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Vagus nerve stimulation therapy

A research update

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Article Abstract

Article abstract Over the past 5 years, and especially within the last year, there has been a rapid expansion of vagus nerve stimulation (VNS)-related preclinical research, as well as clinical studies in indications other than epilepsy. The research advances in understanding VNS are occurring in the midst of a blossoming of other forms of therapeutic brain stimulation, such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS). In general, improved understanding of the neurobiological effects of VNS therapy as a function of the different use parameters (frequency, intensity, pulse width, duration, dose) is beginning to guide clinical use and help determine which diseases, in addition to epilepsy, VNS might treat.

Introduction

What is the best approach to determining whether vagus nerve stimulation (VNS) has therapeutic potential in addition to its anticonvulsant properties? In theory, in a perfect world it would be simple to determine which additional neuropsychiatric diseases VNS might treat. As a first step, one would simply outline the full and known neurobiological effects of VNS (both the functional neuroanatomy and the cascade of neurobiological

effects that VNS sets into motion). Next, one would list the functional neuroanatomic maps and pathophysiological cascades of the different neuropsychiatric diseases (step 2). In step 3, one would then simply look for overlaps between the VNS effects and anatomy and the pathogenesis and anatomy of neuropsychiatric diseases. One would carry out preclinical and then clinical trials in those diseases with a high probability of a VNS therapeutic effect, using the precise parameters that are known to affect the diseased portion of the brain.

Unfortunately, we are still a long way from realizing this dream. First, despite over two decades of research with functional neuroimaging, there is still inadequate understanding of which areas of the brain are affected in most of the major neuropsychiatric disorders. (Movement disorders, strokes, multiple sclerosis, and Alzheimer's disease are exceptions.) As examples, the dysfunctional neuroanatomy and regional neuropharmacology associated with depression, the anxiety disorders, schizophrenia, autism, obesity, and addictions are still poorly understood. Moreover, despite extensive recent research, scientists do not fully understand which pathways are critical to the VNS signal in the brain. There is inadequate information about the immediate and longer-term translational changes that VNS produces, and how the neurobiological effects of VNS differ as a function of the various use parameters (see the article by Henry, this supplement). Therefore, applying VNS to the different neuropsychiatric disorders, in the absence of much of the needed knowledge about VNS neurobiological effects, still requires informed guesswork rather than strict deterministic applications of known rules. The clinical applications to date have been guided by both observations in the clinic in co-morbid diseases (see, e.g., the article by Harden in this issue about co-morbid depression and epilepsy) and knowledge of vagus nerve function in the light of the disease pathophysiology.

Recent research about VNS neurobiological effects.

Elsewhere in this supplement, Henry describes recent advances in understanding VNS mechanisms of action. Below, we highlight some of the recent animal and clinical research findings that help delineate the neurobiological effects of VNS.

In the past, many scientists believed that VNS activated unmyelinated C-fibers and then the reticular activating system. This early theory might be labeled the "cortical desynchronization theory."[1-3] Several researchers were skeptical of this theory, in part because the effective VNS parameters used to treat epilepsy are subthreshold for activating C-fibers.

This past year, Krahl et al.[4] demonstrated that C-fibers are neither necessary nor sufficient for VNS to suppress seizures. In freely moving rats, vagus stimulation of myelinated A- and B-fibers were able to suppress seizures. Zagon and Kemeny[5] also pursued this area using animal studies at a cellular level. These authors found that weak stimuli predominantly affect the myelinated A- and B-fibers and activate cortical pyramidal neurons. Trains of vagus stimuli lead to prominent slow hyperpolarization of pyramidal cell neurons, reducing excitability. This work suggests that perhaps VNS affects cortical excitability through mechanisms other than that proposed in the cortical desynchronization hypothesis. Recent work by Dean et al.[6] in epilepsy patients with VNS implanted for 6 to 12 months relates to the preclinical work. These researchers used transcranial magnetic stimulation (TMS) to study the effects of acute VNS on motor threshold (MT) and the cortical silent period (CSP) after a TMS pulse. These are TMS measures of cortical excitability. Most interestingly, motor cortex excitability decreased significantly while VNS was on in patients who had been receiving TMS for over 6 months, compared with the following 30 minutes while VNS was turned off. Obviously, more work is needed to understand which fibers are being stimulated by VNS as a function of the use parameters, and how this correlates with clinical effects.

