Mechanism of Action of Non-Invasive Cervical Vagus Nerve Stimulation for the Treatment of Primary Headaches

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ABSTRACT

Stimulation of the cervical vagus nerve with implanted vagus nerve stimulation (iVNS) has been used clinically for more than 20 years to treat patients with epilepsy. More recently, a non-invasive cervical vagus nerve stimulation (nVNS), gammaCore, was developed, which has been purported to also stimulate the vagus nerve without the cost and morbidity associated with an iVNS system. gammaCore has been used to acutely treat various types of primary headaches, including migraine and cluster headaches (CH), and for the prevention of episodic, chronic, and menstrual migraines and CH. The gammaCore device was cleared by the FDA for the acute treatment of pain in episodic CH patients. In this review, we summarize the clinical work that has been published in the use of gammaCore for treating primary headache disorders, present an overview of studies demonstrating that nVNS does indeed stimulate similar vagus nerve fibers as the implantable VNS system, and then present several animal headache-related studies that address the mechanism of action of nVNS.

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For author information and disclosures, see end of text.

The vagus nerve is the major parasympathetic branch of the autonomic nervous system, whose primary functions include regulation of breathing, heart rate, and digestion. Through its afferent projections, which account for 80% of its fibers, to the brainstem's nucleus tractus solitarius (NTS), the vagus can regulate brain physiology, chemistry, plasticity, and behavior.[1] In addition, it has been shown to play an important role in the regulation of the body's inflammatory responses, both centrally and peripherally, with a significant body of research elucidating an efferent, anti-inflammatory pathway mediated by acetylcholine and/or norepinephrine.[2-5]

The most common clinical use of vagus nerve stimulation (VNS) is for the treatment of refractory epilepsy; however, VNS has been shown to be a potential treatment for multiple disease states, many of which have an inflammatory component, including Alzheimer's disease,[6-8] traumatic brain injury,[9-12] stroke,[13-16] posttraumatic stress disorder,[17] rheumatoid arthritis,[18] Crohn's disease,[19,20] tinnitus,[21,22] fibromyalgia,[23,24] epilepsy,[25-27] depression,[28-31] and various primary headache disorders.[32-36]

Until recently, VNS required an implanted pulse generator with electrodes coiled around the cervical branch of the vagus. Now, new, non-invasive vagus nerve stimulation (nVNS) approaches using transcutaneous stimulation of the cervical branch of the vagus at the neck (gammaCore)[37-39] or of the auricular branch of the vagus at the concha of the outer ear (Nemos), have been developed.[22,28,40,41] The effectiveness of these devices for epilepsy, depression, primary headaches, and other conditions has been investigated, although mostly in small pilot studies. These new devices avoid the need for surgical implantation of a stimulator, and for the associated cost and morbidity, and have the potential to dramatically increase accessibility to this strategy.

Clinical evidence that VNS provides relief from pain associated with headache (including migraine and cluster headache [CH]) has been observed in published accounts of implanted VNS (iVNS).[32-36] Mauskop published a prospective case series consisting of 6 nonepileptic patients who underwent VNS implantation specifically for intractable primary headaches. Two of the 6 patients were

diagnosed with chronic CH. They improved markedly after 2 months, with scores on the Migraine Disability Assessment questionnaire dropping from 265 to 15 in 1 patient and 210 to 8 in the other.[34] A similar prospective case series was reported by Cecchini in 2009, consisting of 4 patients with chronic migraine. All of them were refractory to multiple medications combined with a history of substantial medication overuse. Although only a case series, the 4 patients seemed to show a positive benefit from the treatment.[32]

Due largely in part to these promising findings, the use of the gammaCore nVNS has been studied in a number of primary headache clinical trials, and it continues to be the subject of sham-controlled randomized clinical studies, primarily in the United States and Europe.

