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Review Article

Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I

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The vagus nerve (VN), the "great wondering protector" of the body, comprises an intricate neuro-endocrine-immune network that maintains homeostasis. With reciprocal neural connections to multiple brain regions, the VN serves as a control center that integrates interoceptive information and responds with appropriate adaptive modulatory feedbacks. While most VN fibers are unmyelinated C-fibers from the visceral organs, myelinated A- and B-fiber play an important role in somatic sensory, motor, and parasympathetic innervation. VN fibers are primarily cholinergic but other noncholinergic nonadrenergic neurotransmitters are also involved. VN has four vagal nuclei that provide critical controls to the cardiovascular, respiratory, and alimentary systems. Latest studies revealed that VN is also involved in inflammation, mood, and pain regulation, all of which can be potentially modulated by vagus nerve stimulation (VNS). With a broad vagal neural network, VNS may exert a neuromodulatory effect to activate certain innate "protective" pathways for restoring health.

Key words: vagus nerve, vagus nerve stimulation, neuromodulation

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The vagus nerve (VN; cranial nerve X; Latin: wandering), the longest cranial nerve, travels from the medulla to the colon predominantly innervating the thoracic and abdominal organs. It is involved in autonomic, cardiovascular, respiratory, gastrointestinal, immune, and endocrine systems and has been called the "great wandering protector."[1]

The vagal afferents sense a variety of interoceptive stimuli including pressure, pain, stretch, temperature, chemical, osmotic pressure, and inflammation. The sensory information converges at the vagal nuclei, which transmit information to multiple brain regions and convey regulatory information through the descending vagal efferents. The VN and its central connections (the VN system) serve as an "unconscious inner brain" that integrates "feelings" from the body and provides metabolic homeostatic regulation to various organs.[2] The VN regulates heart rate, blood pressure, vascular resistance, airway diameter, respiration, and feeding. Luminal nutrients trigger not only the vago-vagal reflex to initiate digestion and peristalsis, but also the release of enteroendocrine mediators that interact with the VN (gut-brain signaling pathway).[3] VN stimulation (VNS) has been used to

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Table 1.——VN Fiber Types and Their Functions[1,6]

Fiber Type	Fiber Size (mm)	Conduction Velocity (m/s)	Main Function	
			Afferent	Efferent
Aα fiber	13-20	8-120	somatic; touch; pain, temperature	muscle
Aβ fiber	6-12	35-75	somatic; touch	muscle, preganglionic
Aδ fiber	1-5	3-30	visceral; pain, stretch, chemical, temperature	preganglionic
B fiber	1-5	3-15	visceral	preganglionic
C fiber	0.4-2	0.5-2	visceral; pain, stretch, chemical, temperature	preganglionic

demonstrate a role of the VN system in regulating the neuro-endocrine-immune axis, mood, pain, and memory. The astrocytes surrounding vagal neurons also play a regulatory role through neuroactive mediators and neurometabolic coupling.[4] In addition to the acute response, a probable long-term neuromodulatory effect may provide a therapeutic pathway for certain disorders. Numerous studies have demonstrated the potential of VNS in addition to FDA approved indications: refractory epilepsy and depression. Trials are investigating its potential in headache, arthritis, asthma, pain, fibromyalgia, bipolar disorder, and dementia.

The VN system is a complicated neural network that maintains our body in psychophysiological balance. Here, in part I, we review the anatomy and physiology of the VN. In part II, we discuss the history and recent development of both invasive and transcutaneous VNS. In part III, we address the latest VNS-related trials and research involving epilepsy, inflammation, pain, and asthma.

ANATOMY

The VN contains A-, B-, and C-fibers defined by Erlanger and Gasser in accordance with their conduction velocities, which are proportional to their sizes (Table 1). Each has a unique physiological role: (1) large myelinated A-fibers carry mostly somatic afferent and efferent information, and small myelinated A-fibers primarily transmit visceral afferent information; (2) B-fibers provide efferent sympathetic and parasympathetic preganglionic innervation; and (3) small unmyelinated C-fibers primarily carry afferent visceral information. Most VN fibers (60-80%) are afferent C-fibers from the visceral organs.