There has been some recent progress in understanding the brain effects of VNS use parameters [pulse width, intensity, frequency, duty cycle (on, off)], specifically as a function of age. Koo et al.[7] measured threshold current intensity for a single stimulus at various pulse durations and conduction velocity of the vagus nerve in 21 patients (aged 4 to 31 years) during VNS implantation surgery. They found that the vagus nerve is probably not completely myelinated until full adulthood. They demonstrated that, in adults compared with children, the vagus is faster and requires less stimulus current and a shorter pulse width to send a signal to the cortex.

Studies combining functional brain imaging with VNS offer the promise of determining which brain areas are activated by VNS. Fast imaging methods, such as functional MRI (fMRI), can demonstrate the *immediate* effects (2 to 6 seconds) of VNS. Slower imaging methods, such as SPECT and PET, can demonstrate the *longer-term changes* associated with constant VNS over time. Recently, at the Medical University of South Carolina (MUSC) we have succeeded in performing blood oxygenation level-dependent (BOLD) fMRI studies in depressed patients receiving VNS as part of an initial pilot study[8-10] and a more recent and larger double-blind trial. An initial study using the interleaved VNS/fMRI technique showed that VNS immediately activates many anterior limbic regions, including the orbitofrontal cortex, insula, and medial temporal lobe.[11] A follow-up study using the same technique showed that VNS at 5 Hz had a much smaller brain effect than did VNS at 20 Hz.[12] In this small sample there was no statistically significant increase in blood flow with 5 Hz, whereas in the same subjects 20 Hz produced many regions with increased blood flow. Most recently, this same group has used real-time fMRI analysis and repeated within-individual scans to demonstrate the effects of different use parameters on regional brain activity (figure 1). This technique offers the promise of perhaps finding the optimal VNS parameters for a given patient.

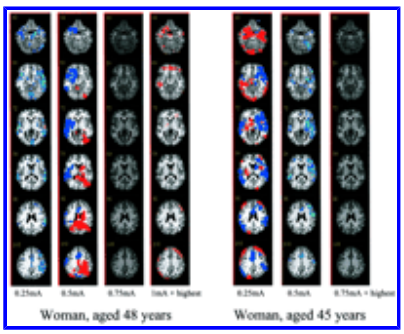

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Figure 1. Acute vagus nerve stimulation effects: VNS-induced regional cerebral activity using fMRI in two different depressed subjects, each studied on multiple sessions within the same day, each time with a different VNS intensity. Significant VNS-induced increases are displayed in red, with decreases in blue ($p < 0.05$ for display, merged onto a standard MRI scan in Talairach Space). Note that the acute effects of VNS in these subjects change as a function of frequency. There are acute increases in brain regions known to receive vagus sensory input, i.e., the orbitofrontal cortex, cerebellum, insula, and medial and dorsolateral prefrontal cortex. These same regions are consistently implicated in patients with depression. An important area of research is whether individualized imaging such as this might help determine effective clinical settings. From work in progress at MUSC; figure courtesy of MUSC Center for Advanced Imaging Research (CAIR) and Brain Stimulation Laboratory (BSL).

Performed before and after several months of VNS therapy, PET scans provide a view of the long-term changes induced by VNS. Figure 2 is an interim analysis in six depressed subjects with VNS. This analysis suggests that VNS over 3 months increases resting metabolism [^{18}F]-fluorine-2-deoxy-D-glucose (FDG PET) in the orbitofrontal cortex, the cingulate gyrus bilaterally, and the left insula.[13] Thus, functional imaging studies are beginning to provide information about the immediate and longer-term changes associated with VNS, and how these are influenced by different VNS parameters and related to clinical response.

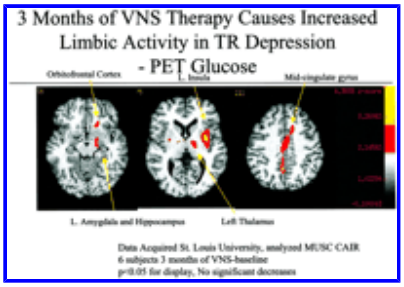

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Figure 2. Chronic VNS changes: These PET scans highlight the effects of VNS as a long-term therapy, which is different from the immediate effects of VNS as seen with fMRI. These are preliminary pooled data from St. Louis University in depressed patients involved in the DO2 depression trial.[13] Each person was scanned twice, once at baseline and then again after 3 months of therapy with the device once again turned off 30 minutes before the second scan. The pooled difference images show that, over time, there are increases in many of the same regions at which VNS acts acutely. There were no areas with decreased activity over time. These limbic regions (orbitofrontal, medial prefrontal, insula, and cingulate cortex) are involved in mood and anxiety regulation. Whether these changes are specific to depression in general, or to treatment response in particular, remains to be studied. An important area of future research is to understand how the acute effects of VNS initiate changes over time that then result in clinical effects.

