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Anatomy and Neurophysiology of Cough
CHEST Guideline and Expert Panel Report

Brendan J. Canning, PhD; Anne B. Chang, MBBS, PhD, MPH; Donald C. Bolser, PhD; Jaclyn A. Smith, MBChB, PhD; Stuart B. Mazzone, PhD, FCCP; and Lorcan McGarvey, MD; on behalf of the CHEST Expert Cough Panel

Bronchopulmonary C-fibers and a subset of mechanically sensitive, acid-sensitive myelinated sensory nerves play essential roles in regulating cough. These vagal sensory nerves terminate primarily in the larynx, trachea, carina, and large intrapulmonary bronchi. Other bronchopulmonary sensory nerves, sensory nerves innervating other viscera, as well as somatosensory nerves innervating the chest wall, diaphragm, and abdominal musculature regulate cough patterning and cough sensitivity. The responsiveness and morphology of the airway vagal sensory nerve subtypes and the extrapulmonary sensory nerves that regulate coughing are described. The brainstem and higher brain control systems that process this sensory information are complex, but our current understanding of them is considerable and increasing. The relevance of these neural systems to clinical phenomena, such as urge to cough and psychologic methods for treatment of dystussia, is high, and modern imaging methods have revealed potential neural substrates for some features of cough in the human.

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ABBREVIATIONS: ATP = adenosine triphosphate; GERD = gastroesophageal reflux disease; GIT = gastrointestinal tract; nTS = nucleus tractus solitarius; RAR = rapidly adapting receptor; SAR = slowly adapting receptor; TRPA1 = transient receptor potential A1; TRPM8 = transient receptor potential M8; TRPV1 = transient receptor potential vanilloid 1

Cough preserves the gas-exchanging functions of the lung by facilitating clearance of aspirate, inhaled particulate matter, accumulated secretions, and irritants that are either inhaled or formed at sites of mucosal inflammation. An impaired cough reflex can have acute, dire consequences.[1-4] Under normal conditions, therefore, cough serves an important protective role in the airways and lungs. However, cough is also a mechanism for the spread of life-threatening respiratory tract infections, including many

CORRESPONDENCE TO: Lorcan McGarvey, MD, Centre for Infection and Immunity, The Queen's University of Belfast, 97 Lisburn Rd, Belfast, BT9 7BL, Northern Ireland; e-mail: l.mcgarvey@qub.ac.uk

forms of influenza, TB, severe acute respiratory syndrome, and *Bordetella pertussis*, the gram-negative bacteria responsible for whooping cough. Furthermore, in diseases such as asthma, COPD, gastroesophageal reflux disease (GERD), and rhinosinusitis, cough may become excessive and harmful to the airway mucosa and adversely impact patient quality of life.[5,6] These contrasting functions and consequences of cough highlight the importance of balancing therapy-targeting cough, such that the defensive functions of the reflex are preserved, while limiting the role of cough in spreading harmful illnesses and adversely impacting patient sense of well-being.

Most of our understanding about the afferent (sensory) neuronal pathways regulating the cough reflex comes from studies performed in animals. These studies implicate vagal afferent nerves innervating the larynx, trachea, carina, and large intrapulmonary bronchi with terminations largely confined to the airway mucosa,[7-10] which we describe, as well as their role in regulating cough. In this article we provide an update to the 2006 Diagnosis and Management of Cough: ACCP Evidence-Based Clinical Practice Guidelines by detailing the recent research, including an increasing number of studies conducted in human subjects designed to elucidate the anatomic and neurophysiologic components of cough. In addition, we have attempted to provide a clinical perspective with particular emphasis on what is known about cough in patients as well as mechanisms accounting for the excessive coughing and cough hypersensitivity associated with acute, subacute, and chronic conditions associated with cough.

Properties of Airway Afferent Nerve Subtypes and Evidence for Their Potential Role in Regulating Human Cough

Bronchopulmonary vagal afferent nerves arise bilaterally from the inferior (nodose) and superior (jugular) vagal ganglia and differ in their chemical and mechanical responsiveness, in addition to their anatomic, embryological, and physiologic attributes.[11,12] When evaluated in isolation, these attributes are often not sufficiently specific to differentiate afferent nerves. When combined, clear patterns of anatomy and physiology emerge that help distinguish specific nerve subtypes (Fig 1). Understanding the differences in vagal afferent nerve subtypes is critical to understanding the physiology and pathophysiology of cough, and thus the functional, anatomic, and neurochemical attributes of vagal afferent nerve subtypes are described below.
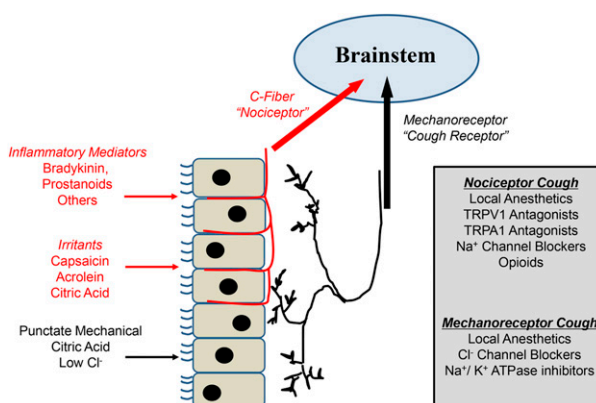

Figure 1 – *Peripheral mechanisms of cough. A dual-sensory neuron model subserving cough. Extensive studies in animals and humans support the concept that at least two subtypes of primary sensory neurons can induce coughing when stimulated. C-fiber nociceptors, which have their terminals in and around the mucosa surface of the airways, are sensitive to a wide variety of inhaled or locally produced chemical mediators, which may either activate or sensitize nociceptor nerve endings. Mechanically sensitive "cough receptors" are positioned beneath the epithelium in the large airways and are relatively insensitive to most chemical mediators (with the exception of low pH) but are exquisitely sensitive to punctate stimuli delivered to the mucosal surface (for example, inhaled particulate matter). A number of peripherally acting compounds that block nociceptor and or mechanoreceptor activation to reduce coughing are listed in the gray box. TRPA1 = transient receptor potential A1; TRPV1 = transient receptor potential vanilloid 1.*

