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Vagus nerve stimulation for epilepsy: A review of central mechanisms

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Abstract

In a previous paper, the anatomy and physiology of the vagus nerve was discussed in an attempt to explain which vagus nerve fibers and branches are affected by clinically relevant electrical stimulation. This companion paper presents some of vagus nerve stimulation's putative central nervous system mechanisms of action by summarizing known anatomical projections of vagal afferents and their effects on brain biogenic amine pathways and seizure expression.

Key Words: Locus coeruleus, norepinephrine, raphe nuclei, serotonin, vagus nerve stimulation, seizures

INTRODUCTION

The first epilepsy patient was implanted with a vagus nerve stimulation (VNS) system by Penry and Dean in 1988.[38] Since then, VNS has been implanted in more than 50,000 patients. VNS is considered a low-risk surgery with few complications. The surgery involves the placement of helical electrodes on the left cervical vagus nerve, with intermittent stimulation provided by a remarkably small neurocybernetic prosthesis implanted subcutaneously in the upper chest. Most patients are stimulated at 20-30 Hz, with a stimulation cycle of 30 seconds on, and 5 minutes off. Clinical trials demonstrate that 20-40% of patients achieve greater than 50% reduction in seizure frequency in the first year of use.[17,51] This number increases with time,[12,35] while the number of concomitant antiepileptic drugs necessary to maintain satisfactory seizure control after VNS decreases.[48]

This year marks the fifteenth anniversary of the U.S. Food and Drug Administration's approval of VNS as a treatment for medication-refractory seizures. Despite the passing years and the advent of several promising neuromodulation technologies, such as deep brain stimulation and trigeminal nerve stimulation, VNS today remains the only FDA-approved device-related therapy for epilepsy. Several theories exist regarding the therapeutic mechanisms of VNS, but it is certain that activation of vagal afferents through electrical stimulation influences seizure-related circuitry within the brain.

To understand how stimulation of the vagus nerve reduces or eliminates seizure activity, an understanding of the peripheral anatomy and physiology of the vagus nerve and its central afferent projections is critical. Previously, we reviewed the peripheral aspects of VNS in seizure attenuation.[28] This companion review will focus on the anatomy and physiology of the hindbrain and midbrain

as they relate to putative mechanisms of VNS-induced seizure suppression.

AFFERENT VAGUS NERVE PROJECTIONS

The cervical vagus nerve is composed of afferent sensory and efferent motor fibers in a rough 4-to-1 ratio, respectively. The nucleus of the solitary tract, or nucleus tractus solitarius (NTS), is the recipient of most afferent sensory fibers, but the vagus also sends ipsilateral projections to the area postrema, dorsal motor nucleus of the vagus, nucleus ambiguus, medullary reticular formation, and the spinal trigeminal nucleus.

The NTS is an important processing and relay center for a variety of vital functions, so in addition to these vagal projections, it also integrates inputs from the glossopharyngeal, facial, and trigeminal nerves, and numerous brain regions.[5] Studies indicate that the sensory afferents innervate the NTS in a topographic distribution, with the vagus nerve terminating ipsilaterally in both the rostral portions of the medial NTS and the caudal portion of the lateral NTS.[25,44] The vagus projects bilaterally to the caudal portion of the medial NTS.[5,25]

The NTS, in turn, sends monosynaptic projections to diffuse regions of the brain. The rostral portion of the NTS sends axons to the facial, trigeminal, and hypoglossal nuclei, while the caudal extent projects to the dorsal motor nucleus of the vagus and nucleus ambiguus.[37] The NTS also sends fibers to the parabrachial nucleus, pons, and the respiratory and cardiovascular centers located on the ventral surface of the medulla.[9] Importantly, monoamine nuclei in the brainstem, the locus coeruleus (LC) and the raphe nuclei, receive direct and/or indirect projections from the NTS.[2,52] Forebrain and limbic structures also receive NTS projections, including the bed nucleus of the stria terminalis, paraventricular, dorsomedial, and arcuate hypothalamic nuclei, preoptic and periventricular thalamic nuclei, and central amygdaloid nucleus.[20,42]

LOCUS COERULEUS

Anatomy

The LC contains about 1,500 neurons per side in the rat and about 12,000 neurons in humans. The LC is the A6 nucleus as designated by Dahlstom and Fuxe[11] and this designation is still used in the current literature on the LC. The nucleus designated as A4 by Dahlstrom and Fuxe[11] is now considered to be a caudal extension of A6.[30]

Using discrete injections of retrograde tracers into the LC proper, Aston-Jones and colleagues[2] found heavily labeled cells only in the nucleus paragigantocellularis (Pgi) and the perifascicular area of the nucleus prepositus hypoglossi (PrH). Areas previously reported to project to the LC (such as the NTS, central nucleus of the amygdala, frontal cortex, dorsal raphe nucleus, and ventral tegmentum) were labeled only when tracers were injected into either the pericoerulear or central gray regions. These results were confirmed using electrophysiological means. Stimulation of the LC resulted in antidromic activation of Pgi and PrH neurons; however, stimulation of the LC did not antidromically activate neurons in other structures.[2]

Further work has demonstrated that cell bodies residing in the LC proper have an extensive dendritic network in the pericoerulear region.[45] Therefore, areas that do not project directly into the LC proper still influence LC activity either indirectly, through the Pgi or PrH, or directly, through projections into the pericoerulear region.