The FDA's approval of gammaCore is based on subgroup analyses from 2 trials in the Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache (ACT) clinical trial program evaluating the safety and efficacy of gammaCore for the acute treatment of episodic cluster headache (eCH). Both trials (ACT1 and ACT2) were prospective, double-blind, placebo-controlled, randomized studies evaluating the use of gammaCore versus placebo. Results from ACT1, which evaluated a subgroup of 85 patients with eCH from a larger (133) population of patients with cluster headache, found that 34.2% of patients in the eCH group experienced pain relief at 15 minutes compared with 10.6% of patients treated with placebo ($P = .008$).[38] Results from ACT2, which evaluated 182 attacks in 27 patients with eCH, found that a significantly higher percentage of attacks were aborted (pain free) at 15 minutes in patients treated with gammaCore (47.5%) versus placebo (6.2%; $P = .003$).[42] In both trials, gammaCore was found to be safe and well tolerated, with the majority of adverse events reported as mild and transient and occurring during the time of active treatment.

Evidence That nVNS Stimulates the Vagus Nerve

Previously, it did not seem possible to non-invasively stimulate the cervical vagus nerve without causing significant nociceptive pain, due to the high-capacitive skin-electrode impedance and the large currents required to generate an appropriate electric field gradient at the location of the vagus nerve. However, in the case of iVNS, the electrode is essentially in direct contact with the vagus nerve sheath and requires relatively small currents, at least to excite the A and B fibers implicated in the mechanism of action (MOA) of VNS.[43] Different nerve fibers have different functions (eg, sensory or motor), electrical thresholds, and conduction velocities. The larger the fiber diameter (A>B>C) and the greater the degree of myelination (A>B and C fibers have none), the lower the electrical threshold. gammaCore uses an alternating current electrical signal consisting of five 5000-Hz pulses repeating at a rate of 25 Hz. The waveform of the gammaCore pulse is approximately a sine wave, which allows the passage of currents more than 15 times larger than those used in the implantable device, while causing only minimal nociceptive pain. There is only a mild skin sensation and muscle contraction due to the proximity to the sternocleidomastoid muscle (SCM).

It is possible to directly compare the effects of iVNS with that of nVNS in animal studies. Chen et al[44] used an animal model of cortical spreading depression (CSD) to show that acute treatment with VNS, either with electrodes directly on the vagus nerve or with a gammaCore device modified for rat stimulation, could inhibit CSD frequency and elevate the electrical thresholds required to initiate a CSD, both to the same degree. Ay et al[45,46] compared the effects of iVNS with those of nVNS (using the same stimulator as described above) in a rat middle cerebral artery occlusion ischemic stroke model, and the results showed similar degrees of reduction in ischemic volume and behavioral deficit. The anatomy of the rat and electrical properties of rat skin are certainly different from those of humans, so these studies are only suggestive, but they show that in principle, nVNS can work.

A more direct demonstration of vagus nerve activation can be obtained from functional magnetic resonance imaging (fMRI) studies. The majority of afferent vagal fibers enter the brain through the jugular foramen and synapse onto the nucleus tractus solitarius, the first central relay of vagal afferents, which then project directly and indirectly to various structures in the brain (eg, locus coeruleus, dorsal raphe nucleus, periaqueductal gray) implicated in the mechanism of action of VNS in epilepsy.[47] Frangos et al[48] compared the effects of nVNS versus control SCM stimulation and reported activation of the NTS and parabrachial area, primary sensory cortex, basal ganglia, frontal cortex, and insula with nVNS. Deactivations were found in the hippocampus, visual cortex, and spinal trigeminal nucleus (STN). These changes were similar to those reported in fMRI studies of iVNS in patients with epilepsy and in a study from the same group on the effects of nVNS of the external ear in regions innervated by the auricular branch of the vagus nerve.[49] Of note, deactivation of the STN in response to nVNS has been implicated in the MOA of nVNS in headache and other pain disorders. As described in the following section, results from several animal studies have demonstrated that nVNS produces a long-lasting inhibition of pain-specific nerve firing and excitatory neurotransmission activity in the STN and related structures. The fMRI findings provide evidence in humans that cervical vagal afferents can be accessed non-invasively via transcutaneous electrical stimulation.