The VN efferent fibers are primarily cholinergic using acetylcholine (ACh) as their major neurotransmitter. Non-adrenergic non-cholinergic (NANC) fibers whose neurotransmitters include nitric oxide (NO), vasoactive intestinal peptide (VIP), and calcitonin gene-related protein (CGRP) are also abundant. Up to 20% of the VN cross-sectional area in cervical and thoracic vagal trunks contains tyrosine hydroxylase, the enzyme responsible for dopamine and noradrenaline biosynthesis, suggesting a potential cross-talk to the sympathetic system in VN function.[5]

VN efferent fibers arise from the nucleus ambiguus (NA) and the dorsal motor nucleus of the VN (DMN). VN afferent fibers terminate primarily in the area postrema (AP), spinal nucleus of the trigeminal nerve (SNT), and nucleus of the solitary tract (NST). VN afferent cell bodies are located in two ganglia, the jugular (superior) ganglion and the nodose (inferior) ganglion (Fig. 1). Neurotransmitters present in these ganglia include glutamate, CGRP, and substance P (SP).

Structurally, VN fibers emerge from the medulla, where numerous rootlets merge into a single trunk before entering the jugular foramen. After passing caudally through their ganglia, the

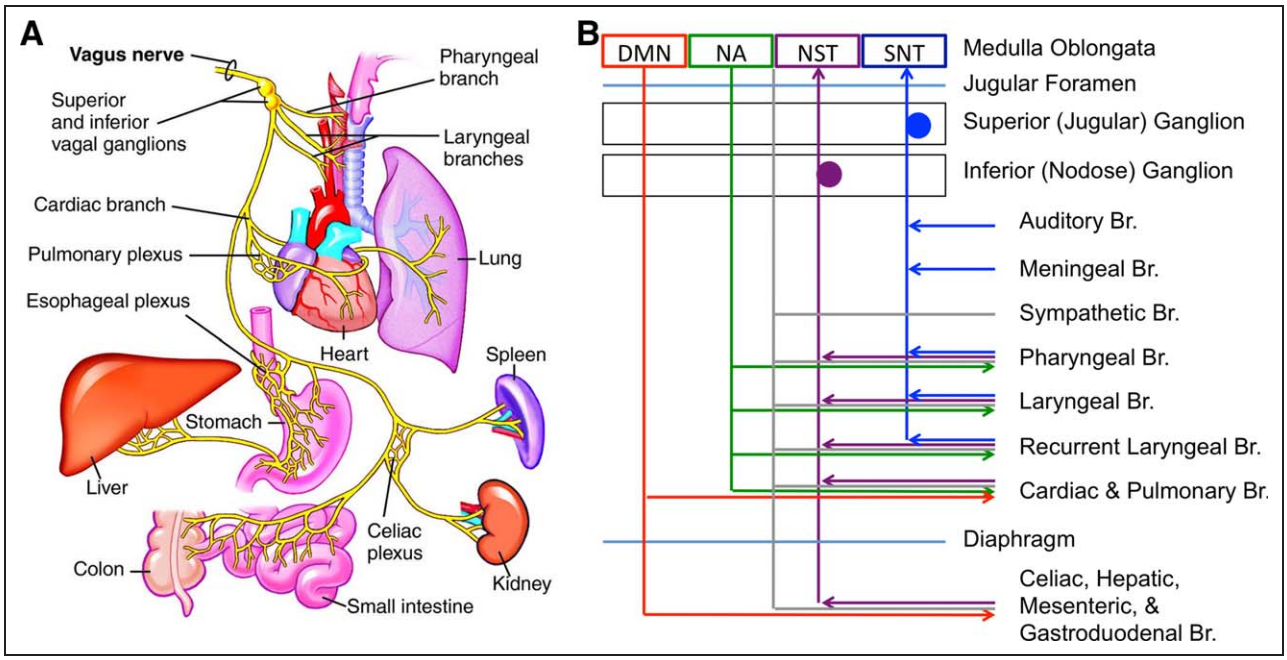

Fig. 1.—(A) Illustration of the VN anatomy (retrieved March 10, 2015 from http://medical-dictionary.thefreedictionary.com/vagus+nerve). (B) Schematic of the vagal nuclei connections. Located in the medulla, the VN comprises four nuclei: DMN, NA, NST, SNT. Vagal afferents terminate in the SNT (blue line) and NST (purple line) with their neuron bodies inside the superior and inferior ganglia, respectively. The DMN (orange line) and NA (green line) send vagal efferents to terminal ganglia. The sympathetic fibers (gray line) can be found in the VN but their function and transmission direction is not clear.

VN divides into the auricular branch (innervating external acoustic meatus), the meningeal branch (innervating posterior fossa dura), the sympathetic branch (joining the superior cervical sympathetic ganglion), the pharyngeal branch (joining the glossopharyngeal nerve), and the laryngeal branch (innervating the cricothyroid muscle, pharyngeal plexus, and sensation above vocal cord). The VN travels along the carotid artery and jugular vein in the carotid sheath and bifurcates to form the recurrent laryngeal nerve (RLN), which loops around the aortic arch (left RLN) or right subclavian artery (right RLN). Both RLNs send branches to the larynx (all intrinsic laryngeal muscles except cricothyroid, and somatic/visceral sensation below