Recent clinical studies.

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Several studies have investigated the clinical effects of VNS in neuropsychiatric diseases other than epilepsy (table 1).

View this table: Table 1 *Recent clinical and preclinical VNS studies other than epilepsy*
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Depression.

VNS was initially tested as a potential treatment for depression beginning in July of 1998. This trial was begun on the basis of animal[14] and human brain imaging data showing that acute VNS affects limbic and paralimbic regions known to modulate mood.[15] There was additional support of a potential antidepressant effect of VNS from the positive mood effects of VNS observed in epilepsy patients,[16-18] the knowledge that some anticonvulsants are also antidepressants, and neurochemical studies indicating that VNS has effects on brain monoamines.[19]

An initial pilot open study of VNS in 30 adult outpatients with severe, nonpsychotic, treatment-resistant major depressive episodes reported a 40% response rate after 8 weeks of VNS therapy, using ≥50% reduction in baseline Hamilton Depression Rating Scale ($HDRS_{28}$) total score to define response (12/30 responders).[8] This medication-resistant group had been depressed in the current episode for an average of 10 years and had failed to respond on average to more than five research criteria medication trials in that episode. They had averaged 17 clinical trials of medications or electroconvulsive therapy (ECT). There was a 17% complete remission rate (exit $HDRS_{28} < 10$), suggesting the efficacy of this technique in depression. This study was extended for longer-term follow-up, and after 6 months of treatment 17/30 (57%) of the treatment-resistant patients met criteria for response.[10] An additional 30 subjects were added to this open trial, and these subjects had a 21% acute response rate. There was an overall response rate after 8 weeks of therapy (combined in 59 completers) of 30%.[9] An additional analysis found that VNS appeared to be most effective in patients with low to moderate but not extreme antidepressant treatment resistance.[9] That is, those who had failed only two or three

research level attempts at antidepression therapy in the index episode were more likely to respond to VNS than were those who had failed more than five research level trials. The device was generally well-tolerated and there was no evidence of adverse cognitive effects.[20] To overcome the limits of these open design studies, a multisite randomized, sham control study has been conducted, with full results pending. It is challenging to conduct a double-blind study with a device and, for this study, all subjects were implanted with a generator. One-half of the subjects had the device turned on 2 weeks after implantation and the other half had the device turned off for the first 12 weeks. Patients and raters did not know whether or not the device was on. A recent press release from Cyberonics has stated that, in this trial, the VNS group failed to show a statistically significant difference in acute response from the sham group. The longer-term response rates appear encouraging. The company and investigators are discussing further studies. Based on the strength of the open pilot data discussed above, VNS has been approved as a treatment for resistant unipolar or bipolar depression in Europe and Canada. It is still considered experimental by the FDA.

Anxiety disorders.

Norepinephrine (NE) has long been considered a key neurotransmitter involved in the pathogenesis and regulation of anxiety. A device such as the VNS that directly stimulates the locus ceruleus, which is the primary NE control site, would potentially have important effects on anxiety. The historical importance of this pathway can be seen in the oldest theory about the brain origins of fear, called the James–Lange theory of emotions.[21] William James[21] and C. Lange[22] proposed the radical argument that all emotion actually resided in the body and that it was the brain's interpretation of this signal through the vagus nerve that caused someone to be anxious. They argued that rather than one becoming anxious and then the heart beating fast and one becoming short of breath, the causal change went the other way. You think you are anxious because your heart beats fast, and then your brain gets this signal (through the vagus) and you experience anxiety. Interestingly, this theory has been hard to disprove, and most modern anxiety researchers think that the ultimate answer lies in feedback loops between the brain and the body. However, all agree that the information flowing through the vagus nerve is probably an important part of anxiety regulation, both afferent and efferent. Obviously, a device that could directly affect that information flow would potentially be a powerful way of altering anxiety. Indeed, strong anti-anxiety effects of VNS were seen in the pilot study in depressed subjects.[8] That is, VNS caused improvements measured on the Hamilton Anxiety Scale that were as clinically and statistically robust as those seen on depression scales. On the basis of this clinical observation of an anti-anxiety effect in the depression study and the theoretical justification given above, a 30-patient pilot open study was recently launched in patients with anxiety disorders (either obsessive–compulsive disorder, panic disorder, or post-traumatic stress disorder).