Recently, a high-resolution, multiscale, computational model for nVNS was described.[50] Briefly, T1 and T2 MRI scans of the head and neck were used to construct a finite element model, which incorporated the electrical properties of each specific tissue type. This model was unique in that it was the first to accurately reproduce details of macroscopic (eg, fat, skin, muscle) and mesoscopic

(vertebra, cerebrospinal fluid, anatomical details, nerve sheath) tissues; reproducing both was shown to be important for determining activation thresholds. Electric fields were calculated in the tissues using the dimensions and electrical properties of gammaCore as boundary conditions. Activation thresholds of various axon types (A, B, and C fibers) were calculated from the electric field and/or the electric field gradient profiles. The results of the modeling demonstrated that the gammaCore device, at typical clinical voltage settings, was capable of activating A and B fibers, but not C fibers.

VNS has been shown to produce vagus somatosensory-evoked potentials (VSEPs) arising from the brain stem with both auricular and iVNS. Polak et al[51] reported a specific far-field electroencephalogram (EEG) potential occurring 2 to 6 minutes after auricular vagus stimulation. The EEG signal consisted of a positive waveform followed by a negative one (referred to as P_1N_1). It is suggested that these potentials arise from far-field dipole generators due to the similarity of waveform, polarity, and latencies independent of EEG electrode positions. Usami et al,[52] using iVNS in patients undergoing surgery for epilepsy, performed a similar study and reported a similar P_1N_1 signal. By moving the electrode cuff along the vagus nerve and recording VSEP latencies, the nerve conduction velocity (27 m/s) was calculated. The authors concluded that the signal arose from alpha delta (Aδ) fibers at the point where the vagus nerve enters the jugular foramen due to changes in impedance around the nerves as they entered the skull.

A similar study was undertaken with cervical nVNS using the gammaCore device.[53] P_1N_1 VSEPs were observed for cervical nVNS in 11 of 12 subjects with latencies similar to those described previously, whereas control SCM stimulation revealed only a muscle artifact with a much longer latency. A dose-response analysis showed that at an intensity of 15 volts, cervical nVNS elicited a clear VSEP response in more than 80% of the subjects. As evidenced by the recording of far-field VSEPs similar to those seen with iVNS and non-invasive auricular stimulation, cervical nVNS can activate vagal afferent fibers.

Mechanisms of Action in Primary Headache

Oshinsky et al[54] described the effects of nVNS in a rat model of trigeminal allodynia. Rats were sensitized by repeated dural infusions with inflammatory mediators, which led to a state of chronic trigeminal allodynia, as defined by decreased periorbital sensitivity to von Fry filament testing in the periorbital region.

Two minutes of nVNS rapidly (<5 minutes) decreased periorbital sensitivity for up to 3.5 hours. Previous work from this lab[55] showed that glyceryl trinitrate (GTN), a nitric oxide donor that causes prolonged migraine-like headaches in migraineurs but not in healthy controls, causes a further decrease in sensitivity, which correlates with increased levels of extracellular glutamate in the trigeminal nucleus caudalis (TNC). High levels of glutamate in the TNC are a marker for increased trigeminal pain. Allodynic rats that received nVNS had only a 2-fold increase in extracellular glutamate after GTN compared with a nearly 8-fold increase in untreated animals. Even when nVNS was delayed until 2 hours after GTN treatment, the stimulation could still reverse the elevated levels of glutamate, bringing them back to naïve levels, which were maintained for the duration of the experiment. These data suggest that nVNS may treat headache pain by a direct, acute, inhibitory modulation of headache pain pathways that increase nerve activity in the TNC and therefore in its projections to the thalamus and the cortex where the perception of pain occurs.

