Peripheral Neural Regulation of the Laryngopharynx

Peripheral Course of the Vagus Nerve

Peripherally, the vagus nerve exits the skull through the posterolateral portion of the jugular foramen called the pars vascularis and then runs with the internal carotid artery within the carotid sheath, with the artery lying anteromedial to the nerve and the jugular vein lying laterally. In the upper mediastinum, the right and left vagus nerves take different courses. The right vagus nerve crosses the right subclavian artery anteriorly and then travels into the adipose tissue behind the innominate vessels. It then courses medially and posteriorly toward the right side of the trachea. Then, the nerve travels superiorly, posterior to the hilum of the right lung and then medially toward the esophagus. Here, it forms the esophageal plexus with the left vagus nerve. The left vagus nerve descends anterior to the left subclavian artery, entering the thorax between subclavian and left common carotid arteries. It descends on the left side of the aortic arch and travels posterior to the phrenic nerve. It then travels superiorly posterior to the hilum of the left lung and traverses inferomedially to reach the esophagus and join the right vagus nerve to form the esophageal plexus [1].

The vagus nerve has several branches, and in this section, we will focus on the branches of the vagus nerve located in the neck and highlight their anatomic...
pathways. These branches are the recurrent laryngeal nerve, superior laryngeal nerve, pharyngeal branches, and superior cardiac nerve [2].

Illustration of the VN anatomy. (Retrieved October 7, 2019 from http://medical-dictionary.thefreedictionary.com/vagus+nerve)

**Recurrent Laryngeal Nerve**

All intrinsic laryngeal muscles apart from the cricothyroid muscle are innervated by the recurrent laryngeal nerve, also known as the inferior laryngeal nerve. The right recurrent laryngeal nerve branches from the vagus nerve just distal to the right subclavian artery. It travels superiorly in the tracheoesophageal groove to enter the larynx between the esophagus and the cricopharyngeus muscle. The left recurrent laryngeal nerve has a similar course as the right but remains anterior to the subclavian artery and loops around the arch of the aorta on the left side, distal to the ligamentum arteriosum at the level of the aorto-pulmonary window. From this point, it ascends along the left tracheoesophageal groove toward the larynx. Both the left and right recurrent laryngeal nerves enter the larynx through the inferior constrictor muscles at the level of the cricothyroid joint. The nerve passes under the ligament of Berry before entering the larynx [3].
**Superior Laryngeal Nerve**

The superior laryngeal nerve branches from the vagus nerve near the inferior half of the nodose ganglion, roughly 40 mm above the carotid bifurcation and 36 mm below the jugular foramen. It then travels inferiorly, dividing into the internal and external branches. The internal branch pierces the thyrohyoid membrane and provides sensory innervation to the supraglottis, whereas the external branch travels to and innervates the cricothyroid muscle. There is some variation in the course of the superior laryngeal nerve, specifically relating to the superior constrictor as well as the superior thyroid vessels. At the tip of the hyoid, the superior laryngeal nerve divides into internal and external branches. The internal branch, which supplies sensory innervation to the majority of the supraglottic mucosa, has three divisions: first, middle, and inferior. The external branch travels with the superior thyroid vessels inferiorly to the inferior pharyngeal constrictor, supplying the cricothyroid muscle. The ramus communicans, also known as the nerve of Galen, connects the superior and the recurrent laryngeal nerves. It provides motor innervation to the tracheoesophageal mucosa and smooth muscle [4].

**Superior Cardiac Nerve**

The superior cardiac nerve has two to three branches. These branches communicate with the sympathetic fibers.

**Pharyngeal Branches**

The pharyngeal branches, containing both sensory and motor fibers, arise from the inferior ganglion. The motor branches cross between the external and internal carotid artery and travel to the middle constrictor muscle and then reach the pharyngeal plexus, which is formed by the glossopharyngeal nerve and the sympathetic chain. Branches from the pharyngeal plexus supply the pharyngeal mucous membranes and muscles excluding the tensor palatini. Vagal fibers from the pharyngeal plexus also form the intercarotid plexus, located at the carotid bifurcation. These fibers mediate impulses sent from carotid body chemoreceptors [5, 6].

**Laryngopharyngeal Sensitivity Receptors**

Sensory receptors are the starting point for neural activity [7, 8]. The receptors outlined in this section include the following:
• **TRPVI:** transient receptor/ion channel potential vanilloid 1, stimulated by acids, protons and capsaicin
• **TRPA1:** transient receptor potential ankyrin, stimulated by cigarette smoke and toluene diisocyanate
• **Cough receptors:** myelinated nerves with a conduction velocity of 5 m/s
• **RAR:** rapidly adapting receptors, a type of mechanoreceptor
• **SAR:** slowly adapting receptors, sense stretch
• **C-fiber afferent nerves:** small diameter, slow-conducting nerve (velocity of <1–2 m/s)

**C-Fibers**

The majority of bronchopulmonary vagal afferent nerves are unmyelinated C-fibers. In addition to their conduction velocity (<1 m/s), airway vagal afferent C-fibers are distinguished from lung stretch receptors in a number of ways. C-fibers are relatively insensitive to mechanical stimulation and lung inflation. C-fibers also are sensitive to capsaicin and bradykinin and activate ion channels, including TRPVI (e.g., capsaicin, protons) and TRPA1 (e.g., ozone, allyl isothiocyanate).