C-Fibers

The majority of bronchopulmonary vagal afferent nerves are unmyelinated C-fibers.[13-16] In addition to their conduction velocity ($<$ 2 m/s), airway vagal afferent C-fibers are distinguished from lung stretch receptors by their relative insensitivity to mechanical stimulation and lung inflation (Fig 2). C-fibers are further differentiated from lung stretch receptors by their sensitivity to bradykinin and activators of the ion channels, transient receptor potential vanilloid 1 (TRPV1) (eg, capsaicin, protons), and transient receptor potential ankyrin 1 (TRPA1) (eg, ozone, allyl isothiocyanate). Other inflammatory mediators and environmental irritants that somewhat selectively activate bronchopulmonary C-fibers include prostaglandin E2, ozone, nicotine, adenosine, and serotonin.[13-20]

Morphologic studies in rats and in guinea pigs have identified afferent C-fiber terminations in the airway epithelium as well as other effector structures within the airway wall.[21-24] Such studies are aided by the unique expression of TRPV1 and substance P in rat and guinea pig C-fibers. Comparable structures have been identified in human airway mucosa and the airway mucosa of other species, including terminals labeled immunohistochemically for TRPV1, but their identity as C-fiber terminations has not been proven.[25-28] Considerably less
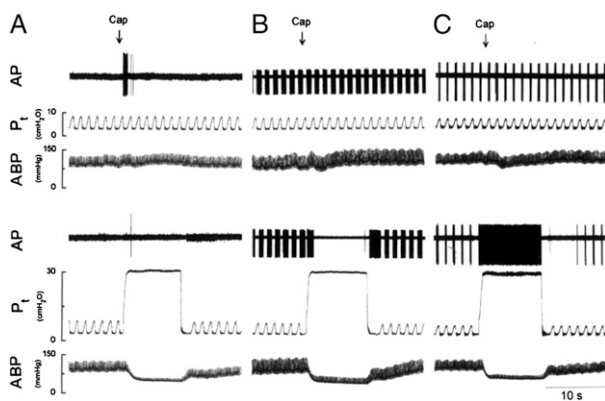
Figure 2 – *Representative traces of single-unit recordings from airway vagal afferent nerve subtypes in anesthetized rats. A, Airway C-fibers are quiescent during tidal breathing and relatively unresponsive to lung inflation. However, C-fibers respond vigorously to IV injected capsaicin. B and C, Rapidly adapting receptors (RARs) (B) and slowly adapting receptors (SARs) (C) are sporadically active during the respiratory cycle. Neither subtype of mechanoreceptor responds to capsaicin, but both respond intensely when the lungs are inflated. Note that RARs are easily differentiated from SARs by their rapid adaptation during sustained lung inflation. ABP = arterial BP; AP = action potential; Cap = capsaicin; P_t = tracheal pressure. (Reprinted with permission from Ho et al.[11])*

substance P-containing innervation has been localized to human airways, in comparison with that seen in rats and guinea pigs.[26] This makes it unlikely that neurokinin-dependent axonal reflexes play a prominent role in humans (see later).

Bronchopulmonary afferent C-fiber subtypes have been described in several species.[13,15,16] These subtypes are differentiated by their ganglionic origin (nodose vs jugular), sites of termination in the airways and lungs, chemical sensitivity, neurochemistry, and the reflexes initiated upon their activation. Whether similar physiologic distinctions between bronchial and pulmonary afferent C-fibers can be defined in humans is unknown.

C-fibers are activated somewhat selectively by capsaicin, bradykinin, TRPA1 activators, and protons, and each of these stimuli initiate coughing in patients and awake animals. The coughing evoked by these stimuli in animals is prevented by prior capsaicin desensitization (which selectively renders C-fibers unresponsive to subsequent challenges). In animals, these cough responses are inhibited by neurokinin receptor antagonists. As described above, neurokinins, such as substance P, are uniquely expressed by airway C-fibers in animals. All of these observations provide compelling evidence for an essential role of C-fibers in cough.[9,10,29]

Widdicombe Cough Receptors

More than one-half a century ago, John Widdicombe described a subtype of myelinated vagal afferent nerves innervating the trachea, mainstem, and segmental bronchi that played an essential role in cough reflexes evoked from the airways mucosa of anesthetized cats.[30-32] He called these afferent nerves "cough receptors," a flawed term, but a term that has persisted in the literature in the nearly 6 decades since. This seminal work by Widdicombe has been substantiated in multiple studies since, and it is now well established that, in addition to C-fibers, a subset of myelinated, mechanically sensitive, capsaicin-insensitive vagal afferent nerves plays an essential role in cough.[10,33]

Cough receptors can be differentiated from C-fibers and lung stretch receptors by their axon conduction velocity (5 m/s), which is considerably faster than C-fibers (< 1 m/s) but slower than lung stretch receptors (≥ 15 m/s). These mechanically sensitive vagal afferents do not normally express the ion channels TRPV1 or TRPA1 and are, thus, insensitive to the chemical irritants capsaicin and allyl isothiocyanate. These afferents are, however, activated by protons, perhaps through expression of acid-sensing ion channels. In guinea pigs, the cell bodies of the cough receptors are located in the nodose ganglia, whereas the cell bodies of the C-fibers regulating cough are located in the jugular ganglia. Cough receptors do not synthesize neuropeptides under normal conditions but use glutamate as their primary transmitter at their central terminals in the brainstem.[33-35]

At various times since his original discoveries, Widdicombe referred to the cough receptors by other terms, including rapidly adapting receptors (RARs) (see later) and irritant receptors.[7,12] Because they are myelinated and adapt rapidly to a punctate (touch-like, as opposed to stretch-like) mechanical stimulation, it is tempting to conclude that the cough receptors are merely RARs that innervate the extrapulmonary airways. But unlike RARs, which primarily innervate the intrapulmonary airways, the cough receptor terminations are found exclusively in the extrapulmonary airways (larynx, trachea, mainstem bronchi). Also, unlike RARs, the cough receptors are utterly unresponsive to a wide variety of irritants, spasmogens, and autacoids that induce airway smooth muscle contraction and decrease lung compliance, including methacholine, histamine, leukotriene C4, substance P, neurokinin A, 5-hydroxytryptamine, adenosine triphosphate (ATP), and adenosine.[10] All of these stimuli have been shown to activate RARs, and yet none of them reliably evokes coughing in animals or in patients.[36-39]

