-fibers evoke defensive reflexes that include apnea, rapid shallow breathing, mucus secretion, bronchoconstriction, and cough (11).

Vagal C-fibers are found throughout the respiratory tract from the nose to the alveoli. In large airways, the C-fibers form a dense nerve plexus just beneath the epithelium. In the region of gas exchange in the lung parenchyma, they are found next to the capillaries (these are sometimes termed juxtacapillary receptors or J-receptors [12]). Based on their anatomic location, C-fibers have been subclassified as bronchial and pulmonary C-fibers (11). Bronchial C-fibers are experimentally identified as those most accessible through bronchial circulation, whereas the pulmonary C-fibers are more readily accessed from pulmonary circulation.

The subclassification of bronchopulmonary C-fibers has been extended, at least in guinea pigs, by considering the ganglionic location of the cell soma (13). Two sensory ganglia form an hourglass figure on the most cervical aspect of the vagus nerves. The swelling closest to the brain is referred to as the jugular ganglion, whereas the lower ganglion is referred to as the nodose. Neurons situated in the nodose ganglion are embryonically derived from the epibranchial placodes, whereas jugular ganglion neurons are derived from the neural crest (14). The nodose neurons project all the stretch-sensitive mechanoreceptors to the guinea pig lungs and to the touch-sensitive nociceptors. Neurons in both ganglia project C-fibers to the guinea pig respiratory system. The jugular (neural crest) C-fibers innervate the larynx, trachea, main bronchi, and intrapulmonary airways (5, 13). The nodose (placodal) C-fibers innervate intrapulmonary tissues but are rarely found in extrapulmonary airways. It would seem that the nodose fibers at least loosely correspond to pulmonary C-fibers and that jugular fibers correspond to bronchial C-fibers, but more work is needed in this area. The activation profile of C-fibers depends on the fiber subtype. For example, in guinea pigs, jugular and nodose C-fibers respond to capsaicin and bradykinin, but only nodose C-fibers respond to serotonin (15), ATP (13), and adenosine (unpublished observations). Differences in chemical activation have also been noted between bronchial and pulmonary C-fibers in dogs and cats (16). In addition to nodose and jugular C-fibers, the lungs are innervated by C-fibers derived from the dorsal root ganglia. These "spinal C-fibers" have not been extensively studied, but, based on preliminary data, we find that they are more similar to jugular C-fibers than nodose C-fibers.

SENSORY NERVES IN COPD

Activation of Stretch-Sensitive Nerves

The activation of stretch-sensitive afferent fibers (RAR and SAR) is dependent on the rate and depth of breathing (tidal volume). To the extent to which respiratory rate and tidal volume change in COPD/emphysema, one would expect different patterns of activity of stretch-sensitive nerves. When the disease reaches a state where the subject is breathing at a state of dynamic hyperinflation, it is likely that the activity of SAR fibers are increased. If the rate of breathing is increased, one might expect a corresponding increase in activity of RAR fibers.

How the mechanical energy of stretch is transduced to neural activity in these fibers is unknown. It is likely that the nerve terminals are tethered to the tissue matrix in a fashion that results in perturbations in the nerve terminal membrane during tissue distention. The nerve membrane distortion results in the opening of undefined mechanically gated ion channels, effecting membrane depolarization and nerve activation. The efficiency of this transduction process is probably susceptible to local anatomic changes that occur during airway wall remodeling, but there is little experimental evidence that sheds objective light on this speculation. Changes in lung compliance also influence the activity of stretch-sensitive nerves. For example, there is an inverse relationship between lung compliance and efficacy of RAR activation (17).

Stretch-sensitive afferent nerves are relatively unimodal nerves. Other than mechanical distortion of their receptive fields, few stimuli lead to their activation. Chemicals that lead to an increase in smooth muscle tension can indirectly increase the activity of RAR and SAR fibers. The bronchoconstriction that can accompany COPD could, therefore, increase the activity of stretch-sensitive nerves. Stimulation of P2X receptors with ATP can activate stretch-sensitive fibers in guinea pigs, and this seems to be a direct effect on the nerves, independent of mechanical activation (5, 13). Whether extracellular ATP is increased in the relevant locations within the lungs of patients with COPD is unknown.