Other inflammatory mediators and environmental irritants that selectively activate C-fibers include prostaglandin E2, ozone, nicotine, adenosine, and serotonin. Bronchopulmonary afferent C-fiber subtypes have been described in several species, with subtypes being differentiated by their ganglionic origin (nodose vs. jugular), sites of termination in the airway/lungs, chemical sensitivity, neurochemistry, and reflexes initiated by their activation. It is unknown whether similar physiologic distinctions between bronchial and pulmonary afferent C-fibers can be defined in humans. Neurokinins, such as substance P, are uniquely expressed by airway C-fibers in animals.

**Mechanoreceptor: Widdicombe Cough Receptors**

More than 50 years ago, John Widdicombe described a type of myelinated vagal afferent nerves innervating the airway that play an essential role in cough reflexes of anesthetized cats. He called these afferent nerves “cough receptors,” a flawed term, but one that has persisted in the literature since. Widdicombe’s claims have been substantiated in multiple studies since, and it is now well-established that, in addition to C-fibers, a subset of myelinated vagal afferent mechanoreceptors plays an essential role in laryngeal sensitivity. Cough receptors differ from C-fibers and lung stretch receptors by their axon conduction speed. Cough receptor axon conduction velocity is 5 m/s, which is faster than C-fibers (<2 m/s) but slower than lung stretch receptors (15 m/s). These mechanoreceptors also differentiate themselves with their insensitivity to capsaicin, as they do not normally express the ion channels TRPVI
or TRPA1. Cough receptors are, however, activated by protons, possibly through expression of acid-sensing ion channels.

Widdicombe, at various times since his seminal work, referred to cough receptors by other terms, including irritant receptors and rapidly adapting receptors (RARs). Although cough receptors are myelinated and adapt rapidly to a tactile rather than stretch-like mechanical stimulation, cough receptors are simply RARs that innervate the extrapulmonary airways. RARs primarily innervate the intrapulmonary airways, whereas cough receptor terminations are found exclusively in the extrapulmonary airways (larynx, trachea, mainstem bronchi). Furthermore, unlike RARs, cough receptors are unresponsive to a wide variety of spasmogens, irritants, and autacoids that induce airway smooth muscle contraction and decrease lung compliance (e.g., histamine, ATP, methacholine, substance P, leukotriene C4, neurokinin A, 5-hydroxytryptamine, and adenosine). All of these stimuli have been shown to activate RARs.

**RAR/SAR**

Rapidly adapting receptors (RARs) and slowly adapting receptors (SARs) are lung stretch receptors characterized by their responses to sustained lung inflation and deflation. RARs and SARs are both activated by sustained lung inflation, but RARs are active predominately during the dynamic phase of lung inflation, whereas SARs continue firing throughout lung distension.

| Receptor          | Stimuli                                      | Myelinated? | Conduction velocity (m/s) |
|-------------------|----------------------------------------------|-------------|----------------------------|
| TRPV1             | Acids, protons, and capsaicin                | N/A         | N/A                        |
| TRPA1             | Cigarette smoke, toluene diisocyanate        | N/A         | N/A                        |
| Cough receptors   | Protons                                      | Yes         | 5                          |
| RAR               | Wide variety of spasmogens, irritants, and autacoids, Lung inflation | Yes         | 4–18                       |
| SAR               | Lung inflation                               | Yes         | 15                         |
| C-fibers          | Capsaicin and bradykinin, protons, nicotine, and the TRPA1 agonists cinnamaldehyde and AITC | Mostly no   | <1                         |

The precise anatomy of RAR terminations in the airway wall is not well understood. Studies suggest that RARs terminate in or beneath the epithelium in the intrapulmonary airways. This location might explain RAR sensitivity patterns to lung collapse and deflation. However, RAR responsiveness to alterations in dynamic lung compliance also suggests a likely association with airway smooth muscle. RARs may, thus, be better thought of as dynamic airway mechanoreceptors. SARs are highly sensitive to the mechanical forces imposed upon the lung during breathing. SAR activity sharply increases during inspiration and peaks just before the initiation...
of expiration. SARs are therefore thought to be the primary afferent fibers involved in the Hering-Breuer inflation reflex, which terminates inspiration when the lungs are adequately inflated and initiates expiration. Anatomically, SAR terminal structures have been identified in the intrapulmonary airways and lungs of rabbits. 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).