Chen et al[44] looked at the effects of iVNS and nVNS in a rat model of CSD. CSDs are waves of propagating neuronal depolarization thought to be the electrophysiological correlate of migraine aura, which are the visual disturbances reported by migraineurs that often precede headache. The frequency of continuous CSDs, induced by placing a potassium chloride-soaked cotton ball on the dura, or electrical thresholds, determined by measuring the minimal amount of injected current needed to induce a single CSD, are surrogates for cortical excitability. This model has been used to screen migraine drugs now used clinically. These drugs were shown to reduce CSD frequency and increase electrical thresholds, although many weeks of daily infusions were necessary.[56]

Chen et al[44] showed that both iVNS and nVNS reduced CSD frequency by almost 50% and increased electrical thresholds by about 3-fold. Further, the effects of two 2-minute stimulations lasted more than 3 hours and were equally effective on CSDs in the ipsilateral or contralateral hemispheres. If indeed aura precedes and causes a subsequent headache, these results suggest nVNS may work preventively by reducing the frequency of aura and the resulting migraine headaches.

Akerman et al[57] studied the effects of nVNS on the firing of trigeminocervical pain neurons in a rat model of migraine-like and cluster-like acute head pain. A single 2-minute dose of ipsilateral or contralateral VNS suppressed dural-evoked trigeminocervical neuronal firing, both spontaneous and noxious, within 15 minutes. This effect was dose dependent, with 2 doses of ipsilateral VNS prolonging suppression of ongoing spontaneous firing for up to 3 hours and of noxious dural-evoked responses for more than 2 hours. As in the previous study, both ipsilateral and contralateral stimulations were equally effective. To model the trigeminal-autonomic pathway implicated in CH, superior salivatory nucleus (SUS)-evoked trigeminocervical neuronal responses were studied. Two doses of VNS suppressed SUS responses for 2.5 hours. The degree of inhibition with VNS (between 20% and 50% for evoked responses) was similar to that found with other abortive headache treatments, including triptans, in the same model, suggesting a similar site of action.[58] Consistent with clinical observations, VNS did not affect normal somatosensory nociceptive processing. Further

experiments will be needed to determine if the inhibition of firing of trigeminocervical neurons is a direct effect of VNS-induced descending inhibition by release of inhibitory neurotransmitters, like gamma-aminobutyric acid or serotonin, or by an upstream effect on other targets involved in intracranial trigeminovascular nociceptive transmission.

A large body of literature describes the anti-inflammatory effects of VNS (referred to as the cholinergic anti-inflammatory pathway), pioneered by Kevin Tracey and colleagues.[4] Stimulating appropriate efferent or afferent fibers of the VN inhibits splenic (and other organ) macrophage production of several inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1, and interleukin-6.[4] A recent study in human rheumatoid arthritis patients with iVNS showed a reduction in disease symptom severity that paralleled changes in TNF-α and C-reactive protein, a measure of inflammation.[18] nVNS has been shown to also activate this pathway in 2 human studies.[59,60] In addition, Brock et al[49] showed a sustained elevation of cardiac vagal tone (a measure of parasympathetic activity indicative of VN stimulation) that lasted up to 24 hours after a 2-minute treatment with gammaCore. A reduction in inflammation and an increase in vagal tone may also play a part in the mechanism by which VNS alleviates headache.

Conclusions

Non-invasive stimulation of the cervical branch of the vagus nerve is an exciting new teCHnology that may increase access to the clinical use of VNS by avoiding the need for surgical implantation of a stimulator and for the associated cost and morbidity. Preliminary clinical studies in various primary headache disorders are encouraging. Human studies and modeling have demonstrated that nVNS activates vagus nerve fibers similar to those implicated in the clinical benefits of iVNS. Continuing human and animal research will be necessary to further elucidate the MOA and to help define optimal signal parameters and treatment paradigms for headache and other disorders. ■

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