Vagus Nerve Stimulation: A New Tool for Brain Research and Therapy*

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Biological psychiatry has a long history of using somatic therapies to treat neuropsychiatric illnesses and to understand brain function. These methods have included neurosurgery, electroconvulsive therapy, and, most recently, transcranial magnetic stimulation. Fourteen years ago researchers discovered that intermittent electrical stimulation of the vagus nerve produces inhibition of neural processes, which can alter brain electrical activity and terminate seizures in dogs. Since then, approximately 6000 people worldwide have received vagus nerve stimulation for treatment-resistant epilepsy. We review the neurobiology and anatomy of the vagus nerve and provide an overview of the vagus nerve stimulation technique. We also describe the safety and potential utility of vagus nerve stimulation as a neuroscience research tool and as a putative treatment for psychiatric conditions. Vagus nerve stimulation appears to be a promising new somatic intervention that may improve our understanding of brain function and has promise in the treatment of neuropsychiatric disorders. Biol Psychiatry 2000;47:287–295

Key Words: Vagus nerve, locus ceruleus, antidepressant, brain stimulation, depression

*See accompanying Editorial, in this issue.

Historical Introduction

An Overview of Somatic Interventions (Table 1)

Since its inception, biological psychiatry has embraced the use of somatic interventions for brain research and clinical treatment. Indeed, many of the founders of the 55-year-old Society of Biological Psychiatry were researchers who were interested in understanding the mechanisms of action of electroconvulsive therapy (ECT).

Although the revolution in neuropsychopharmacology over the last 40 years has captured much interest, recent advances in somatic interventions (e.g., physical, nonpharmacological) are causing a resurgence of interest in other methods that directly and, in some cases (transcranial magnetic stimulation [TMS]), noninvasively affect brain function. The field of ECT continues to advance, with recent demonstrations of the need for dosage titration (Sackeim et al 1987b) and regional specificity of ECT effects (Sackeim et al 1987a, 1993) and even the recent production of ECT-like seizures using magnetic instead of electrical currents (Lisanby et al 1999). There has also been considerable interest in TMS (without seizure production), which holds promise as a research tool with potential clinical applications (George and Belmaker 1999; George et al 1999).

The most anatomically discrete and most invasive currently employed method of stimulating deep brain structures is deep brain stimulation (DBS), in which a thin electrode is inserted directly into the brain and different currents are applied at varying depths until the desired effects are found. Recently, high-frequency (>80 Hz) electrical stimulation of the middle thalamus or subthalamic nucleus has been found to be effective in Parkinson's disease (Damier 1998; Limousin et al 1998). Whereas DBS has the advantage over brain surgery (pallidotomy) of being reversible, it has significant morbidity and mortality associated with the implant procedure. Although this technique has not been used to treat major depression, mood effects of the stimulation have been reported. In one Parkinson's disease patient who had never suffered from depression in her life, the testing of the stimulation caused the acute onset of tearfulness, sadness, and despair. These symptoms remitted immediately when the surgeon moved the stimulator away from the substantia nigra, directly below the subthalamic nucleus (Bejjani et al 1999). Parkinson's disease researchers lead the neuropsychiatric field in terms of understanding a dis-

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Table 1. Current and Potential Somatic Interventions for the Treatment of Depression

Somatic intervention	Regionally specific?	Clinically applicable?	Invasive?
Electroconvulsive therapy	++ (+++ if induced by magnets	++++	++ (anesthesia, generalized seizure)
Transcranial electrical stimulation	+	++	+ (scalp irritation)
Transcranial magnetic stimulation	++++	+++ (clinical trials underway)	+ (painful at high intensities)
Vagal nerve stimulation	++ (discrete brainstem nuclei initially, unclear if different parameters selectively involve other brain regions)	+++ (on the market for epilepsy, clinical trials in depression [see Rush et al 2000])	+++ (surgery for generator implant)
Deep brain stimulation	++++	+++ (approved in the United States for treatment in movement disorders, pain syndromes; no work in depression yet)	++++ (brain surgery)

+, a little; ++++, a lot.

ease's involved pathologic circuitry. Thus it is natural for DBS to be used first in Parkinson's disease. However, as the neuroanatomy of other neuropsychiatric disorders (mood, anxiety, and psychosis) becomes better understood, it is conceivable that DBS may be helpful to otherwise treatment-resistant patients, although to date DBS has only been shown to cause depression symptoms rather than relieve them.