the vocal cord), and upper esophagus. The VN then travels to the lower esophagus, lung, aorta, heart, and their related plexuses (esophageal, pulmonary, and cardiac). The remaining VN fibers pass through the diaphragm, exchange bilateral fibers near the esophagus (esophageal commissure), and innervate multiple abdominal organs (eg, liver, portal veins, bile ducts, stomach, kidneys, adrenal glands, intestines, and uterus) and related ganglia or plexuses (eg, celiac, hepatic, suprarenal, gastroduodenal, mesenteric, and myenteric).[6]

PHYSIOLOGY

The VN has three afferent (sensory) types: general somatic afferent (GSA), general visceral afferent (GVA), and special visceral afferent (SVA), and two efferent types: general visceral efferent (GVE) and special visceral efferent (SVE) (Table 2). They originate or terminate in four different vagal nuclei, as described below.

Spinal Nucleus of the Trigeminal Nerve.—The spinal nucleus of the trigeminal nerve (SNT) in the lateral medulla receives GSA central terminations from VN neurons whose cell bodies reside in the jugular (superior) ganglia. It receives sensory input from the external auditory meatus, the posterior fossa meninges, the larynx, and the upper

Table 2.——VN Nuclei and Their Characteristics

Nuclei	Type	Distribution and function related to VN
SNT	GSA	Somatic sensory from posterior external auditory meatus, tympanic membrane, dura in posterior fossa, hypopharynx, larynx and upper esophagus
NST, rostral	SVA	Taste sensation from the epiglottis and pharynx
NST, caudal	GVA	Visceral sensation from hypopharynx, larynx, heart, lungs, alimentary tract, aortic arch (baroreceptors and chemoreceptors) Also senses hormonal and cytokine information
DMN	GVE	Most abdominal and thoracic organs by way of parasympathetic ganglia
NA, branchiomotor	SVE	Visceral motor control of skeletal muscles of the pharynx (except stylopharyngeus muscle), larynx, and upper esophagus
NA, external formation	GVE	Cardiac ganglia for cardiac inhibition Pulmonary ganglia for airway size and secretion regulation

SNT = spinal nucleus of the trigeminal nerve; NST = nucleus of the solitary tract; DMN = dorsal motor nucleus of the VN; NA = nucleus ambiguus.

esophagus. It is responsible for touch, pain, and temperature sensation. Other somatic inputs to the SNT come from the trigeminal, facial, and glossopharyngeal nerves. Axons from the SNT cross the midline in the lower brainstem and project, via the anterior trigeminothalamic tract, to the contralateral ventral posteromedial nucleus (VPM) in the dorsal thalamus, which in turn projects to the sensory cortex.