The alterations in gas tensions in the patient with COPD can also modulate the activity of stretch-sensitive nerves. Modest increases in pulmonary arterial P_{CO_2} markedly suppresses the activity of SAR fibers (18). This effect likely contributes to the ventilatory reflex response to hypercapnia. The effect of increasing P_{CO_2} on RAR fibers is less consistent.

Activation of Nociceptive Nerves

Like the stretch-sensitive nerves, the touch-sensitive, cough-evoking fibers in the larynx and large airways are relatively unimodal in their activation profile (6). We have found that they are resistant to most types of stimulation other than punctiform mechanical stimulation. Relevant mechanical perturbation may occur as a consequence of mucus impinging on the receptive field. These fibers are also sensitive to decreases in pH. Their pH sensitivity is a function of the rate of pH changes (8). If the

change in pH is rapid, the fibers can be activated by a pH of 6.8. It is conceivable that rapid pH changes at the receptive field could occur in reflux disease if acidic esophageal contents are microaspirated into the trachea. The trachea cough-evoking fibers are not activated by steady-state decreases in pH that may accompany tissue inflammation.

Bronchopulmonary C-fibers, in common with nociceptive C-fibers throughout the body, are designed to respond to tissue inflammation. Numerous inflammatory mediators effectively activate bronchopulmonary C-fibers (16, 19). From a pharmacologic perspective, these chemicals can be subdivided into those that depolarize the nerve by directly gating ligand-gated ion channels and those that act through classical G-protein signaling mechanisms. Autocoids that can activate ligand-gated ion channels on bronchopulmonary C-fibers include serotonin (5-HT_3 receptors), ATP (P2X receptors), and nicotine (nicotinic receptors). The capsaicin receptor is a ligand-gated ion channel found on nearly all bronchopulmonary C-fibers. The capsaicin receptor belongs to the transient receptor potential family of ion channels and is activated by certain vanilloids (transient receptor potential [TRP]V1 receptors) (20). The TRPV1 receptor can also be gated by various lipoxygenase metabolites of arachidonic acid that are likely to be elevated in inflamed tissues (21–23). A decrease in pH in the interstitial fluid can also activate ligand-gated ionic channels in bronchopulmonary C-fibers, including TRPV1 and possibly members of the acid-sensing ion channel family (24). The pH is likely to be decreased in COPD lungs at sites of tissue inflammation and hypercapnia. Two examples of G-protein–coupled receptors that are capable of leading to bronchopulmonary C-fiber activation are the bradykinin B_2-receptor and the adenosine A_1-receptor (11, 25).

Bronchopulmonary C-fibers are effectively stimulated by the pulmonary congestion and edema that can accompany COPD. In this regard, the pulmonary C-fibers are more sensitive to changes in vascular volume than the bronchial C-fibers (11). In contrast to the stretch-sensitive SAR, increasing P_{CO_2} does not inhibit nociceptors. There is uncertainty in the literature regarding the role of bronchopulmonary C-fibers as effective sensors of changes in P_{CO_2}. To the extent that elevations in P_{CO_2} modulate bronchopulmonary C-fibers, the response is one of activation (11).

Plasticity

Many autacoids can act via cell surface receptors to increase the excitability of bronchopulmonary C-fibers without overtly evoking action potential discharge (activation). By increasing the excitability, the nociceptors become more responsive to a given activating stimulus. In some instances, the increase in excitability caused by inflammatory mediators has increased the mechanical sensitivity of C-fibers to the extent that they begin responding to eupneic respiration (26).

Mediators of inflammation can also lead to changes in the nerve phenotype by influencing expression of various genes in the cell's nucleus. For example, respiratory virus infections can lead to the induction of tachykinin synthesis in touch-sensitive A-fibers, which normally do not express this peptide (27). Neuropeptide production has also been observed after allergic inflammation (28). Release of neuropeptides from the central terminals of the nerves would substantively change the way the central nervous system interprets the incoming information from mechanosensors in the lungs and airways. The mechanisms for this change in tachykinergic phenotype are unknown, but it is likely that they involve neurotrophins, such as nerve growth factor (29). A similar phenomenon in the somatosensory system has been observed in response to joint inflammation, which might explain allodynia (inappropriate pain sensations) (30).