The History of Vagus Nerve Stimulation (VNS)

Another, less invasive means of directly affecting central function is to stimulate the cranial nerves that are direct extensions of the brain. For years, scientists have been interested in whether and how autonomic functions modulate activity in the limbic system and higher cortex. Numerous studies have identified extensive projections of the vagus nerve via its sensory afferent connections in the nucleus tractus solitarius (NTS) to many brain areas (Bailey and Bremer 1938; Dell and Olson 1951; Maclean 1990). As early as 1938, Bailey and Bremer reported that VNS in the cat elicited synchronized activity in the orbital cortex. In 1949, MacLean and Pribram stimulated the vagus nerve and recorded electroencephalograms from the cortical surface of anesthetized monkeys and found inconsistent slow waves generated from the lateral frontal cortex (Maclean 1990, p. 468). Moreover, Dell and Olson (1951) found that VNS evoked a slow-wave response in the anterior rhinal sulcus, *as well as in the amygdala*, in awake cats with high cervical spinal section.

Reasoning from this body of literature, Zabara demonstrated the anticonvulsant action of VNS on experimental seizures in dogs (Zabara 1985a, 1985b). Although the vagus is an autonomic nerve, Zabara, basing his conclusions on known anatomy, hypothesized that VNS could prevent or control the motor, autonomic, and conscious components of epilepsy. Interestingly, he also observed that the inhibitory effect on seizures outlasted the VNS period by approximately a factor of four in the acute model, and probably would be much longer in a chronic model. Zabara (1992) initially hypothesized that VNS had two distinct antiepileptic mechanisms of action: 1) a direct inhibition terminating the beginning or ongoing seizure and 2) a long-lasting inhibition that increased with continued periods of stimulation to prevent seizures. Dr. Kiffin Penry (Penry and Dean 1990) and others (Rutecki 1990) ushered in the modern use of VNS with the first human implant for the treatment of epilepsy in 1988.

Vagus Nerve Anatomy

Traditionally the vagus nerve has been considered a parasympathetic efferent nerve (controlling and regulating autonomic functions such as heart rate and gastric tone); however, the vagus (cranial nerve X) is actually a mixed nerve composed of about 80% afferent sensory fibers carrying information to the brain from the head, neck, thorax, and abdomen (Foley and DuBois 1937). The sensory afferent cell bodies of the vagus reside in the nodose ganglion and relay information to the NTS. These fibers are different from those that go to the other motor nuclei of the vagus (Figure 1).

The NTS relays this incoming sensory information to the rest of the brain through three main pathways: 1) an autonomic feedback loop, 2) direct projections to the

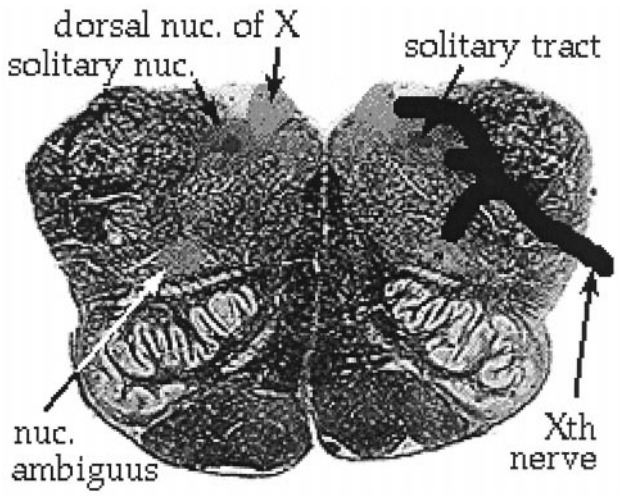

Figure 1. This cross-sectional view of the brainstem illustrates the origins of several components of the vagus nerve, a mixed sensory and motor nerve. Efferent motor fibers originate in the dorsal nucleus of the vagus, whereas afferent motor fibers go to the nucleus ambiguous. Afferent sensory fibers, which make up 80% of the left vagus, terminate in the nucleus of the solitary tract, which then projects to the midline raphe and locus and likely is the path by which vagus nerve stimulation has antiseizure and other neuropsychiatric effects.

reticular formation in the medulla, and 3) ascending projections to the forebrain largely through the parabrachial nucleus (PB) and the locus ceruleus (LC). The PB sits adjacent to the LC (one of the primary norepinephrine-containing areas of the brain; Figure 2). In fact, lesioning the LC in rats eliminates the ability of VNS to suppress seizures (Krahl et al 1998), demonstrating how important this connection is for the antiepileptic action of VNS (Figure 2).

