

Vagus nerve stimulation for epilepsy: A review of the peripheral mechanisms

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Abstract

Vagus nerve stimulation (VNS) is a unique epilepsy treatment in that a peripheral intervention is used to treat a disease that is entirely related to pathological events occurring within the brain. To understand how stimulation of the vagus nerve can be used to stop seizures, an understanding of the peripheral anatomy and physiology of the vagus nerve is essential. The peripheral aspects of the vagus nerve are discussed in this review, with an explanation of which fibers and branches are involved in producing these antiepileptic effects, along with speculation about the potential for improving the therapy.

Key Words: Epilepsy, vagus nerve stimulation, peripheral nerves

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INTRODUCTION

A series of experiments conducted by Zabara demonstrated that vagus nerve stimulation (VNS) could be used to stop experimentally induced seizures in dogs.^[35] These findings led directly to the development of a commercial VNS device^[30] which was first implanted clinically in 1988 by Penry and colleagues.^[22] After several large clinical studies, the European Community approved the use of VNS for seizures in 1994, followed by approval by the Food and Drug Administration (FDA) in the United States in 1997. VNS is currently used in more than 40,000 patients as an adjunctive therapy for medication-resistant epilepsy and, as of this writing, remains the only FDA-approved device-related treatment for refractory seizures.

Compared to other neurosurgical interventions in which the focus is surgically removed, VNS offers a lower-risk surgery with fewer complications.^[6] The surgery involves the placement of helical electrodes on the left cervical

vagus nerve, with intermittent stimulation provided by a neurocybernetic prosthesis implanted subcutaneously in the upper chest.

Stimulus parameters vary; however, studies suggest that maximum protection from seizures can be achieved with stimuli given periodically at 20–30 Hz.^[35] Most patients are currently stimulated at 30 Hz, with a constant stimulation cycle of 30 seconds on and 5 minutes off.^[26] Clinical trials have found the device to reduce the incidence of complex partial seizures in the majority of patients tested, with 20–40% of patients achieving a greater than 50% reduction in seizure frequency.^[11,33] The number of responders increases with time,^[7,19] while the number of anti-epileptic drugs (AEDs) necessary to maintain satisfactory seizure control decreases after VNS.^[28]

Side effects of VNS are generally limited to coughing and/or hoarseness of the voice. These side effects can be universally produced with sufficient VNS amplitude

or pulse width, but they are not necessary to produce the therapeutic response. Often, these side effects will be elicited when the VNS settings are adjusted, but are usually transient, or can be eliminated immediately by reducing the relevant VNS parameters.

VNS is a unique epilepsy treatment in that a peripheral intervention is used to treat a disease that is entirely related to pathological events occurring within the brain. While it is often stated that VNS's therapeutic mechanisms have not been fully elucidated, it is clear from numerous studies that activation of vagal afferents through electrical stimulation directly and indirectly influences well-defined seizure-related circuitry within the brain.

To understand how stimulation of the vagus nerve can be used to stop seizures, an understanding of the peripheral anatomy and physiology of the vagus nerve and its central projections is critical. Only the peripheral aspects of the vagus nerve are discussed in this review, explaining which fibers and branches are involved in the antiepileptic effects of VNS. The central mechanisms of VNS will be discussed separately.

VAGUS NERVE ANATOMY

Vagus is the Latin term for “wandering.” The name alludes to the complexity of connections that the branches of this nerve form within the body. The vagus nerve is a composite of afferent sensory and efferent motor fibers traveling together in a common pathway, each with its own origin, destination, and activation threshold.

Despite the emphasis placed on the motor effects of the vagus nerve in most introductory texts, the sensory afferents far outnumber the motor efferents, comprising approximately 65–80% of all vagal fibers.^[9] The vagus nerve contains branchial and visceral motor components, as well as visceral and general sensory components. Most of the sensory afferents conduct information to the brain concerning the internal milieu, while most of the motor efferents provide parasympathetic outflow to the organs. These fibers exit or enter the medulla in 8–10 rootlets on both sides and coalesce into a nerve trunk that passes through the jugular foramen. All the major thoracic and abdominal organs are innervated by the vagus, providing profuse brain/body interaction.

Efferent fibers

The branchial motor fibers of the vagus nerve innervate the skeletal muscles of the neck and face. The cell bodies for these fibers are located in the nucleus ambiguus. The fibers leave the vagal trunk in three main branches. The pharyngeal branch provides most of the motor innervation of the pharynx and soft palate striate muscles and a portion of the tongue. The superior laryngeal

branch supplies the inferior constrictor and cricothyroid muscles of the larynx, and the pharyngeal plexus. The recurrent laryngeal branch leaves the vagal trunk more distally than the others and follows a rather circuitous route to innervate all of the laryngeal muscles, except the cricothyroid. The left recurrent laryngeal branch passes under the aorta, while the right branch passes under the subclavian artery.