Nucleus of the Solitary Tract (NST).—The nucleus of the solitary tract (NST) is, in reality, a series of nuclei that form a vertical column of grey matter in the medulla oblongata. The solitary tract runs in its center. There is a topological segregation of the NST; taste input is mostly rostral and intestinal input is mostly caudal.

The rostral NST receives SVA information from the taste buds on the anterior two-thirds of the tongue (via the facial nerve), the posterior one-third of the tongue (via the glossopharyngeal nerve), and the epiglottis (via the VN). The VN taste SVA unipolar cell bodies are located in the nodose (inferior) ganglion. Rostral NST axons travel uncrossed to the VPM of the thalamus, which projects to the gustatory cortex (area 43).

The caudal NST receives GVA central terminations from neurons whose cell bodies reside in both (right and left) petrous (inferior) ganglia of the glossopharyngeal nerve and both nodose ganglia of the VN. The nodose ganglia express clock genes resulting in circadian variations in gastric vagal afferent input from mechanical stimulation.[7] The caudal NST receives input from multiple visceral organs and senses interoceptive information (eg, mechanical, thermal, chemical, metabolic, and hormonal).[8] The NST also receives afferent signals from the spinal cord (lamina I neurons), brain stem (AP, periaqueductal gray [PAG], parabrachial nucleus [PBN]), cerebrum (hypothalamus, thalamus, amygdala), and cerebellum.[2]

The major function of the caudal NST (including the surrounding astrocytes) is to regulate body homeostasis.[4] The NST sends information to PBN (integrates information from lamina I neurons), vasomotor interneurons in the caudal ventrolateral medulla (inhibits sympathoexcitatory neurons in rostral ventrolateral medulla), A1 catecholamine cell group (inhibit vasopressin secretion), NA motor neurons (swallowing, heart rate), DMN motor neurons (heart rate/respiratory rate, peristalsis), spinal cord preganglionic sympathetic neurons (decreases peristalsis), and cervical C1-C3 propriospinal cells (modulates distal spinal segments). Beside neurons, astrocytes in the NST are activated by vagal afferents through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. These astrocytes react to blood-born peripheral signals and modulate neuronal networks

through neuroactive mediators and neurometabolic coupling to maintain homeostasis in response to various internal conditions.[4]

In cardiac angina, afferent C and/or Aδ-fibers are activated by chemoreceptors and, to a lesser degree, by mechanoreceptors in the myocardium and endocardium. They transmit nociceptive information via sympathetic nerves and VNs. The sympathetic nerves terminate in lamina I in C8-T9 then join the spinothalamic tract (STT). The VNs travel to the NST then descend to excite the spinothalamic tract at C1-C3.[9,10] Myocardial injury may stimulate chemoreceptors in the ventricle, activate vagal C-fibers, and induce a triad of hypotension, bradycardia, and dilatation of blood vessels (Bezold–Jarisch reflex).

Nonchromaffin paraganglia (glomus cells) in the carotid and aortic bodies are chemoreceptors sensing O_2, CO_2, pH, and temperature. Baroreceptors (stretch receptors) sense blood pressure in the atria (Bainbridge reflex) and carotid body/aortic arch (arterial baroflex). Both stretch receptors and chemoreceptors send information via the VN for the aortic body and the glossopharyngeal nerve for the carotid body to the NST, and participate in autonomic regulation of cardiac functions.