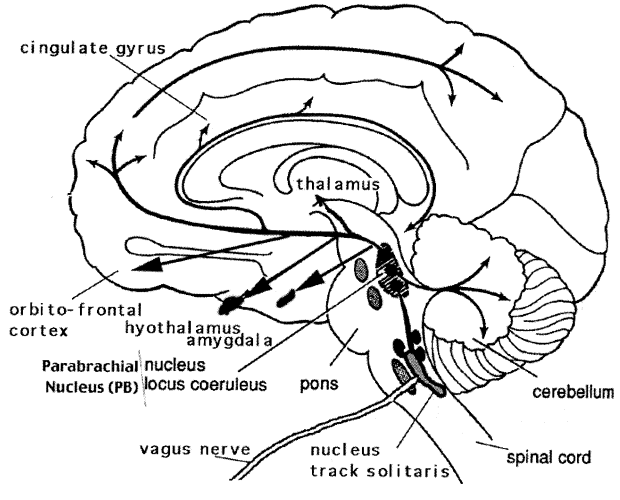

Figure 2. This diagram shows the known connections of the nucleus tractus solitarius to the parabrachial nucleus and the locus ceruleus (LC). Lesioning the LC in rats eliminates the antiepileptic properties of vagus nerve stimulation. The LC is the site of many norepinephrine-containing neurons that have important connections to the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic regions linked to mood and anxiety regulation.

The PB/LC sends direct connections to every level of the forebrain, including the hypothalamus, and several thalamic regions that control the insula and orbitofrontal and prefrontal cortices. Perhaps important for mood regulation, the PB/LC has direct connections to the amygdala and the bed nucleus of the stria terminalis—structures that are implicated in emotion recognition and mood regulation (Van Bockstaele et al 1999; for review of the functional neuroanatomy of depression, see George et al 1997; Ketter et al 1997).

These brainstem and limbic anatomic connections have functional consequences. The oncogen C-fos is a general marker for cellular activity. C-fos studies in rats during VNS reveal increased activity in the amygdala, cingulate, LC, and hypothalamus (Naritoku et al 1995). Recently, Walker and colleagues (1999) outlined a possible role of the NTS in how VNS reduces seizures. By microinjecting the NTS with either γ-aminobutyric acid (GABA) agonists or glutamate antagonists, they found that increased GABA or decreased glutamate in the NTS blocked seizures. These findings suggest that VNS may change NTS GABA and glutamate concentrations, with secondary changes in the function of specific limbic structures noted above.

Some have suggested that because of the rotation of the body during embryonic development the left and right vagus nerves carry different information. This theory implies that the right vagus is closely associated with the cardiac atria and the left vagus with cardiac ventricular function, perhaps explaining the lack of cardiac effects of left VNS. Additionally, the NeuroCybernetic Prosthesis (NCP) System stimulating electrode is intended to be positioned below the cardiac branch of the vagus nerve. However, this line of thinking is not totally supported by early animal VNS research. There is even one patient who has been treated on the right side without complication (G.L. Morris, personal communication, October 1999). An alternative theory holds that the cardiac functional response is more a function of stimulation parameters than whether the right or left nerve is stimulated.

In sum, incoming sensory (afferent) connections of the vagus nerve provide direct projections to many of the brain regions implicated in neuropsychiatric disorders. These connections reveal how vagus nerve stimulation might be a portal to the brainstem and connected regions. These circuits likely account for the neuropsychiatric effects of VNS, and they invite additional theoretical considerations for potential research and clinical applications.