Changes in electrical excitability and changes in gene expression can long outlast the initial causal stimulus and are therefore often categorized as neuroplasticity. For example, subjecting baby monkeys to airway inflammation leads to persistent increases in the excitability of second-order neurons in the brain stem that can be observed subsequently in an *in vitro* analysis (31). Persistent changes in synaptic function in the brain stem may also arise as a consequence of the constant alterations in primary afferent nerve input. This so-called "use-dependent" plasticity in nerve function is commonly seen in neuronal networks and is manifest as a long-term potentiation or as a depression of synaptic efficacy. Use-dependent plasticity has been used to help explain such phenomena as persistent pain syndromes and respiratory insufficiency syndromes (32, 33). The use-dependent plasticity may be particularly relevant in diseases such as COPD, where the nature of the pathology likely results in persistent and chronic changes in primary afferent nerve activity.

VAGUS NERVES AND SYMPTOMS IN COPD

Dysregulation of vagal afferent nerves in COPD can be expected to contribute to increases in cholinergic smooth muscle tone, mucus secretion, cough, and dyspnea. This is difficult to prove, however, because there has been little research carried out on vagal neurobiology in humans. Moreover, because of neuroplastic changes that accompany diseases such as COPD, the understanding of the neurophysiology in COPD requires that the nerves be studied within the context of the disease state. Nevertheless, generalities emerge from the extensive literature on the neurobiology of the respiratory system that allow informed speculation as to the role of nerves in respiratory disease.

Bronchoconstriction and Mucus Secretion

Increased bronchial smooth muscle tone in COPD is due in large part to augmentations in parasympathetic drive. The increased parasympathetic drive also contributes to the excessive mucus secretion in this disease. These conclusions are based primarily on pharmacologic evidence. Several studies have shown that if the dose is large enough, anticholinergic drugs, such as ipratropium or tiotropium, can relax the airways in patients with COPD to the same extent as a maximally effective dose of a β-agonist (34). One can infer from this that acetylcholine accounts for nearly all the smooth muscle tone in the COPD airway. It would seem, therefore, that to the extent that inflammatory mediators constrict bronchial smooth muscle in COPD, they do so by evoking or enhancing parasympathetic cholinergic reflex activity. This may not be surprising because parasympathetic postganglionic cholinergic nerves are the dominant regulators of airway smooth muscle tone in all mammalian species studied to date (35). The postganglionic parasympathetic nerves can also increase mucus secretion in most mammals, including humans (36), although it is unlikely that parasympathetic mechanisms account for all of the mucus secretion in COPD.

Little is known about the mechanisms underlying increases in parasympathetic tone in COPD. The three major sites at which parasympathetic tone can be regulated include the preganglionic nerves situated in the brain stem, the synapses between the preganglionic nerves and the postganglionic nerves within the parasympathetic ganglia, and the postganglionic neuroeffector cell junction. Although there is evidence that airway inflammation can modulate the activity at each of these sites, the major determinant of parasympathetic tone in the airways is likely preganglionic nerve activity. The preganglionic parasympathetic activity is tightly controlled by stretch-sensitive afferent nerves (37) and by nociceptive nerves, making this a likely dominant site at which the parasympathetic tone is upregulated in COPD.

Stimulation of RAR fibers seems to lead to increases in airway

parasympathetic drive (38, 39). Increasing the rate of respiration causes an increase in activity of RAR fibers, which correlates with an increase in the parasympathetic outflow to the airways. Conversely, input from SAR fibers strongly inhibits parasympathetic preganglionic nerve activity. Modest elevations in CO_2 effectively inhibit SAR activity, releasing the brake on autonomic outflow and increasing parasympathetic drive. On the other hand, breathing at higher lung volumes could increase SAR activity in COPD. In any event, changes in the balance of RAR and SAR input to the brain stem could explain the elevated cholinergic bronchial smooth muscle tone often observed in patients with COPD.

Activation of nociceptive afferent fibers is another likely mechanism for increases in parasympathetic nerve activity in the airways. For reasons outlined previously, the activity of bronchopulmonary nociceptors is likely to be elevated in the lungs of patients with COPD. In all species studied thus far, increases in bronchopulmonary nociceptive C-fiber activity lead to increases in parasympathetic nerve–mediated bronchial smooth muscle contractions and mucus secretion (16).