In the cough reflex, the NST receives afferent input from the larynx, trachea and large bronchi following activation of chemosensitive C- and Aδ-nociceptors, and mechano-sensitive, rapidly-adapting receptors (RAR) and cough receptors.[11] The NST sends efferent fibers to the nucleus retroambigualis and NA, which innervate respiratory and pharyngolaryngeal muscles, respectively.[12] In the Hering–Breuer reflex, both slow- and rapid-adapting small bronchial stretch receptors send input to the NST.[13] They are relayed to the medullary respiratory center and to cardiac vagal motor neurons. The resulting heart rate variation due to respiration is also known as respiratory sinus arrhythmia.

In the vago-vagal reflex, the NST receives signals from gut wall receptors sensitive to mechanical and chemical stimuli. The NST integrates hormonal and visceral neural signals (eg, cholecystokinin [CCK], and tumor necrosis factor [TNF]) and sends information to the parvocellular reticular formation and DMN to control feeding behavior, gut motility, secretion, inflammatory responses, and mucosal defense.[3] The NST also sends visceral information to parabrachial nucleus (PBN) and paraventricular nucleus (PVN) to regulate feeding behavior and autonomic activities. For instance, the vago-vagal reflex is subject to central regulation, which is responsible for the "cephalic phase" and emotional digestive changes. Appetite is regulated by reciprocal connections to the arcuate nucleus, amygdala, and nucleus accumbens where pro-opiomelanocortin neurons (POMC) play an important role in depressing appetite.[14] POMC are modulated by β-endorphin, α-melanocyte-stimulating hormone (α-MSH), corticotropin, leptin, and CCK.

In the mediation of pain sensation, the NST projects to the PAG and visceral nuclei in the spinal cord (for descending inhibition). It projects to monoamine nuclei (eg, locus coeruleus [LC]) via excitatory paragigantocellularis (Pgi) and inhibitory prepositus hypoglossi (PrH) to modulate mood and pain.[15] The NST then connects to paralimbic structures. It reaches the bed nucleus of the stria terminalis in the amygdalofugal pathway. It projects to the PBN and VPM, and reaches the viscerosensory portion of the insular cortex.

During pregnancy and lactation, kisspeptin modulates magnocellular neurosecretory oxytocin secretion, via peripheral vagal afferents and the NST.[16] The VN also provides a spinal cord bypass pathway for vaginal-cervical sexual sensibility in patients with complete spinal cord injury.[17]

Dorsal Motor Nucleus of the Vagus Nerve.—The dorsal motor nucleus of the vagus nerve (DMN) lies medial to the solitary tract and underneath the fourth ventricle. It integrates input from the amygdala, AP, hypothalamus, olfactory system, reticular formation, raphe nuclei, and NST. It transmits monosynaptic vago-vagal feedback to the GI tract but the role of the feedback remains uncertain.[18] Most DMN neurons are modulated by tonic glutamatergic, cholinergic, and GABAergic inputs, primarily from the NST.[19] DMN is the origin of GVE preganglionic parasympathetic fibers innervating all thoracic and abdominal organs. The vagal

parasympathetic nerve does not participate in cranial innervation. Vagal DMN neurons, in contrast, synapse with parasympathetic ganglia lying directly on or in the viscera of the thorax and abdomen. Post-ganglionic fibers then travel to their termini.

More than 80% of DMN neurons project to GI organs. Some project to parabrachial nucleus (PBN) and cerebellum. Abdominal visceral DMN innervation is organized into a series of longitudinally arrayed columnar subnuclei that correspond to specific vagal abdominal branches.[19] Microinjections of glutamate into the rostral or caudal DMN produce gastric contractions or relaxation, respectively, in a dose-related manner.[20] Many peptides and hormones (eg, pancreatic peptide, leptin, ghrelin, CCK, and oxytocin) have receptors in the DMN, NST and AP. Together, they play a major role in the vago-vagal reflex, which regulates gastric motility and secretion.[19]

Nucleus Ambiguous.—The nucleus ambiguus (NA) lies dorsolateral to the inferior olive and can be subdivided into a dorsal branchiomotor division, which gives rise to SVE fibers, and an external formation, which gives rise to GVE parasympathetic fibers.