The peripheral terminals of cough receptors have been described in guinea pigs (Fig 3). These terminals are
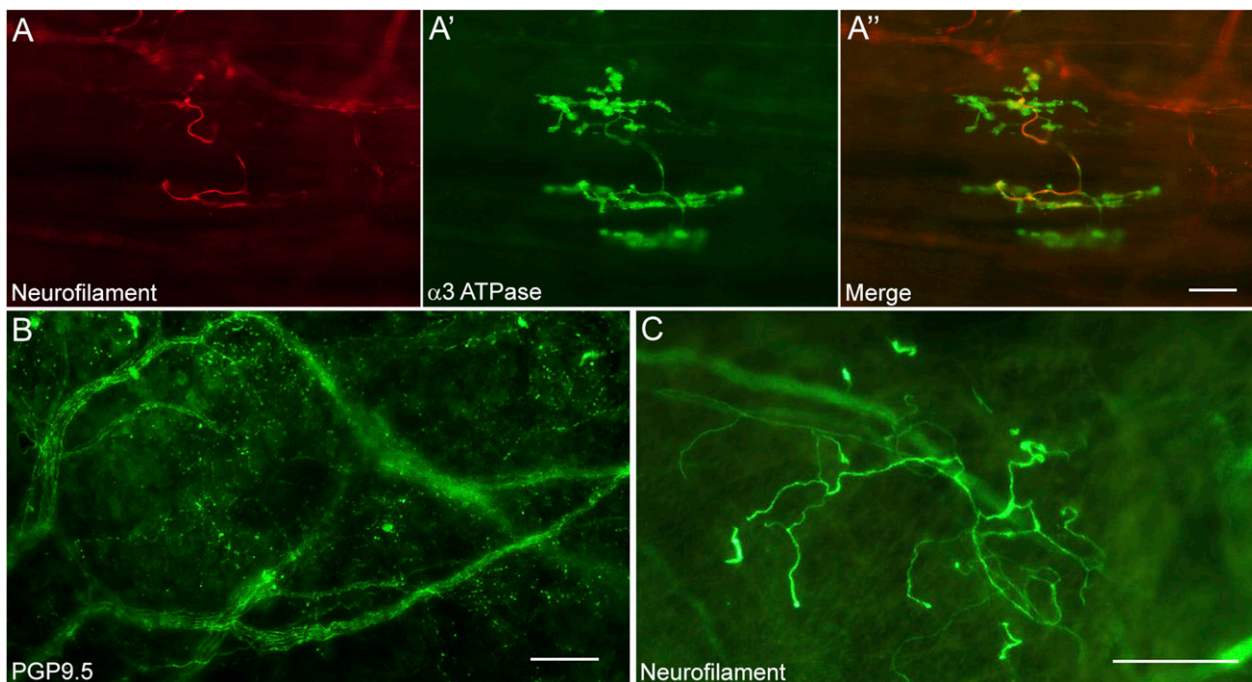
Figure 3 – *Structural organization of airway nerve terminals in guinea pigs and humans. A-A′′, The arrangement of a cough receptor terminal in the guinea pig airways. Heavy chain neurofilaments (A) are expressed in the cough receptor axon and major branch points, indicative of the myelinated nature of these sensory nerve subtypes. These major branch points give rise to a more complex terminal structure (A′) that is defined by the expression of an isozyme of the Na$^+$/K$^+$ ATPase containing the α3 subunit (α3 ATPase). B, Staining of nerve fibers innervating the human airways revealed using the pan-neuronal marker protein gene product 9.5 (PGP9.5) (original magnification × 20). C, Some of these fibers express heavy chain neurofilament proteins and are comparable to the structures in guinea pigs that give rise to cough receptor terminals (original magnification × 10). Scale bars represent 50 μm.*

found in abundance in the airway mucosa, assuming a stereotypical position in the airway wall, with complex dendritic arbors that are invariably arranged along the circumferential axis of the airways.[23] Terminations are confined to the space between the smooth muscle and the epithelial cell layers. This location for cough receptor terminations may explain the relative insensitivity of cough receptors to epithelium removal or airway smooth muscle contraction. It is of interest that this location in the extracellular matrix is a site of extensive remodeling in several chronic diseases in patients.[40] Comparable structures have been identified in the airway mucosa of other species, including humans.[12,41]

Pulmonary Stretch Receptors

Lung stretch receptors are characterized by their responses to sustained lung inflation. Both RARs and slowly adapting receptors (SARs) are activated by sustained lung inflation, but RARs are active primarily during the dynamic phase of lung inflation, whereas SARs continue firing throughout the distension. RARs are also differentiated from SARs by their responses to lung deflation/lung collapse.[11,42-46]

The anatomy of RAR terminations in the airway wall is unknown. Functional studies of RARs suggest that they terminate within or beneath the epithelium, primarily in the intrapulmonary airways.[31,44] Such terminal sites might explain RAR sensitivity to lung collapse and/or lung deflation, although their responsiveness to alterations in dynamic lung compliance (and thus their sensitivity to bronchospasm) also suggests an association with the airway smooth muscle. The sustained activation of RARs, produced by dynamic lung inflation, bronchospasm, or lung collapse, indicates that adaptation of RARs is not attributable to an electrophysiological adaptation. RARs may, thus, be better defined as dynamic airway mechanoreceptors.

SARs are highly sensitive to the mechanical forces imposed upon the lung during breathing. SAR activity increases sharply during inspiration and peaks just prior to the initiation of expiration.[11,43] SARs are, thus, believed to be the primary afferent fibers involved in the Hering-Breuer inflation reflex, which terminates inspiration and initiates expiration when the lungs are adequately inflated.[43] SAR terminal structures have been identified in the intrapulmonary airways and lungs of rabbits.[47] These terminals assume a complex

and varying position within the airway wall but are found primarily in the peripheral airways (associated with alveoli or bronchioles). Occasionally, but not uniformly, SAR dendritic arbors are associated with the bronchiolar smooth muscle, in which case they have been termed smooth muscle-associated receptors. Some species variations in SAR termination patterns (eg, extrapulmonary vs intrapulmonary) have been described.[10,43]