**Proposed Mechanisms of Hypersensitivity**

Laryngeal sensitivity can be related to a type of sensory neuropathy. The apparent paradox of hypersensitivity is that sensory neuropathy is generally thought of as a reduction of nerve sensitivity, yet the clinical presentation is that of a hyperexcitable condition. Neurogenic cough, a type of hypersensitivity, often presents after a viral infection, so it is helpful to consider the evidence and mechanisms of virally induced nerve injury in the larynx and elsewhere [9, 10]. In otolaryngology, strong anecdotal evidence supports a viral causality for sudden sensorineural hearing loss, vestibular neuronitis, facial palsy, and idiopathic vocal paralysis. Association with herpes simplex virus, varicella zoster, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus (HIV) have all been documented. The mechanism of injury causing a neuropathy in these and other conditions has been investigated, and the thought is damage may occur indirectly to the nerve through its blood supply, as is the case with varicella zoster viral-induced optic neuropathy and its association with temporal artery vasculitis and hepatitis B virus-induced Guillain-Barre syndrome and its link to mononeuritis multiplex. Viral infection may also have a direct effect on the nervous system, as with cases of HIV peripheral neuropathy where viral RNA has been seen in the spinal cord, as well as in hepatitis C virus infection found in diffuse tissues throughout the body.

Multiple factors can act concurrently to induce airway hypersensitivity, including topical airway infectious agents, viscosity of the airway mucus, inflammatory cytokines, gene regulation producing pathologically altered mucus, and the temperature and pH of the airway surface [11, 12].

Activity within the submucosa, including vascular dilation and smooth muscle constriction, can affect sensory receptor excitability. Neurokinin and substance P have been shown to affect C-fiber and cough receptor excitability in guinea pigs, though this has not yet been documented in humans [13].

**Laryngopharyngeal Sensitivity: Etiologies Beyond Reflux**

Functional laryngeal disorder may be considered a diagnosis of exclusion in patients who do not have objective findings of reflux on pH testing and in whom other etiologies of laryngeal dysfunction – such as Parkinson disease, multiple sclerosis,
amytrophic lateral sclerosis, essential tremor, and dystonia – have been ruled out. Laryngeal hypersensitivity can be a common feature of neuropathic laryngeal pathologies with overlapping symptoms such as paradoxical vocal fold movement, globus pharyngeus, chronic cough, and muscle tension dysphonia [14, 15]. Certain events have been proposed as possibly pre-disposing people to develop laryngeal sensitization, such as an aspiration event, history of intubation, upper respiratory tract infection, asthma, and chronic rhinosinusitis.

Quantitative testing such as hypertonic saline challenge, capsaicin cough reflex sensitivity, acoustic voice testing, timed swallow test, cough frequency monitor, and the voice stress test have been shown to be significantly impaired in patients with functional laryngeal disorder. Below is a brief description of these quantitative voice measures.

The **hypertonic saline challenge test** acts as a physical stimulus to the walls of the airway, aimed at causing bronchoconstriction to assess airway hyperresponsiveness in patients with normal spirometry.

The **capsaicin cough reflex test** uses solutions of capsaicin in varying concentrations delivered in a nebulized fashion aimed at triggering an airway response to assess airway dynamics.

The **timed swallow test** measures the swallowing speed in ml/s and is highly sensitive and moderately specific for neurogenic etiologies of dysphagia.

The **acoustic voice test** consists of recording a speaking or singing voice and measuring acoustic parameters including pitch, loudness, and range with computer software. Cough frequency monitors are objective tools to measure the frequency and quality of cough using microphones. **Voice stress testing** aims to assess the frequency of the voice when certain questions are posed to the patient in order to make predictions on that person’s thoughts and behaviors.

Multiple studies have tried to evaluate the role of laryngeal hypersensitivity with tests using a combination of patient-reported outcome measures and direct testing using laryngoscopy or laryngeal electromyography [16]; however, use of these tests in the clinical setting is limited by variable sensitivity and specificity, as well as lack of access to equipment. Therefore, diagnosis of laryngeal sensitivity is often made clinically after exclusion of other etiologies.

The symptoms of laryngopharyngeal reflux can be sensory alone, a combination of sensory and true reflux exacerbation, or reflux alone. These sensory changes are the main reason the gold standard remains elusive. Testing focused on reflux alone will not capture the alterations in sensory receptors, and addressing these sensory changes can be critical for controlling symptom severity.

There is also evidence to suggest that viral infection may indirectly upregulate the cough reflex via the sensitizing effects of cytokines and inflammatory cells induced by the infecting virus [17]. Viral infection of bronchial cells has been demonstrated to induce upregulation of acid (ASIC) receptors, TRPV1 and TRPA1 channels potentially increasing sensitivity [18]. In addition, a direct sensitizing effect on afferent nerves of the airway needs to be considered also. Sensory nerves themselves have been shown to express the viral receptor ICAM-1, in addition to toll-like receptors (TLRs), which have an integral role in host immunologic defense
during microbial infection. Reducing triggers, such as nasal drainage and reflux, can improve cough severity by decreasing stimulation of a hypersensitive laryngopharynx [19]. More research is needed to elucidate precisely how viruses may exert a direct effect on human airway sensory nerves and consequently laryngeal hypersensitivity.

Conflict of Interest Neither author has any pertinent disclosures or conflicts of interest.

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