SVE fibers in the dorsal branchiomotor division of the NA innervate the stylopharyngeus muscle (via the glossopharyngeal nerve), and the striated muscles of the palate, larynx, and pharynx (via the VN and the spinal accessory nerve). The NA receives input from the laryngeal motor cortex, SNT, NST, and AP. It is involved in controlling several reflex activities (eg, gagging, coughing, and vomiting) and receives GABAergic, glycinergic, glutamatergic, adrenergic, and dopaminergic inputs. Gag reflex afferent signals arise from the palate and pharynx, and are transmitted via the SNT and the trigeminothalamic tract to bilateral NA nuclei, which then send signals to the pharynx resulting in bilateral pharyngeal elevation and gagging.

The NA and DMN send preganglionic parasympathetic GVE fibers to pulmonary ganglia (eg, peribronchial, esophageal) for maintaining airway caliber and secretion, as well as to epicardial cardiac ganglia (eg, sinoatrial [SA], atrioventricular [AV], and cranioventricular) for cardio-inhibitory effect. CGRP-immunoreactive (CGRP-ir) neurons are abundant in NA motor neurons that may influence parasympathetic neurons terminated in the lower esophagus and other thoracic organs.[21,22]

In controlling the airway caliber, parasympathetic nerves predominate. Airway smooth muscle lacks direct sympathetic innervation but expresses β_2 adrenoceptors that respond via systemic epinephrine. Preganglionic cholinergic fibers projected from NA (B-fiber) and DMN (C-fiber) travel to two distinct pulmonary ganglia, the peribronchial ganglia, and the esophageal myenteric plexus, respectively; the former send cholinergic fibers for airway smooth muscle contraction, the latter send NANC (VIP, NO) fibers for airway smooth muscle relaxation.[23] Both fiber types are involved in airway secretion. As the airway branches, the size and number of pulmonary parasympathetic ganglia decrease. Modern studies suggest that these pulmonary ganglia not just relay but integrate incoming signals from multiple central sites, including vagal nuclei, amygdala, PAG, hypothalamus, LC, and raphe nuclei. They also receive input from local tachykinergic fibers that release tachykinins into ganglia on nociceptive stimuli.

In controlling heart rate and cardiac function, vagal efferents join cardiac sympathetic nerves to form cardiac ganglia. Cardiac vagal neurons in NA are intrinsically silent; they rely on inputs from glutamatergic, cholinergic, GABAergic, and glycinergic pathways.[24] The stimulation of the ventrolateral rostral and caudal NA inhibits cardiac functions through the AV and SA ganglia, respectively.[6] The NA activates the cardiac ganglia via fast B-fibers in a beat-by-beat short-term manner through a nicotinic mechanism. In contrast, the DMN modulates cardiac functions via slower C-fibers, in a smaller magnitude less phasic manner, through a muscarinic mechanism.[10,25] In addition to increasing SA automatism and systolic contractility through β_1 receptors, the adrenergic system also influence cardiac vagal function. There is a basal tonic activation of α_1-adrenergic receptors in the brainstem that facilitates inhibition of cardiac vagal neurons. Alpha $(\alpha)_1$-adrenergic agonists (eg, phenylephrine) increase GABAergic and glycinergic inhibitory

neurotransmission to cardiac vagal neurons; hence, increased inhibition decreases parasympathetic output resulting in tachycardia. In contrast, alpha $(\alpha)_2$-adrenergic agonists (eg, clonidine) decrease GABAergic neurotransmission to cardiac vagal neurons.[26] Bateman et al also showed that β_1, but not β_2, activation of the presynaptic nerve terminals surrounding cardiac vagal neurons decreases GABAergic, glycinergic, and glutamatergic neurotransmission to cardiac vagal neurons.[27] In addition, oxytocin, which has receptors in the NST but not the NA,[28] modulates the parasympathetic outflow to the heart via NA.[29]

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