The parasympathetic innervation of human airways comprises cholinergic and noncholinergic nerves (35). The noncholinergic nerves provide the only relaxant innervation to human bronchial smooth muscle. These nerves use nitric oxide and neuropeptides, such as vasoactive intestinal peptide, as their neurotransmitters. The cholinergic and noncholinergic parasympathetic nerves have been shown to represent separate pre- and postganglionic nerve pathways (40). Therefore, the cholinergic and noncholinergic parasympathetic input to the lungs may be regulated differentially. The role of nociceptors and stretch-sensitive afferent nerves in regulating the noncholinergic parasympathetic pathway is poorly understood. It can be reasoned that an imbalance between cholinergic and noncholinergic parasympathetic nerve activity could account for increases in smooth muscle tone and mucus secretion in COPD.

Cough

The problem of cough is often left unmentioned in discussions of COPD, yet chronic and unrelenting cough can substantially diminish the QOL of those suffering from this disease (41). Cough is a natural consequence of the mucus hypersecretion and airway obstruction that typify the disease. In many patients with inflammatory airway diseases such as COPD, the cough reflex may be pathologically altered, leading to an exaggerated sensitivity of the reflex pathways. An inappropriately sensitized cough reflex may lead to persistent urge-to-cough sensations that result in cough in excess of functional requirements.

Several studies have shown that afferent nerves in patients with COPD may be hypersensitive to a given amount of a tussive stimulus (42, 43). That is, the amount of afferent activation required to trigger cough (the cough threshold) is decreased. This likely occurs through changes in excitability and plasticity of the afferent nerves.

The afferent nerves that are responsible for cough have not been described in humans. In most mammals, mechanical perturbation of the larynx, trachea, and large bronchi, especially at bifurcations, evokes a rapid cough response. The touch-sensitive nociceptive A-fibers responsible for this response have been described in the guinea pig. In other species, the cough-evoking fibers have been termed "irritant receptors" that are closely related to RAR fibers (2).

Inhalation of chemicals that are known to activate nociceptive C-fibers can also lead to cough in humans. Whether the cough-evoking C-fibers are bronchial or pulmonary C-fibers or both is unknown. In contrast to the A-fiber cough, the C-fiber cough is difficult to evoke in anesthetized animals. It may be that the C-fiber–mediated cough is secondary to the conscious urge-to-cough sensations of itch and irritation. Injection of the nicotinic receptor agonist lobeline, an agonist known to activate bronchopulmonary C-fibers, causes strong urge-to-cough sensations in humans. After bilateral lung transplantation (lung denervation), these sensations are reduced or absent (44).

Dyspnea

Mammals have evolved powerful perceptions of the need for food, water, and oxygen. Among the respective perceptions of hunger, thirst, and dyspnea, the latter is the most acute and frightening. Dyspnea is a complex set of perceptions and is experienced in different ways, including "hunger for air," "suffocating sensations," "chest tightness," "difficulty breathing," etc. (45). These sensations are the primary symptom of COPD. It is not surprising that this critical and complex sensation is subserved by multiple redundant sensory pathways (45).

The major drivers of dyspneic sensations are thought to be sensory nerves in the chest wall that sense the movement of the lungs and the work of breathing and peripheral and central chemosensors that sense abnormalities in blood gases (46, 47). In addition to these dyspneic drivers, experimental evidence supports the hypothesis that vagal afferent nerves in the airway wall amplify dyspneic sensations. The neuronal substrates for dyspnea are likely dependent on the provocative stimulus (breath holding, hypercapnea, exercise, etc). The most complex situation occurs when the dyspneic stimulus is layered atop airway pathophysiology, such as in COPD.

Intrapulmonary vagal afferents are not a *sine qua non* for dyspnea. Nevertheless, afferent activity in the vagus may alter the quality and severity of dyspneic sensations. Inasmuch as vagal afferent nerve discharge is elevated in COPD, it may be that the vagal nerves make a major contribution to the overall state of dyspnea in the disease setting.

Evidence for at least some role of vagal afferent nerves in dyspnea comes from a series of studies in which the vagus nerve is sectioned or pharmacologically anesthetized (48). These studies consistently show a contribution of vagal input to dyspneic sensations caused by breath holding. Vagal blockade has a more variable effect on dyspnea associated with various pulmonary pathologies. Bradley and coworkers (49) found that unilateral vagus nerve section (right side) resulted in improvement of dyspnea in four of five patients with emphysema. Bupivacaine inhalation leads to inhibition of the cough response to inhaled citric acid and to a decrease in exercise-induced dyspneic sensations (48).