Despite some imprecise semantics, whereby researchers group cough receptors with the intrapulmonary RARs into a single, heterogenous class of vagal afferent nerves that are called either "irritant receptors" or RARs, there is little evidence to suggest that either RARs or SARs, defined here as those afferents responding to sustained lung inflation, directly initiate coughing upon activation. Both RARs and SARs are spontaneously active during eupnea, and it would be hard to envision a scenario whereby their action potential patterning could change, such that cough and not eupnea is encoded. Electrophysiologic recordings from the vagus nerve in rabbits suggest that SAR activity does not increase prior to or during evoked cough responses.[48] Conversely, SARs are activated by sustained lung inflations and RARs are activated by negative intraluminal pressures (such as those produced by inspiratory efforts against a closed glottis), and neither stimulus reliably initiates coughing in animals or in humans.[49,50] Bronchospasm is also an effective stimulus for RARs but largely ineffective at initiating cough.[9,10,36-39] Both subtypes of stretch receptors play a critical role in regulating respiratory rate and tidal volumes at eupnea, and their activity likely modulates sensitivity to tussive stimuli. RARs may regulate the duration and magnitude of the inspiratory and expiratory phases of coughing. A primary role in cough initiation for either RARs or SARs seems unlikely. Unlike their role in regulating the duration of inspiratory and expiratory phases during breathing, volume-related feedback from SARs has no effect on the duration of breathing phases of tracheobronchial cough.[51]

Interactions Between Afferent Nerve Subtypes Evoking Cough

Peripheral Interactions

Although C-fibers and the cough receptors subserve primary roles in cough initiation, other bronchopulmonary afferent nerve subtypes likely modulate cough pattern and sensitivity to tussive stimuli. Some of these sensory nerve interactions depend upon the peripheral

consequences of the reflexes initiated upon their activation.[9,10,13] These reflexes include changes in respiratory rate and tidal volume and also alterations in autonomic nerve activity in the airways and lungs and throughout the cardiovascular system. For example, SARs and RARs regulate tidal volumes and the timing of inspiration and expiration.[43,44] The peak expiratory flows achieved during cough are directly related to inspiratory volumes,[52] and in this way lung stretch receptors will modulate cough. Lung stretch receptors also indirectly regulate airway caliber and, thus, resistance to airflow through airway autonomic pathways.[53,54] Although there are conflicting results in the literature, anticholinergics have been shown to modulate cough responsiveness and at least partially reduce cough severity in some patients.[55] Airway sympathetic nerves may also regulate cough by modulating mucosal blood flow, which may clear irritants contained in airway surface liquid and thus reduce their concentrations in the biophase, thereby reducing excitation of underlying sensory nerves.[56]

Axonal reflexes, which result in the release of neuropeptides from the peripheral terminals of afferent C-fibers, independent of any involvement of the CNS, are unlikely to regulate human lung physiology and pathophysiology, given the paucity of neuropeptide-containing sensory nerves in the human airway mucosa.[9,57] This contrasts sharply with previous studies performed in rats and guinea pigs, wherein the majority of C-fiber terminals in the airways mucosa contain the neuropeptides substance P, neurokinin A, and calcitonin gene-related peptide. In these species, neuropeptide-dependent axonal reflexes play a prominent role in lung responses to inflammation and other noxious insults.[58] Comparable nerve terminals lacking neuropeptides have been localized to human airways.[25-27] However, these nerve terminals have the subcellular machinery for peripheral neurotransmitter release. Perhaps nonpeptide transmitters, including the purine transmitter ATP, may be released peripherally from human airway C-fibers by axonal reflexes. Administered exogenously, ATP evokes coughing and sensation of dyspnea in patients, and a clinical study described a profound reduction in chronic cough rates upon administration of a potent purinergic/P2X3 receptor antagonist in patients with chronic cough.[59-61]

Central Interactions

Vagal afferent nerves may also interact in the CNS to regulate cough. Anatomic and functional studies have

demonstrated convergence of vagal afferents at sites of brainstem integration, particularly in the nucleus of the solitary tract (nTS), a region in the caudal brainstem where many vagal sensory nerves project.[62,63] Such convergent projections lead to synergistic regulation of reflex bronchospasm.[64] Evidence for synergistic interactions between cough receptors and C-fibers has also been documented in studies of cough. Thus, in anesthetized guinea pigs, C-fiber activation does not evoke cough but greatly sensitizes the cough reflex evoked by activating the cough receptors.[65] This sensitizing effect of bronchopulmonary C-fiber activation through CNS-dependent mechanisms is comparable to the processes of central sensitization described in studies of pain in somatic tissues.[66,67] Comparable central interactions may contribute to the enhanced cough responsiveness evoked by allergic inflammation and associated with gastroesophageal reflux and upper airway diseases, presumably reflecting facilitatory central interactions of esophageal or trigeminal afferent pathways with cough circuits in the brain.[9,10,68]

Not all central interactions among afferent pathways promote enhanced cough responsiveness. Activation of a subset of pulmonary C-fibers has been shown to inhibit evoked coughing in dogs, cats, and guinea pigs, and circumstantial evidence suggests a comparable inhibition of cough evoked by pulmonary C-fiber activation in patients.[10,69,70] These inhibitory effects occur coincident with pulmonary chemoreflexes, which results in profound changes in respiration and dyspnea and almost certainly depends upon inhibitory interactions between respiratory pattern generators and central pattern regulators of cough. Cough may also be inhibited by activation of cold-sensitive/menthol-sensitive trigeminal afferent nerves innervating the upper airways and nose (see later). The central pathways accounting for these upper and lower airway nerve interactions have not been determined.

Complex and poorly defined central (and perhaps peripheral) interactions between cough neural pathways and changes in arterial oxygen and CO_2 can also regulate coughing. Hypoxia depresses cough in animal models and increases capsaicin thresholds in humans.[71,72] Repetitive coughing in animal models induces profound hyperventilation and metabolic alkalemia, such that central arterial levels of CO_2 fall well below apneic threshold.[73] These low levels of CO_2 do not depress cough efforts as they would respiratory muscle activity during breathing.[74]

Extrapulmonary Modulation of Cough

Cough Evoked From the Ear (Arnold Reflex)

Afferent nerves carried by the auricular branch of the vagus nerve (Arnold nerve) innervate the external auditory meatus.[75] In a small subset of individuals (< 5%), several visceral reflexes, including cough, may be evoked by mechanical stimulation of the ear. Tracing studies in cats show that the cell bodies of the afferent neurons carried by the Arnold nerve are located in the jugular ganglia and terminate in several areas throughout the brainstem, including the nTS.[76] It is interesting that, in guinea pigs, the nociceptors that modulate cough also have their cell bodies in the jugular ganglia and terminate centrally in the same region of the nTS.[9,10] It seems likely that the cough initiated by stimulation of the ear involves integration of both ongoing airway vagal afferent nerve input and the additional afferent input arising from the ear.