Fiber tracts emanating from the LC form an extensive network of noradrenergic projections throughout the brain and spinal cord.[24,30,50] The largest pathway, the dorsal bundle (DB), leaves the LC and ascends through the central tegmental tract. Along its course through the hypothalamus, the DB merges with the medial forebrain bundle (MFB) and projects to most parts of the telencephalon and diencephalon. The DB provides essentially all of the noradrenergic innervation to the hippocampus and parts of the neocortex. A second ascending pathway is the dorsal periventricular tract, a component of the dorsal longitudinal fasciculus, projecting to medial and midline thalamic, pretectal, and hypothalamic regions. The descending fibers arising from the LC project to the spinal cord through the ventral funiculus to innervate the dorsal and ventral horns.[39] Another descending pathway enters the superior cerebellar peduncles and terminates in the cerebellum, mainly on Purkinje cells. Depending on the recipient structure, LC projections can release norepinephrine and neuropeptides from classical synaptic terminals or from non-classical synaptic varicosities.[4] This latter type provides a distribution method capable of influencing large regions of the brain, emphasizing the neuromodulatory nature of norepinephrine.

Effects of vagus nerve stimulation on the locus coeruleus

Takigawa and Mogenson[47] were the first researchers to systematically examine the effects of peripheral nerve stimulation on LC activity. They found in rats that the majority of LC neurons are transiently inhibited by VNS (for approximately 50 msec), followed by a much longer excitation phase. Groves and colleagues[16] also found that VNS increased LC activity up to 24% above baseline rates. Naritoku and others[36] have also shown the induction of c-fos in the LC following VNS, indicating VNS-induced LC activation. All of these studies involved acute VNS only, but chronic VNS also has profound effects on the LC.

Dorr and Debonnel[13] implanted rats with a clinical system and provided VNS at clinically relevant parameters, including cycling of 30 sec on/5 min off, for up to 90 days. Acute VNS (1 hour) produced a modest increase in LC activity of approximately 33% above baseline, but chronic VNS (beginning at 3 days and lasting up to 90 days) produced substantial and prolonged activation of LC neurons double that of baseline.

While such studies show that VNS increases LC activity, it is equally important to demonstrate that VNS also increases downstream release of norepinephrine. Using microdialysis during acute VNS in rats, several studies have demonstrated significant increases in norepinephrine levels in the neuropil of the amygdala,[18] hippocampus,[41,43] and the prefrontal cortex.[14,43]

RAPHE NUCLEI

Anatomy

Unlike the LC, which has a rather restricted afferent innervation, the raphe nuclei receive projections from a vast number of areas found throughout the brain, including the LC. While a small number of studies have reported direct neuronal connections between the NTS and the dorsal raphe nucleus (DRN),[1,19] electrophysiological studies have cast doubt on a monosynaptic NTS-to-DRN connection (see below), and there are no studies suggesting direct projections from the NTS to any other raphe nuclei.

The serotonergic neurons in the raphe nuclei, not unlike the noradrenergic neurons in the LC, represent a diffusely projecting system that innervates virtually all areas of the CNS from the cortex to the spinal cord. In general, the rostral group of raphe neurons provides innervation to the forebrain (telencephalon and diencephalon), while the caudal group innervates the brainstem and spinal cord. This kind of polarity, where the rostral nuclei are entirely ascending and the caudal nuclei are descending in their projections, is rather unique and characteristic of the serotonergic system. The ascending projections are predominantly from the DRN and median raphe nuclei (MRN). The DRN contains the largest number of serotonergic neurons in the brain, whereas the MRN contains the second largest number. While there is a great deal of overlap in the targets of ascending serotonergic neurons, there is also significant topographical organization of these systems. For example, the DRN provides the serotonergic innervation to the striatum while the MRN provides the vast majority of serotonergic projections into the hippocampus. The neocortex receives innervation from both the DRN and MRN. Like the striatum, the substantia nigra receives its serotonergic innervation from the DRN with a highly topographic projection from the DRN innervating specific areas of the substantia nigra.[10,34]