Visceral motor preganglionic fibers originate in the dorsal motor nucleus of the vagus, except for cardiomotor neurons which probably originate in the nucleus ambiguus.^[25] These preganglionic fibers synapse on ganglia providing parasympathetic innervation for the extensive cardiopulmonary and gastrointestinal systems, and the glands of the pharyngeal and laryngeal mucosa. The latter are served by the pharyngeal, superior laryngeal, and recurrent laryngeal branches, respectively, following the paths described above.

The pulmonary, esophageal, and cardiac motor branches leave the vagal trunks at various points within the neck and thorax, and synapse in ganglia within their target. Pulmonary branches leave the trunk in the thoracic cavity and form anterior and posterior pulmonary plexuses along with the fibers from the thoracic sympathetic trunk ganglia. These pulmonary branches innervate the bronchial smooth muscles. Esophageal plexuses are also formed from vagal branches in the thoracic cavity along the entire length of the esophagus. These fibers innervate the smooth muscles of the esophagus. The heart is served by several branches from each side: the superior and inferior cervical cardiac branches, which leave the main trunk in humans approximately at the level of the thyroid gland, and the thoracic cardiac branch, which exits as the vagal trunk passes near the heart. The left and right cardiac motor fibers innervate the heart asymmetrically, with fibers originating from the left vagus nerve supplying the atrioventricular (AV) node (causing decremental conduction) and those from the right vagus nerve innervating the sinoatrial (SA) node (reducing depolarization rates and producing bradycardia).^[21] The remaining vagal motor fibers follow the esophagus through the esophageal plexus of the diaphragm. It is estimated that 75% of visceral motor fibers present in the vagal trunk project to subdiaphragmatic organs.^[23]

Afferent fibers

The vast majority of vagal fibers are small unmyelinated afferents.^[9] Most of these unmyelinated afferents are visceral sensory fibers which carry information from the stomach, intestines, liver, pancreas, and spleen.^[5] Nearly all visceral sensory fibers encode non-pain sensations, such as feelings of hunger, satiety, and nausea, which never reach a conscious level of awareness. A small percentage of these fibers may also carry visceral pain information from the heart, esophagus, and trachea.^[18]

These fibers are joined at the cervical level by larger myelinated vagal afferents traveling from baroreceptors located in the aortic arch and pulmonary airways, and also from chemoreceptors located in the aortic body. Stimulation of these cardiac and pulmonary fibers can result in reflex slowing of breathing (Hering–Breuer reflex), bradycardia, and vasoconstriction.

The general sensory fibers have a much less extensive field than the vast visceral sensory system. General sensory fibers carry touch, pain, and temperature information from the ear and parts of the pharynx and larynx. Fibers of the auricular branch, which innervates the pinna and auditory canal, directly enter the jugular (superior vagal) ganglion without joining the vagal trunk. In contrast, general sensory fibers from the pharynx and larynx join the motor fibers in either the superior laryngeal or recurrent laryngeal branches, with their cell bodies located in the nodose (inferior vagal) ganglion. All of the general sensory fibers eventually synapse within the spinal nucleus of the trigeminal nerve.

VAGAL FIBER TYPES INVOLVED IN THE ANTIEPILEPTIC EFFECTS OF VNS

Understanding the location of a VNS electrode on the vagal trunk and evaluating VNS-induced side effects can yield valuable information regarding the vagal branches and fiber types that are activated during clinical VNS. VNS electrodes are implanted on the left cervical vagal trunk, approximately 8 cm above the clavicle. With the exception of the recurrent laryngeal branch, the auricular, laryngeal, and pharyngeal branches are unlikely to be activated by VNS as they exit the main trunk proximal to the VNS electrodes. The same may be said of the superior and inferior cervical cardiac branches. The rest of the vagal branches and fibers described above, however, are present in the trunk at the level of the VNS electrode and, depending on the activation threshold as discussed below, may or may not be stimulated using normal therapeutic VNS parameters.

Small unmyelinated C-fibers make up the bulk of fibers in the cervical vagus nerve, activation of which should result in a host of clinical side effects that would include the cardiopulmonary and gastrointestinal systems. These side effects are rarely, if ever, observed in patients at therapeutically relevant VNS parameters, however, prompting some investigators to suggest that activation of vagal C-fibers probably does not occur.^[3,8] Animal studies seem to support this notion.