Obesity.

An interesting potential use of VNS concerns the regulation of brain satiety signals. The brain knows that the stomach is empty or full, largely on the basis of information transmitted by the vagus nerve.[23] In theory, one could alter the vagus signal and modify eating behavior. This reasoning led to pilot work in a canine model, in which healthy normal-weight dogs implanted with bilateral subdiaphragmatic VNS devices lost weight over time.[24] These encouraging animal studies led to a recent safety study in morbidly obese humans, which has now been expanded into a larger trial. Interestingly, there has been no documentation of weight loss in the epilepsy and depression trials or, for that manner, in the animal model when VNS was applied through the vagus nerve in the neck. It is believed that higher-intensity stimulation is needed, which is done more easily with subdiaphragmatic VNS.

Pain.

Vagus afferents carry pain information to the brain from the gut, and stimulation of the vagus afferents inhibits nociceptive behavior in animal models.[25,26] Therefore, vagus stimulation might, in theory, have a role in the treatment of chronic pain. This area is complex, however, because some studies suggest that low intensities of VNS lead to pronociceptive effects and higher stimulation intensities lead to inhibitory antinociceptive effects.[27,28] Ness et al.[29] confirmed this complexity in

humans by studying eight VNS-implanted epilepsy patients and assessing the acute effects of VNS on pain thresholds. VNS, compared with sham (generator turned off), acutely lowered the pain threshold, with the greatest reduction being at an intensity 66% of that used to control their seizures. In contrast to these acute crossover studies and as a preliminary attempt to address the question of whether long-term VNS might treat pain, Kirchner et al.[30] studied 12 VNS epilepsy patients and 12 age- and gender-matched controls at three different time points. The patients were investigated before implantation, 2 to 5 days after starting VNS therapy, and after 8 to 14 weeks of therapy. Compared with controls, the VNS-treated patients had reduced pain response to two different methods of producing pain, squeezing of finger folds and repeated quick painful impacts on the skin. Further study in this area appears to be warranted, with particular attention paid to the differences between acute and chronic changes and the relationship to VNS dose.

Cognition and memory.

Beginning with some of the first animal studies, researchers and clinicians have noted that VNS patients and subjects frequently look more alert and focused after several weeks of treatment (personal communication J. Zabara to M. George, January 13, 2002). Moreover, Clark et al.[31] demonstrated that epilepsy patients with specific VNS parameters had improved recognition memory. These observations and others[20,32] raise interest in whether VNS may have a cognitive enhancing effect. An ongoing pilot study is assessing VNS in Alzheimer's disease.

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The preclinical, imaging, and clinical trials of VNS are exploring its effectiveness in a variety of nonepileptic conditions. These new data about VNS are emerging at a time when there is renewed interest in the entire area of device-based approaches to neuropsychiatric disorders. These therapies range from ECT for the treatment of depression, to TMS as a research and clinical tool, to deep brain stimulation (DBS) as a treatment for Parkinson's disease.[33] Although these devices differ greatly in their method of entry into the brain, as well as their invasiveness, they share in common the use of electrical stimulation of neurons as a route to therapeutic changes by modulating disease-system pathways. They also share the challenge of understanding the effect of use parameter changes (frequency, intensity, pulse width, total dose) on the brain, and how this relates to the biological effects. Table 2 is an overview of these other related approaches.

View this table: Table 2 *Comparison of VNS and other forms of brain stimulation*
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In summary, the past 5 years have seen a blossoming of preclinical, human imaging, and clinical trials investigating both the mechanisms of action of VNS and other diseases for which VNS might prove useful. This VNS-related work is being conducted in the context of an explosion of interest in the broader concept of electrically stimulating discrete brain regions to treat neuropsychiatric illnesses. Clearly, the next 5 years will determine which of these other disorders is likely to benefit from VNS.

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Footnotes

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