Nasal Afferent Nerve Regulation of the Cough Reflex

Rhinosinusitis and other conditions involving the upper airways are common comorbidities in patients with chronic cough. Precisely why upper airways disease is associated with chronic cough is unclear. Direct stimulation of the nasal mucosa does not initiate cough. There has been speculation that postnasal drip may be responsible for the coughing resulting from upper airways disorders, but there seems to be considerable variance in the prevalence of postnasal drip among patients with chronic cough.[5,6]

An alternative explanation for cough associated with rhinosinusitis would be a sensitizing effect of upper airway afferent nerves, resulting in enhanced cough responsiveness and thus coughing in a subset of individuals. This hypothetical mechanism assumes that trigeminal afferent pathways can promote the likelihood of cough by lowering the threshold of the central cough pattern generator to subsequent vagal afferent input, perhaps to the point where even innocuous or physiologic stimuli arising from the lower airways could promote coughing. Thus, cough reflex sensitivity is enhanced by upper airways disease, and an additional lower airway trigger for cough results in a clinical presentation that is responsive to aggressive medical therapy targeting upper airway disease. There is precedent in animals and in patients for enhanced cough sensitivity evoked by upper airway irritation. Acute allergic inflammation, challenges with mediators

associated with allergic inflammation, or stimulation of TRPA1- or TRPV1-responsive upper airway sensory nerves increases responsiveness to tussive challenge.[77-80]

A subset of upper airway afferent nerves may also reduce cough frequency and responsiveness to tussive challenge. Menthol has been in use clinically for centuries for its soothing effects on mucosal surfaces and is commonly formulated in cough remedies. Menthol and components of eucalyptus and camphor may potentially work, in part, to produce their cooling and soothing effects by activating the ion channel transient receptor potential M8 (TRPM8). Unlike TRPV1 and TRPA1, which evoke painful and noxious sensations and reflexes, TRPM8 activation is soothing, a counterirritant to effects evoked by nociceptors. These opposing effects of TRPA1/TRPV1 and TRPM8 suggest differential expression by sensory nerves. Molecular and functional studies find little, if any, expression of TRPM8 in nerves innervating the lower airways (where C-fibers comprise the majority of vagal afferent innervation) but find a prominent expression of TRPM8 by trigeminal nerves innervating the upper airways. Molecular analyses confirm that a subset of TRPM8+ nasal afferent nerves do not coexpress TRPV1 or TRPA1. Activation of these upper airway afferents reduces cough responsiveness in animals and humans and may reduce cough frequency in patients with acute cough.[81,82]

Cough Initiated From the Pharynx

Infusion of fluid into the pharynx or pharyngeal stimulation with air puffs in awake or anesthetized human subjects can initiate coughing or the urge to cough under certain circumstances.[83-86] The pharyngeal afferent nerves regulating cough are either vagal in origin or arise from the glossopharyngeal nerves or from nerve branches emanating from the trigeminal ganglion.[87] The physiologic properties of the pharyngeal afferent nerves regulating cough are poorly defined, but they may be similar to the cough receptors innervating the larynx, trachea, and bronchi. Thus, mechanical stimulation, postnasal drip, and a water bolus placed into the pharynx evoke vigorous coughing in human subjects and in animals, whereas capsaicin may be unable to initiate coughing when applied selectively to the pharynx.[83-86]

Cough Initiated From the Esophagus

There are conflicting reports regarding the ability of esophageal afferent nerve activation to initiate coughing.[87] In animals, neither distension nor luminal

challenge of the esophagus with acid or capsaicin evokes coughing.[9,10] Comparably negative studies have been reported in humans. However, there are also reports of cough evoked from the esophagus in humans. Moreover, the association between chronic cough and GERD is quite clear, and the ability to markedly reduce coughing in at least a subset of patients with GERD, by effective medical or surgical treatment of the reflux disease, argues strongly for the hypothesis that reflux initiates coughing in susceptible patients.[5,6,88] Studies combining cough monitoring with impedance measurements also implicate reflux as a driver of cough in a subset of patients (Fig 4).[89] The easiest explanation for these results is that refluxate is aspirated into the airways and directly activates the airway vagal afferent nerves regulating cough.[87,90] But pH/impedance monitoring in patients with GERD provides little evidence that refluxate needs to reach the proximal esophagus, much less the airways, to initiate pulmonary symptoms or coughing.[87,89] The available evidence suggests that locally or centrally mediated airway reflexes (promoting mucous secretion, bronchospasm, cough) can be initiated directly from the stomach or the esophagus.[91-93] For example, many species have neuronal projections between esophageal and airway autonomic ganglia that, when activated, produce physiologic effects in the airways (including mucous secretion or bronchoconstriction) that could promote coughing.[93] Alternatively, the interactions between the GI tract (GIT) and airway afferent pathways
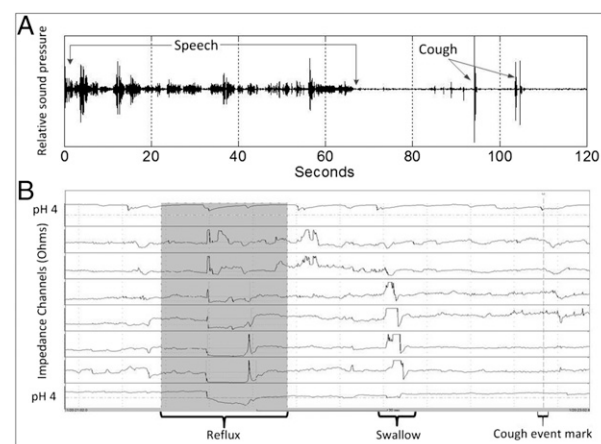

Figure 4 – A, Time-synchronized acoustic recording; B, esophageal pH impedance. Acoustic recording shows a period of speech followed by two cough sound waveforms. The gray area in the impedance trace shows a retrograde fall in esophageal impedance associated with a fall in pH below 4 in the distal pH channel, indicative of an acid reflux event. As the cough sounds commence within 2 min of the start of the reflux event, they are considered associated. The cough event marker is created by the patient pressing a button on the impedance device to document the coughing. (Data from Smith et al.[89])

may occur in the central nervous system. Although untested directly, and thus unproven, esophageal and airway afferent nerves are known to project to similar brainstem regions and could converge centrally to regulate and initiate parallel and overlapping reflex effects in the airways and GIT.[94,95] Alternatively, portions of the GIT and airways share a common blood supply and, as such, it is conceivable that inflammatory mediators or cells arising from the esophagus as a consequence of reflux could impinge upon airway sensory pathways to produce cough.