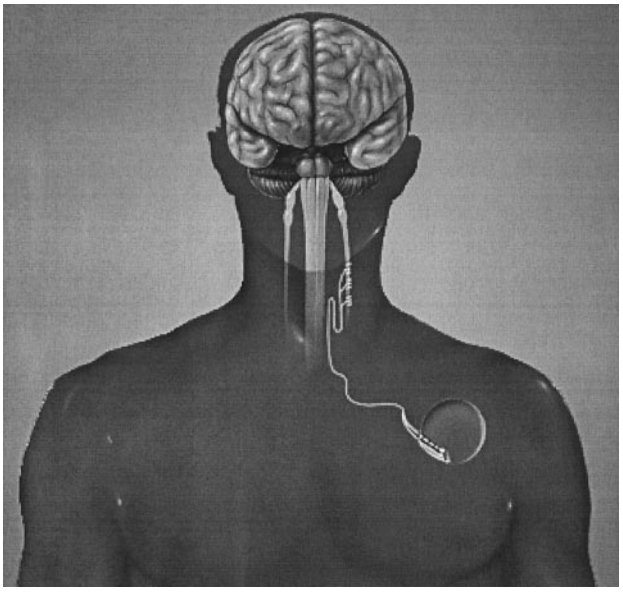

Figure 3. An artist's rendition of how the vagus is stimulated using the NeuroCybernetic Prosthesis System. A generator about the size of a pocket watch is implanted into the left chest wall. Bipolar electrodes are wrapped around the left vagus higher in the neck through a separate incision and tunneled under the skin to the generator. A physician can control the intensity and rate of generator firing by holding over the chest wall (and generator) a telemetric wand connected to a portable computer (not shown).

What Is Vagus Nerve Stimulation?

The term *vagus nerve stimulation* generally refers to several different techniques used to stimulate the vagus nerve, including those in studies in animals where the vagus was accessed through the abdomen and diaphragm. For practically all studies in humans, *Vagus Nerve Stimulation* refers to stimulation of the left cervical vagus nerve using a commercial device, the NCP System (Cyberonics, Houston; Schachter and Saper 1998; Figure 3).

Vagus Nerve Stimulation has been commercially available for the treatment of resistant partial-onset seizures in epilepsy in Europe (since 1994) and in the United States (since 1997). About 6000 people worldwide with over 7000 patient years of experience have had these generators implanted (W. Duffell, Cyberonics, personal communication). Typically, epilepsy patients considering VNS have had unsatisfactory seizure control, commonly with several medications, and for some VNS is an option before brain surgery.

In many ways, VNS delivered through the NCP System is much like the very common practice of implanting cardiac pacemakers. In both cases, a subcutaneous generator sends an electrical signal to an organ through an implanted electrode. In fact, the surgery for implanting the NCP generator in the chest is much like inserting a cardiac pacemaker (Amar et al 1998). The two techniques differ, of course, in the site of stimulation. Vagus Nerve Stimulation with the NCP System is delivered through an implantable, multiprogrammable, bipolar pulse generator (the size of a pocket watch) that is implanted in the left chest wall to deliver electrical signals to the left vagus nerve through a bipolar lead. With VNS, the electrode is wrapped around the vagus nerve in the neck, near the carotid artery using a separate incision, and connected to the generator subcutaneously. Although VNS implantation surgery was initially done almost exclusively by neurosurgeons in patients admitted overnight to a hospital and given general anesthesia, more recently some epilepsy patients have had the device implanted by vascular surgeons or ear, nose, and throat specialists via outpatient surgery with local anesthesia.

The NCP programming wand and software, along with a personal computer, provide telemetric communication with the pulse generator, which enables noninvasive programming, functional assessments (device diagnostics and interrogation), and data retrieval. The NCP System includes mechanical and electrical safety features that minimize the possibility of high-frequency stimulation that could lead to tissue damage. In addition, each patient is given a magnet that, when held over the pulse generator, turns off stimulation. When the magnet is removed, normal programmed stimulation resumes.

How Effective and Safe Is VNS in Patients with Epilepsy?

Two double-blind studies (labeled E03 [Ben-Menachem et al 1994] and E05 [Handforth et al 1998]) were conducted in patients with epilepsy, with a total of 313 treatment-resistant completers. In this difficult-to-treat group, the mean decline of overall seizure frequency was about 25–30% compared with baseline. Data from uncontrolled observations suggest that, contrary to a tolerance effect, improvement in seizure control is maintained or may improve over time (Morris et al 1999; Salinsky et al 1996). In the second controlled study (E05) of VNS in patients with epilepsy, no serious adverse events (AEs) that were judged by investigators to be probably or definitely related to VNS occurred during treatment (Handforth et al 1998; Schachter and Saper 1998). In three out of 199 patients (1.5%), infection following surgery led to device removal. Other surgery-related AEs, all of which dissipated over time, included left vocal cord paralysis (2/199 [1%]), lower facial muscle paresis (2/199 [1%]), and pain and accumulation of fluid over the pulse generator requiring aspiration (1/199 [0.5%]). The perioperative AEs reported by at least 10% of patients were pain (29%), coughing (14%), voice alteration (13%), chest pain (12%), and nausea (10%).