Early VNS work in rats indicated that recruitment of vagal C-fibers is necessary for seizure suppression.^[34] In these experiments, various VNS stimulation parameters were used to evoke compound action potentials in the isolated vagus nerve of anesthetized rats. The parameters

necessary to suppress seizures in awake rats evoked a maximal response from A-, B-, and C-fibers in the isolated vagus nerve in anesthetized rats. Since large myelinated A-fibers and small myelinated B-fibers have much lower activation thresholds than that necessary to suppress seizures in awake rats, it was concluded that activation of these fibers was not sufficient for seizure suppression and that C-fiber activation was necessary. Stimulation in a chronically implanted, awake animal, however, produces electrical shunting through the body, which is not modeled accurately by an acute isolated nerve preparation. Therefore, it is likely that the stimulation parameters necessary to evoke seizure suppression in awake animals are not comparable to those necessary to stimulate C-fibers in the isolated vagus nerve.

Selectively and non-invasively destroying specific vagal fiber types, thereby eliminating the effects of their activation, may be a more preferable method of determining which fiber types are involved in VNS-induced seizure suppression. In one such experiment, rats were pretreated systemically with either capsaicin, a selective C-fiber excitotoxin, or vehicle.^[15] C-fiber destruction was confirmed by testing the chemosensitivity of the eye; a lack of chemosensitivity indicates that pain fibers (which are predominantly C-fibers) have been destroyed. A cuff electrode was then implanted on the left cervical vagus nerve. After two days, the ability of VNS to suppress generalized pentylenetetrazole (PTZ) seizures was tested. Seizure severities in vehicle-treated rats during VNS were significantly reduced compared to baseline severities. Rats receiving capsaicin – thus destroying most C-fibers in the body, including the vagus nerve – did not reduce the effectiveness of VNS despite a lack of chemosensitivity. In agreement with the clinical observations,^[3,8] these results demonstrate that activation of vagal C-fibers is not required to obtain VNS-induced seizure suppression; activation of A- and/or B-fibers is sufficient.

These data are clinically important since A- and B-fibers have a much lower activation threshold as compared to C-fibers, thus reducing the amount of current necessary to produce the antiepileptic effects of VNS. Lack of C-fiber recruitment is also important since activation of these fibers would produce a host of unwanted side effects that are not seen in most patients and may have rendered the therapy intolerable.

VAGAL BRANCHES INVOLVED IN THE ANTIEPILEPTIC EFFECTS OF VNS

Currently, VNS is applied only to the left cervical vagal trunk which contains fibers from the recurrent laryngeal, cardiopulmonary, and subdiaphragmatic vagal branches. Since these branches serve diverse functions, not all of the branches necessarily contribute to VNS-induced

seizure suppression. In fact, evidence suggests that seizure suppression can be achieved with stimulation of lesser vagal branches. In one such study, a cuff electrode was implanted on the ventral (left) subdiaphragmatic vagal branch in rats.^[14] After two days, VNS or sham stimulation was applied and seizures were induced with PTZ. The reciprocal treatment was given 48 hours later so that each rat acted as its own control. Subdiaphragmatic VNS significantly reduced seizure severity compared to baseline. This reduction was comparable to that obtained with cervical VNS in previous experiments, suggesting that stimulation of subdiaphragmatic vagal branches alone is capable of suppressing seizures. While selective stimulation of the subdiaphragmatic branch is effective in seizure suppression, a role for other branches cannot be ruled out.

LEFT- VERSUS RIGHT-SIDED VAGUS NERVE STIMULATION

Kalia and Mesulam^[13] found that the midline and unpaired viscera innervated by sensory and motor fibers of the vagus nerve are, for the most part, bilaterally represented. In contrast, over two-thirds of the projections from paired structures (such as the lungs and bronchi) remain ipsilateral. Studies in the dog show that right-sided VNS results in a greater degree of bradycardia as compared to left-sided VNS.^[24] As discussed above, this is due to the asymmetric innervation of the heart, with right-sided VNS in dogs activating the cardiac motor efferents innervating the SA node. Because of these early dog studies, it is commonly held that right-sided VNS should not be attempted in a clinical setting. In fact, the FDA-approved labeling that accompanies VNS equipment states, “The NCP system is indicated for use only in stimulating the left vagus nerve in the neck area. Safety and efficacy of the NCP system treatment have not been established for stimulation of the right vagus nerve.”

Fortunately, the anatomy of the cervical vagal trunk is different between dogs and humans. The cervical vagal trunk where the VNS electrodes are normally placed in humans does not include the superior or inferior cardiac branches, thereby minimizing clinically relevant cardiac side effects regardless of the side of implant. Only 0.1% of patients undergoing implantation of VNS electrodes on the left vagal trunk experience transient asystole during intraoperative testing.^[2,29] While surgeons abort the implant in approximately half of these patients, no patients have experienced further cardiac complications if the VNS electrodes are left in place,^[1] suggesting an interaction may occur between VNS and intraoperative anesthesia that may exaggerate cardiovascular effects during surgery. In fact, careful monitoring of patients receiving VNS for up to three years has revealed no clinically relevant effects

on cardiac function.^[10] When intraoperative cardiac complications are encountered, possible reasons include abnormal electrode placement, unintended collateral stimulation of the cardiac branches, or abnormal vagal anatomy due to individual differences.^[4]