Studies in patients with GERD provide evidence that refluxate may also sensitize the cough reflex.[94-96] Acid challenges to the esophagus markedly reduce the concentration of inhaled capsaicin required to evoke cough or directly result in coughing. Ing and colleagues[95] reported that this sensitizing effect of the esophageal challenge could be prevented by inhalation of atropine, suggesting that a CNS-dependent reflex, initiated from the esophagus, resulted in bronchospasm and/or mucous secretion in the airways that initiated coughing. Medical treatment of GERD has also been reported to greatly reduce sensitivity to tussive stimuli.[88] This sensitizing effect of refluxate or experimental acid challenges likely depends on CNS integration and amplification of parallel vagal sensory inputs controlling cough.[68]

Central Regulation of Cough

Our current understanding of the central regulation of cough can be separated into three main areas: (1) brainstem processing of afferent information, (2) organization of the brainstem control network, and (3) higher brain (encompassing subcortical and cortical) circuits that support the role of consciousness, perception, and emotion in the expression of cough.

Brainstem Processing of Afferent Information

Vagal afferent fibers enter the brainstem via the nTS, where they synapse on second-order interneurons.[97] The nTS cough-related interneuronal circuit has been proposed to have a "relay" function for transmission of information to populations of neurons in the brainstem that regulate breathing.[98-101] The core of the cough network is located in the ventrolateral region of the medulla and is hypothesized to participate in breathing and rhythm regulation for cough.[98,100-102] However, there are no studies of the response patterns and functional interactions of nTS neurons during cough. Studies have used transneuronal tracing with herpes simplex virus to map central circuits from the extrathoracic trachea.[103]

These studies showed that a broad network of neurons in the nTS participated in central processing of tracheal afferent information. This work supports the idea that the role of the nTS in generating cough has been significantly underestimated. What is clear is that this area of the brainstem does not simply relay vagal sensory afferent information through to the rest of the nervous system.

Cough and breathing can be differentially regulated by primary afferent inputs to the brainstem.[51,104,105] This supports the concept that the regulation of cough is not an extension of our understanding of that for breathing but rather it is customized to the function of the behavior. In particular, the lack of an important role for hyperventilation in the control of cough is consistent with the fact that ventilation increases significantly during this behavior. This alteration in the regulatory system is necessary to prevent a loss of respiratory muscle excitability as CO_2 falls during coughing. The depression of cough induced by hypoxia is less well understood. This effect may be related to a transition in priority of the respiratory muscle control system from maintaining blood gasses under normal conditions while allowing episodes of coughing to clear the airways to a focus on maintaining ventilation during hypoxia, which is a significant threat to normal gas exchange. The specific importance of the permissive/facilitatory effect of SARs on cough is also not well understood but may help optimize respiratory muscle performance[106] and facilitate expulsive airflows that occur when cough is elicited at higher lung volumes.[52]

Organization of the Brainstem Control System

A network of neurons that includes the ventrolateral medulla, raphe nuclei, and pons is responsible for controlling the duration of the inspiratory, compressive, and expulsive phases of coughing as well as the magnitude of motor activation of the respiratory muscles during this behavior.[98,99,101,102,107-109] This network also regulates respiratory muscles to produce breathing.[102] Evidence supporting the concept of an anatomically distributed, but shared, network for both cough and breathing comes from a variety of preclinical studies showing that brainstem neurons in these locations alter their activities during both behaviors.[98,99,101,102,108-110] These neurons are synaptically connected in ways that can explain motor drive to respiratory muscles during both behaviors.[98,99,101] The process by which selected populations of this distributed brainstem network alter their activities to account for both behaviors is known as reconfiguration.[98,101,102]

Although complex, the reconfigured brainstem network hypothesis for cough does not yet account for the differential regulation of this behavior relative to breathing. Furthermore, this network cannot account for the phenotype of response to cough-suppressive drugs, first shown by May and Widdicombe[111] > 50 years ago. Centrally active antitussive drugs suppress cough in a dose-dependent manner at doses that have no effect on breathing.[111,112] By definition, there must be some "neural module" in this brainstem network that is not required for breathing but is important for the full expression of cough. Some investigators have approached this problem using microinjection methods to apply antitussive drugs and/or neurotransmitter agonists and antagonists to various brainstem regions.[113-117] It is clear that familiar brainstem areas, such as the nTS, could participate in the actions of antitussive drugs. It is also clear that other areas not currently believed to have a command function for cough could be substrates for cough suppressants.[113,115] These studies support the concept that there may be no single anatomic brainstem area or "center" that is susceptible to antitussive drugs but that these compounds may act at multiple sites when administered systemically. The extent to which these sites may contain undescribed elements of the brainstem network for cough is unknown, but these findings do support the idea that, even though our current conceptualization of the brainstem cough network is complex, it probably represents an underestimate of its true complexity.

Higher Brain Processing Systems in Cough

Coughing, like swallowing, belching, urinating, and defecating, is unique in that there is higher brain (cortical and subcortical) control of this visceral reflex (Fig 5).[118-120] Higher brain control of coughing can manifest both as inhibition (eg, coughing that is suppressed until a break in a live performance or activity) and also as voluntary cough. Patients with persistent cough typically experience a recurrent need to cough or clear their airways (ie, an urge to cough)[118] and are acutely aware of the ongoing sense of irritation in the airways (which can present, for example, as an itch or scratch in the throat or chest). Perceptual awareness requires cortical processing of the sensory information originating in the airways, and this promotes behavioral coughing in an attempt to clear the airways and satiate the urge. The implications of this conscious control of cough are severalfold. First, behavioral cough, rather than reflex cough, may contribute significantly to chronic cough in disease, and this could have implications for antitussive therapies. For

example, Vertigan and Gibson[121,122] reported that 49% of a patient cohort diagnosed with chronic refractory cough reported coughing deliberately in response to perceived irritations in the throat. Perhaps related to this, placebos can have a profound effect on coughing, the urge to cough having been studied experimentally.[123,124] As such, any study of a novel or existing cough treatment should include a blinded (preferably double-blinded) placebo arm. Furthermore, speech therapy is proving beneficial in a subset of chronic coughers,[122] which may reflect regulatory processes in this higher-order cough circuitry. It is also clear, however, that cough on occasion may be unrelated to a physiologic disease (eg, GERD, asthma), and thus a psychologic issue needs to be considered ("psychogenic cough").[125] Addressing the psychologic impact of coughing on a patient's sense of well-being should therefore be a component of any treatment regimen for chronic cough, whether an underlying cause is identified, because many patients with cough present with symptoms of anxiety, sleep disturbance, and/or depressive illness.[126] Because of this, it may be difficult to resolve whether the behavioral symptoms are due to the impact of intractable and unexplained cough or somehow the cause of the cough itself.

