The Mechanism of Action of Vagus Nerve Stimulation in Treatment-Resistant Depression

Current Conceptualizations

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KEYWORDS

• Major depression • Treatment-resistant major depression • Vagus nerve stimulation
• Neurostimulation

KEY POINTS

- Vague nerve stimulation (VNS) is a neuromodulatory treatment of depression with various proposed mechanisms of action underlying its efficacy, although further studies are still needed.
- Complex afferent vagal pathways target regions known to affect depression, including the monoamine brainstem nuclei, insular cortex, thalamus, and prefrontal cortex.
- Neuroimaging data have demonstrated VNS's potential acute, subacute, and chronic effects on cortical and subcortical brain regions involved in affective regulation.
- VNS also may have effects on monoamine release, with neuroplasticity serving as the link between increased neurotransmitter levels and actual antidepressant effects.

ANATOMY OF THE VAGUS NERVE

The vagus nerve (cranial nerve X) is the longest of the cranial nerves. True to its name, the vagus, derived from the Latin term for "wandering," has an extensive web of innervation spreading throughout the thoracic, abdominal, and pelvic cavities. The nerve subserves numerous critical bodily functions and is composed of various nerve fibers, including afferent (ie, to the brain) somatic sensory, special sensory (taste), visceral sensory, and efferent (ie, away from the brain) visceral motor and somatic motor fibers.[1]

Disclosure Statement: Dr C.R. Conway is a research design consultant to LivaNova, the makers of the vagus nerve stimulation device.
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Psychiatr Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.psc.2018.04.005
0193-953X/18/Published by Elsevier Inc.

The efferent fibers originate from 2 brainstem nuclei: the dorsal motor nucleus and nucleus ambiguous. In contrast, the afferent fibers targeted during vagal nerve stimulation (VNS) originate from the nodose and jugular ganglia localized just below the foramen magnum, or the opening in the skull between brainstem and spinal cord.[1,2] Afferent fibers carry visceral, somatic (tragus of the earlobe), and special sensory (taste) to the brainstem.[3]

During vagal nerve stimulation, the electrical leads are attached to the left vagus in the midinferior cervical region. In the cervical region, the vagus is positioned between and slightly posterior to the carotid artery and jugular vein, all of which are enmeshed in deep cervical fascia known as the carotid sheath. The majority (approximately 85%) of the cervical vagus nerve is composed of afferent unmyelinated C fibers.[4] These fibers have lower stimulation thresholds, which allow VNS's low-current stimulation to be transmitted primarily afferent, or upstream, to the brain and not downstream to thoracic/abdominal organs, thereby minimizing effects on the heart, lungs, or gastrointestinal tract.[4] With higher currents, myelinated efferent fibers can be activated; this is manifested by activation of the laryngeal and pharyngeal muscles as well as associated hoarseness and stridor—symptoms observed in approximately two-thirds of patients during active VNS stimulation. For this reason, patients receiving VNS therapy may elect to temporarily shut the device off by placing a magnet on the skin over the VNS generator when they are engaging in activities requiring speaking or respiratory exertion.

In humans, the left and right vagal nerves supply parasympathetic visceral motor activity to the sinoatrial and atrioventricular nodes, respectively. Hence, to prevent intracardiac conduction abnormalities, VNS is typically implanted on the left vagus nerve.[5] Studies to date have demonstrated that use of the VNS device in the therapeutic range has limited effects on downstream thoracic and abdominal target tissues (eg, pulmonary, cardiac, and gastrointestinal systems). Given that most therapeutic studies of VNS have not enrolled patients with significant cardiopulmonary disease, however, caution is advised in consideration of such patients, especially those with obstructive sleep apnea.[6,7]

AFFERENT BRAIN AND BRAINSTEM VAGAL PATHWAYS

Although well studied in lower mammals, the afferent vagal brainstem and brain pathways are complex and not completely understood. A summary of these pathways is provided later, and a more complete description can be found in Henry.[8]

As discussed previously, the afferent pathways, which are accessed by VNS, carry somatic sensory information from the skin, special gustatory sensation, and sensation from the larynx, pharynx, and thoracoabdominal organs. These afferent fibers enter the brainstem at the medullary level, decussate, and then synapse at several nuclei (**Fig. 1**). The most critical pathway for VNS treatment is the tractus solitarius, which terminates in the nucleus tractus solitarius (NTS).[9–11] Fibers from the NTS primarily project upstream to the pontine parabrachial nucleus (PBN) but also project to various other medullary and pontine nuclei, the cerebellar nuclei, and the periaqueductal gray. The periaqueductal gray region is critical for central pain modulation, and limited studies of VNS's analgesic effects may be taking advantage of this regional innervation[12] (see **Fig. 1**).

The NTS projects to both the medullary and pontine raphe nuclei (RN) (ie, the primary brainstem sites for serotonergic nuclei)[13] as well as the pontine locus ceruleus (LC) (ie, the primary brainstem site for noradrenergic nuclei)[13] (**Fig. 2**). These upstream monoamine projections are likely critical in the mood regulation aspects of VNS. In