If right-sided VNS is safe, the question remains if it is effective. In animal models, the answer is yes. In one study, a cuff electrode was implanted on the left or right cervical vagus nerve in two groups of rats.^[16] After two days, VNS was initiated, then PTZ was injected. The highest seizure stage attained within 15 minutes was rated by a blinded observer. Right-sided cervical VNS was found to be equally effective as left-sided cervical VNS in suppressing these PTZ-induced seizures in rats. In a later animal study, anesthetized pigs were implanted with a cuff electrode on the cervical vagus nerve and then spinal cord seizures were induced with a topical application of penicillin. Cervical VNS, regardless of whether it was applied on the left^[31] or right^[32] side, significantly reduced this seizure activity.

This has now been demonstrated clinically in three separate studies. McGregor and colleagues^[17] published the first case report of patients who received right-sided VNS. All three patients were children who had been implanted with a left-sided VNS system and had the system explanted due to postoperative infection. Although efficacy could not be determined in one of the patients because the system was removed before being initiated, the other two achieved significant seizure reductions from left-sided VNS. After several attempts at re-implanting the equipment on the left side only to fail because of the persistence of the infections, the physicians decided to attempt placement of the equipment on the right side. The surgeries were uneventful; intraoperative lead tests were performed with no detectable effects on cardiac function. Subsequent Holter monitoring of the patients revealed no postoperative VNS-induced cardiac effects. No detectable effects on respiration were observed in two patients; the third developed exercise-induced reactive airway disease which was unresponsive to medication. The right-sided system was explanted in this patient and the respiratory problem resolved. Notably, this was the only patient who did not achieve a good seizure response to right-sided VNS. Both the first two patients had significant seizure reductions with right-sided VNS, and continued treatment with no observable side effects.

The second clinical report of right-sided VNS involved another child who was originally receiving left-sided VNS that was subsequently removed due to postoperative infection.^[27] Because of significant fibrosis around the left vagal trunk, a right-sided approach was adopted. Intraoperative testing revealed significant bradycardia, but this was not seen postoperatively. Holter monitoring revealed no cardiac effects as the VNS parameters were

increased. The patient, who had initially responded to left-sided VNS with a 50% reduction in seizure frequency, returned to this same level of efficacy, albeit at a higher stimulation amplitude.

Finally, in a third case report, two adult patients received right-sided VNS after surgical complications precluded the use of left-sided VNS.^[20] Both patients underwent right-sided surgical implantation without complications. Intraoperative lead tests did not reveal any cardiac events. Holter monitoring was used in both patients when the devices were initiated and after subsequent amplitude increases. No cardiac side effects were noted in either patient, and both experienced at least a 50% reduction in their preoperative seizure frequencies.

Possible lateralization of vagus nerve stimulation effects

In an interesting study, patients with left-sided VNS were studied with surprising results.^[12] All 47 patients studied had pre-surgical evaluations that included a detailed clinical history, magnetic resonance (MR) imaging, and long-term videotelemetry which captured recordings of ictal and interictal events, allowing the investigators to localize seizure onset whenever possible. Of these original 47 patients, 6 (13%) became completely seizure-free with left-sided VNS. After reviewing all of the preoperative data to determine a predictive variable, only one variable was independently correlated with complete seizure remission: lack of bilateral interictal epileptiform discharges. That is, left-sided VNS produced a seizure-free outcome only in patients who had lateralized interictal discharges. Remarkably, when queried about the laterality of the discharges, the investigators reported that five of the six patients who had become seizure-free from left-sided VNS had discharges localized to the left (ipsilateral) hemisphere (Janszky and Ebner, personal communication).

These case reports provide important clues that may have been long overlooked because of the reports from early animal research. Stimulation of the right-sided cervical vagus nerve appears to be feasible, both from a safety and efficacy perspective. Second, the laterality of VNS effects may be important for the ultimate goal of any epilepsy therapy: complete remission of seizures. This laterality hypothesis has yet to be systematically tested, but it is intriguing to speculate that right-sided or even bilateral VNS might be viable alternatives in patients receiving sub-optimal results from left-sided VNS.

CONCLUSIONS

The unique anatomy of the vagus nerve provides a convenient peripheral medium in which to influence the brain without the invasiveness of intracranial surgery. While clinical efficacy is often modest, VNS has been

successful, due in large part to patient acceptability, safety, and a low incidence of side effects. Future studies exploring the possible laterality of VNS effects, possibly leading to bilateral VNS, and further understanding of fiber selectivity may lead to improvements of the therapeutic effect, not only for epilepsy, but also for major depression and other future VNS indications.

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