The sensory and motor pathways composing the higher brain regulation of coughing in humans have received considerable attention.[118-120] Uniquely, more is known about the higher brain control of cough in humans than in animals, which is not the case for other aspects of cough physiology. These processes are complex, but nevertheless it is of value to provide a summary of the major points. The urge to cough evoked by capsaicin inhalation in healthy volunteers is encoded in a brain network that includes the primary sensory, insula, prefrontal, and posterior parietal cerebral cortices.[118,120] The activity patterns in these regions suggest that the primary sensory cortex is principally responsible for encoding urge-to-cough intensity, whereas the insula cortex encodes the magnitude of the incoming sensory input from the airways, and the prefrontal and posterior parietal cortices likely contribute to attention and localizing the site of irritation.[120] Voluntary cough suppression requires brain regions similar to those needed for inhibiting other types of motor patterns, including activity in the inferior frontal gyrus, anterior mid-cingulate cortex, insula cortex, and supplementary motor area,[119,127,128] although it is presently unclear where in the cough reflex pathway these suppressive circuits act. Not surprisingly, voluntary cough is associated with activity in premotor and motor cortices and in the cerebellum. Of particular interest, voluntary cough may
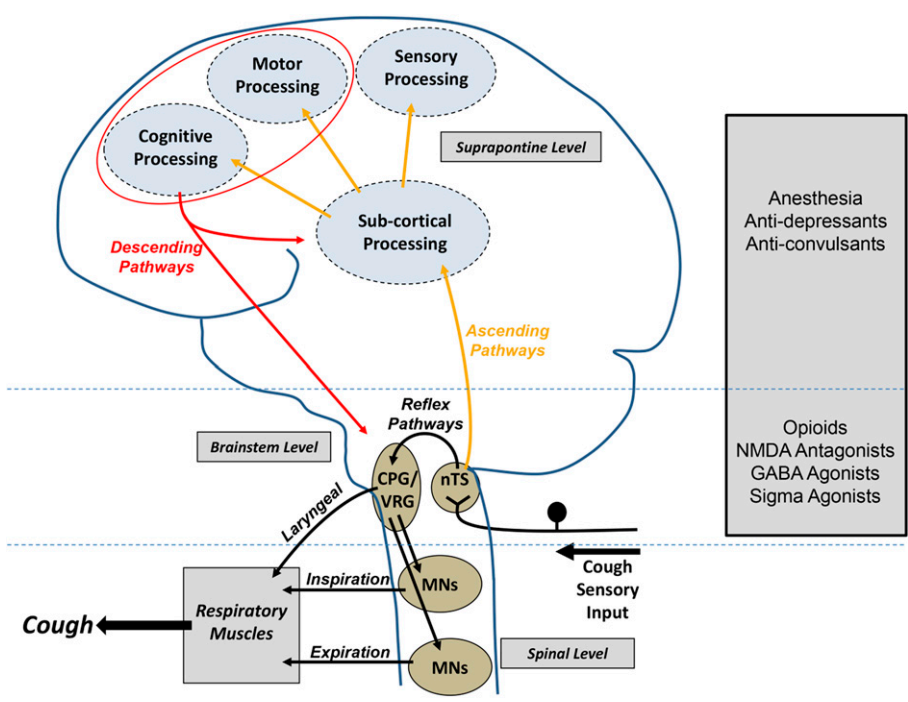
Figure 5 – *Central mechanisms regulating cough. Airway sensory neurons project to the brainstem, where they terminate predominately in the nTS. Projections from the nTS can reflexively induce coughing by modifying activity of the respiratory CPG, a collection of neurons that generates respiratory rhythm in the VRG of the brainstem. Output from the CPG via MNs provides the drive to respiratory muscles needed to elicit the cough motor pattern. Superimposed on this reflex pathway is a complex higher brain network that also receives inputs from the nTS in the brainstem. Higher brain processing gives rise to respiratory sensations and emotions associated with airway irritation as well as enabling a higher level of motor control over the basic reflexive cough pathways. Centrally acting antitussive agents likely affect both brainstem and higher brain processes to modify coughing. CPG = central pattern generator; GABA = gamma-aminobutyric acid; MN = motor neuron; NMDA = N-methyl-D-aspartate; nTS = nucleus tractus solitarius; VRG = ventral respiratory group.*

proceed without input to the brainstem cough circuits described above, presumably relying on direct higher-brain control of respiratory motor neurons in the spinal cord.[119,128] This is obviously in stark contrast to cough evoked by airways irritation. Placebo suppression of cough is correlated with activity in the dorsolateral prefrontal cortex,[97] a region known to be necessary for placebo analgesia.[129] The limbic brain and, in particular, the orbitofrontal cortex contribute to the affective components (such as the sense of unpleasantness) associated with airways irritation and cough.[118,119,130]

The Clinical Perspective

The anatomic and neurophysiologic processes responsible for the initiation and regulation of cough are complex[131] and may not be considered immediately relevant by the clinician managing his/her patient with troublesome cough. However, the body of literature devoted to this area should be viewed as a valuable resource to help the clinician understand how and why his/her patient coughs and provide rationale for a targeted and systematic approach to treatment. In its simplest form, clinical cough is a reflex event beginning with activation of vagal afferent sensory nerves located in pulmonary and extrapulmonary sites that project the "signal" centrally, where it undergoes modulation, resulting in the generation of the appropriate efferent motor response. This concept of distinct afferent sites has

provided the rationale for the use of the "anatomic diagnostic protocol" to evaluate and manage patients with cough.[132,133] This approach of directing investigations and trials of therapy at various anatomic sites has now become embedded in clinical practice, leading to a broad recognition that asthma, GERD, and upper airways disease are, at least in adult patients, the most common causes of chronic cough.[5,134-136] However, why the vast majority of patients with these common conditions do not develop chronic cough remains unclear. Adequate treatment of one or more of these causes is effective in the majority of patients, although a significant minority remains troubled with an unexplained, refractory chronic cough, despite extensive investigation and trials of therapy.[136,137]