Studies on parasympathetic reflexes and cough have shown that vagal afferent nerves may be facilitatory or inhibitory, depending on the afferent nerve type (Table 1). The most obvious example of this is that RAR activation increases parasympathetic outflow and SAR activation inhibits this same reflex. It is therefore possible that some vagal afferent nerves inhibit dyspnea, which adds a layer of confusion to studies in which the entire vagus nerve is blocked. Vagal blockade also inhibits parasympathetic bronchoconstriction, which could indirectly influence dyspneic sensations. Inhalation of drugs that stimulate or inhibit a specific subtype of vagal afferent nerve may prove more informative than studies of vagal blockade. To this end, furosemide, a chloride pump inhibitor that inhibits vagal C-fiber activity, has been investigated and has been shown to increase breath-hold time substantially (50) and to inhibit dyspnea modestly in patients with COPD (51). Conversely, drugs known to stimulate airway nociceptors have been shown to cause dyspnea in humans without affecting airway resistance. Drugs in this category include prostaglandin E_2 and adenosine (52, 53).

Although it is likely that vagal afferent nerves contribute qualitatively and quantitatively to the overall dyspneic sensation in COPD, the type(s) of afferent nerve fiber responsible is un-

TABLE 1. SUMMARY OF VAGAL BRONCHOPULMONARY SENSORY NERVES

Sensory Nerve	Conduction Velocity	Ganglion	Activation Stimulus	Reflexes
Stretch-sensitive				
SAR	Aδ-Aβ 10–50 m/s	Nodose	Lung inflation	Decrease parasympathetic outflow (bronchodilation)
				Hering-Breuer Reflex Dyspnea (?)
RAR	Aδ-Aβ 10–50 m/s	Nodose	Lung inflation and deflation	Increase parasympathetic outflow (bronchoconstriction, mucus)
			Decrease in lung compliance	Tachypnea
			Vascular congestion	Cough (?) mm
Nociceptors				
Extrapulmonary touch-sensitive mechanosensors	Aδ 3–8 m/s	Nodose	Punctiform mucosal perturbations	Cough
			Acidic solutions	
Bronchopulmonary C-fibers	C 0.3–2 m/s	Nodose	Inflammatory mediators	Increase parasympathetic outflow (bronchoconstriction, mucus)
		Jugular	Tissue damage	Cough
			Pulmonary edema	Apnea followed by tachypnea
			Acidic solutions	Dyspnea

Definition of abbreviations: RAR = rapidly adapting receptor; SAR = slowly adapting receptor.

The conduction velocities are approximate and may depend on species. The SAR fibers, RAR fibers, and bronchopulmonary C-fibers have been described in all mammals studied to date. The extrapulmonary touch-sensitive fibers have only recently been described and may not be present in all mammals. The activation stimuli listed are those most prominently associated with the nerve subtype.

known. Based on the pharmacology of adenosine and prostaglandin E_2, one might hypothesize that nociceptive C-fibers contribute to dyspnea. On the other hand, rational arguments can be made that stretch-sensitive mechanosensors are "dyspneagenic" nerves. It is also possible that dyspneic sensations may be the result of the integrated input of nociceptors with stretch-sensitive fibers. This converging integration (central sensitization) has been shown for increases in cough sensitivity (54) and increases in parasympathetic tone (37).

Conclusions

The majority of vagal afferent nerves in the lungs are nociceptors that are adept at sensing the type of tissue injury and inflammation that occurs in the lungs in COPD. In addition, stretch-sensitive afferent nerves are present in the lungs and can be activated by the tissue distention that occurs during eupneic breathing. The pattern of action potential discharge in these fibers depends on the rate and depth of breathing, the lung volume at which respiration is occurring, and the compliance of the lungs. Therefore, the activity of nociceptive and mechanosensitive afferent nerves is grossly altered in patients with COPD. Over time, the alteration in vagal nerve activity can lead to use-dependent changes in the function of vagal nerve pathways. This neuroplasticity can lead to qualitative and quantitative changes in the reflex pathways in patients with COPD. The activity in afferent nerves is integrated in the central nervous system, resulting in responses of subconscious changes in respiration pattern and parasympathetic outflow to bronchial smooth muscle and glands and to conscious urge-to-cough sensations and sensations of dyspnea. The distortion in vagal afferent nerve activity in COPD likely leads to situations where these responses become perverted and out of balance with the body's needs. Drugs aimed at normalizing the activity in bronchopulmonary vagal afferent nerves present a novel approach to limiting the symptoms and suffering that accompany this chronic and devastating disease.

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