The major descending serotonergic projection to the spinal cord arises from the caudal raphe cell groups. These bulbospinal pathways innervate the dorsal horn (substantia gelatinsoa), the intermediolateral cell column in the thoracic region, and the ventral horn.[49] The cerebellum appears to receive its serotonergic innervation from the DRN, MRN, raphe obscures, and raphe pallidus.[6] These fibers apparently reach the cerebellum through the middle cerebellar peduncle. The deep cerebellar nuclei and the cerebellar cortex both receive serotonergic innervation, but apparently from separate neurons.[26,27]

Effects of vagus nerve stimulation on the dorsal raphe nucleus

Using the same methods described above for the LC, Dorr and Debonnel[13] found increased DRN activity, nearly double that of baseline activity, when VNS was given chronically (>14 days). Acute VNS (<3 days) had little to no effect on DRN neurons. Interestingly, this same group demonstrated that the LC must remain intact in order for VNS to affect DRN activity.[31] As before, chronic VNS doubled DRN activity; however, when the LC was lesioned with DSP-4, VNS no longer had any effect on DRN activity.

ANTIEPILEPTIC EFFECTS OF NOREPINEPHRINE AND SEROTONIN

The central noradrenergic and serotonergic pathways represent diffusely projecting systems that are capable of influencing the entire neuraxis, from the cerebral cortex to the spinal cord. Norepinephrine and serotonin exert their effects through numerous receptor subtypes, giving rise to a great diversity of action.

There is a vast literature showing that the noradrenergic and serotonergic neurons of the brain exert antiepileptic effects in a wide variety of seizure models. Pharmacological treatments that increase the concentration of norepinephrine or serotonin at their receptors produce anticonvulsant effects, while treatments that decrease the concentration have proconvulsant effects.[7,15,21-23,32,33,40,46] Given the evidence for anatomical connections between the NTS and the LC and raphe nuclei, it seems reasonable to hypothesize that the antiepileptic effects of VNS are mediated through norepinephrine and/or serotonin.

Norepinephrine as a mediator of the antiepileptic effects of vagus nerve stimulation

Several studies indicate that the LC is a critical structure in the seizure-suppressing effects of VNS. In the first of these experiments, the LC was bilaterally lesioned in rats with 6-hydroxydopamine, while other groups received a sham lesion.[29] Two weeks later, seizures were induced through maximal electroshock (MES). Soon thereafter, a cuff electrode was surgically implanted on the left cervical vagus nerve. The next day, the rats were given

another MES test while receiving VNS. VNS given to the sham control group strongly reduced seizure severity from pretest levels. VNS given to the lesioned group, however, did not significantly affect seizure severity.

In a second experiment, rats were implanted with bilateral cannulae aimed at the LC. As before, seizures were induced with MES, and the rats were then implanted with a left cervical cuff electrode. The next day, in half of the animals, the LC was acutely inactivated with an infusion of the sodium-channel blocker, lidocaine, while the other half received saline. Both groups were then tested with MES while receiving VNS. The next day, animals that had received lidocaine were infused with saline, and vice versa, and the test was repeated, thus allowing a within-group comparison. VNS significantly reduced seizure severity following saline infusion. However, inactivation of the LC with lidocaine prevented VNS from significantly attenuating MES seizures.[29]

More recently, VNS was shown to reduce the severity of a seizure induced by pilocarpine infused into the rat hippocampus. When SKF-86466, an α2-adrenoreceptor antagonist, was also infused into the hippocampus, this VNS-induced seizure suppression was abolished.[41]

Serotonin as a mediator of the antiepileptic effects of vagus nerve stimulation

The evidence that VNS suppresses seizures through activation of the serotonin-containing neurons in the raphe nuclei is less extensive than the evidence linking norepinephrine release by the LC. In an early clinical study, Ben-Menachem and colleagues[3] measured levels of neurotransmitters or their metabolites in the cerebral spinal fluid of patients receiving VNS for seizures. They found a 33% increase in 5-HIAA levels, a marker for serotonin activity, following VNS. Animal studies have also supported a role for serotonin in the antiepileptic effects of VNS. While VNS is capable of suppressing pentylenetetrazole (PTZ)-induced seizures in rats, those antiepileptic effects are abolished when serotonergic neurons are destroyed with 5,7-dihydroxytryptamine (5,7-DHT), a selective serotonin neurotoxin.[8]

CONCLUSIONS

Most clinical papers describing the antiepileptic effects of VNS begin with the statement, "The precise therapeutic mechanisms of action remain to be elucidated." Given the preponderance of evidence described herein regarding the relationship between VNS, the LC, and the DRN, we believe this statement is misleading. While certainly not the only possible mediators of VNS-induced seizure suppression, the LC and DRN undoubtedly play prominent roles. Both have widespread projections to the brain and spinal cord, release neuromodulators with robust antiepileptic effects, are known to be activated by acute and chronic VNS, and abolish VNS-induced seizure suppression when lesioned. Further work can surely be done to determine if other mechanisms of action also contribute to VNS's antiepileptic effects, but there is already sufficient evidence that, at a minimum, elucidates some mechanisms of action.

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