Much of what is known about the regulation of cough by neural structures within the lung and at extrapulmonary sites, such as the nose, pharynx, and esophagus, has been obtained from experiments involving the mechanical probing and chemical stimulation of laboratory animals.[138,139] Although these models, particularly those involving anesthetized animals, may not faithfully reproduce the human condition, they have provided clinically important information. The most sensitive regions of the airways for mechanically eliciting cough are the larynx and the tracheal and bronchial bifurcations.[9,10,138] The idea that "mechanosensitive" receptors are located proximally within the airways

seems entirely logical and consistent with the principal role of cough in protecting the lungs. When these processes are impaired, important clinical problems arise. The extension of the original animal experiments on mechanical activation of the airway to human studies has provided some important information of how cough and airway-protective reflexes may be modified in various clinical scenarios. These include studies designed to determine the impact of premature birth,[139] aging,[140] and disease[141,142] on the integrity of the cough reflex. Cough can also be initiated with chemical stimuli. In experiments conducted in cats, Widdicombe[30-32] reported a more vigorous response to chemical stimulation when delivered to distal bronchi, compared with the trachea and more proximal larger airways. The regional sensitivity of human airways to chemical activation was studied > 30 years later by Hansson and colleagues.[143] Using single-breath aerosols of capsaicin in healthy human subjects, they noted that coughing was more readily induced by small droplet particles (deposited more distally in the airway) than by large droplet particles (deposited more proximally).[143] The notion that "chemosensitive" receptors are present in the distal airways, a region of the lung considered to be sparsely innervated,[144] provides some rationale for cough as a prominent symptom in clinical conditions such as idiopathic pulmonary fibrosis and bronchiolitis, both characterized by disease distributed more peripherally in the airways.

Coughing in response to experimental airway challenge with a range of physical and chemical irritants, including cold air and aerosols of capsaicin, citric acid, histamine, and charcoal dust, has been reported in both healthy subjects and patients with disease.[145-149] A number of clinically relevant observations have emerged from these studies. First, subjects undergoing tussive challenge often report a "tickle" sensation at the top center of their chest, accompanied by the "urge" or desire to cough. These sensory symptoms are also commonly described by patients with chronic cough.[150] Second, it has consistently been observed that female subjects exhibit heightened cough responses to chemical tussive stimuli.[151,152] Whether this explains the predominance of female patients among those seeking help for chronic cough is not known. Third, patients typically report triggering of their cough by low-level physical (mechanical and thermal) and chemical stimuli (eg, scents, odors). This feature can often be the most troublesome cough-associated adverse occurrence to patients and contributes to their impaired health status.[153,154] The notion that the cough reflex may be sensitized is central to current understanding of clinical cough.[150] This

hypersensitive state may exist transiently, as typically seen with a respiratory viral infection, where the accompanying cough is termed "acute" if it diminishes in < 3 weeks. For the majority of patients with cough, however, their cough and associated sensitivity last > 8 weeks, termed "chronic" by definition. It is not yet clear whether this "hypersensitive state" occurs directly from the effects of inflammatory mediators arising from disease in relevant anatomic sites "sensitizing" receptors expressed on afferent nerves. Alternative possibilities include the central amplification of otherwise normal afferent signals or the failure of descending inhibitory pathways in the higher center to exert their suppressing effect. Irrespective of the exact mechanism, a resolution of this sensitization, by whatever means (eg, the natural resolution of the viral infection, the withdrawal of the angiotensin-converting enzyme inhibitor, or the effective treatment of the underlying cause), is critical to the improvement of the cough. On the other hand, it is also unclear why a hypersensitive state is transient in some patients, whereas it becomes permanent in others.

The maturational and developmental aspects of the cough reflex have important clinical implications.[139] Chemical and mechanical activation is effective at initiating protective reflexes, including apneas and swallowing in the newborn. As the infant matures, these responses become less pronounced. The age at which the cough reflex in children becomes fully matured is not known, but aging per se can impact cough to varying degrees. The efficacy of coughing may be reduced, as respiratory muscle strength decreases with age.[155] However, the threshold for initiating coughing does not change.[156-158] By contrast, the elderly's capacity to suppress cough is diminished,[158] as is the sensation of the urge to cough following airways irritation.[157] Whether these characteristics have a bearing on the likelihood of coughing in the elderly is unclear, although aspiration pneumonia is more common in old age.

Conclusions

Coughing is directly evoked by stimulation of a subset of bronchopulmonary C-fibers and a mechanically sensitive, acid-sensitive subtype of myelinated airway mechanoreceptors. Their activation may result directly in coughing, whereas their coincident activation greatly increases responsiveness to tussive stimuli. Cough can also be modulated by other bronchopulmonary, vagal afferent nerve subtypes and afferent nerves terminating in extrapulmonary locations, including the upper airways, pharynx, and esophagus.

Evidence for extensive remodeling of airway afferent innervation in diseases associated with cough has been conflicting.[159-163] Perhaps chronic coughing occurs, not because of a hyperinnervation of the airways, but because there are more triggers for coughing in the airways or in other organs associated with coughing. Consistent with this notion, inflammatory mediators are elevated in the BAL fluid of patients with asthma and chronic coughers without asthma, and therapeutics that target identified triggers of coughing or inflammation have proven effective in treating cough in several patient populations.[164-173] The precise terminal locations of the afferent nerves driving chronic cough are not yet known.

Although effects in animals have been reported,[174] it is unknown whether any meaningful changes in afferent nerve excitability or ion channel expression occur in chronic cough in patients. Therapeutic strategies targeting the interactions between the afferent nerves regulating cough at the level of the CNS, the mechanisms underlying action potential generation, and the encoding mechanisms of cough are all viable therapeutic strategies for cough suppression (Fig 5). Emerging therapeutic research strategies based on these rationales are priorities to advancing the field at this time and include blockers of TRPV1 and/or TRPA1, voltage-gated sodium-channel blockers (selectively targeting the sodium channels [eg, voltage-gated sodium channel 1.7] expressed by airways sensory nerves), N-methyl-D-aspartate-receptor/channel blockers, and other therapeutic strategies aimed at reducing afferent nerve excitability within the airways.[175-177]

Acknowledgments

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