The AEs reported in patients in the treatment group at some time during treatment that were significantly increased from baseline were voice alteration/hoarseness, cough, throat pain, nonspecific pain, dyspnea, paresthesia,

dyspepsia, vomiting, and infection. The only AEs that occurred significantly more often in the treatment group than in the control group were dyspnea and voice alteration. Adverse events were judged to be mild or moderate 99% of the time. No cognitive, sedative, visual, affective, or coordination side effects were reported. No significant changes occurred in Holter monitoring, in the results of pulmonary function tests, or in subjects' hematology values or common chemistry values (Schachter and Saper 1998). No subjects died during the E03 or E05 controlled studies ($N = 313$). In sum, short-term AEs that are surgery related are rare and usually resolve. Stimulation-related AEs (i.e., those that occur only when the vagus nerve is stimulated) can be reduced by lowering the current level. Stimulation-related AEs can also be aborted by the patient placing a handheld magnet over the generator that turns the device off until a physician decreases the stimulation intensity. These AEs rarely lead to VNS therapy discontinuation (Morris et al 1999; Schachter and Saper 1998). Although the neurology community was initially skeptical about VNS, a recent reassessment by the American Academy of Neurology concluded that VNS for epilepsy is both "effective and safe" (Fisher and Handforth 1999).

Does VNS Affect Cardiac Function?

It is logical to carefully evaluate potential cardiac and gastrointestinal effects of vagus nerve stimulation. Cardiac evaluations have been performed on more than 250 epilepsy patients in clinical trials while receiving VNS. Holter monitoring results from clinical studies in epilepsy indicated no significant changes from baseline in cardiac function during stimulation (Handforth et al 1998).

Only during the implantation procedure itself, six cases of 10–20-sec asystole have been reported in epilepsy patients. No cases were reported in either the epilepsy or the depression clinical trials (Rush et al 2000). All six asystoles were encountered during the diagnostics test (Lead Test) stimulation—the first stimulation that a patient receives after implantation while in the operating room. The Lead Test entails approximately 15 sec of stimulation at 1.0 mA, 500 μsec, and 20 Hz of VNS. Of these six patients, three went on to have the implant (in three others the generator and leads were removed). No long-term sequelae have been reported from any asystolic events in these patients. Most importantly, no cardiac events when the device is turned on for the first time outside the operating theater have been reported in the clinic (Asconape et al 1999; Tatum et al 1999).

What about Longer Term Efficacy and Tolerability?

In patients with epilepsy, the long-term efficacy of VNS is either maintained or improved (Morris et al 1999), and the frequency of AEs generally decreases as patients accommodate to the stimulation (Salinsky et al 1996). The patient with the longest exposure to VNS has had the system operating for 10 years (W. Duffell, Cyberonics, personal communication, October 1999).

Extensive experience in epilepsy patients provides important safety data on VNS used continuously for 1 year or longer. Side effects tend to decrease over time as patients accommodate to the effects of stimulation. Two years after initial implantation over 80% of epilepsy study patients (142/172) continued with VNS, suggesting that it is well tolerated over the long term (Cyberonics 1998).

How Much Does VNS Cost, Relative to Other Treatment Modalities?

In the United States, VNS delivered with the NCP System costs roughly $9200 for the generator and electrode. The surgical and hospital costs for the implantation surgery vary widely and are more difficult to quantify but are less expensive now with the recent trend toward outpatient surgery and local anesthesia. Typically the total charge for the NCP System plus implantation varies from $12,000 to $25,000 (B. Barrett, Cyberonics, personal communication, October 1999). Most federal and private insurance companies reimburse this procedure for treatment of refractory epilepsy. After implantation the cost of the device is minimal, as the battery lasts many years and there is no required maintenance. Adjustments of the VNS settings are done by treating neurologists in their office using the personal computer and attached programming wand.

If the initial open results in depression were confirmed in a double-blind study and FDA approval granted for VNS treatment of depression, the cost of VNS would compare to about $1000 for a year of a single antidepressant medication or $10,000 to $30,000 for an acute course of ECT followed by a year of maintenance ECT (Hu and Rush 1995; Olfson et al 1998); however, since VNS is continuous and a maintenance treatment modality, true cost comparisons should be made against maintenance therapies, and the relative cost of VNS improves with each year of continued use and compares favorably to maintenance ECT, as most of the costs are associated with the initial device purchase and implantation.

Unfortunately, only a few epilepsy patients achieve full seizure remission and are able to reduce other antiepileptic medications. Most combine VNS with medications. Thus VNS, as now delivered, has not been shown to be a substitute for anticonvulsant medications. As the neuroscientific basis of VNS is better understood, there is hope that refinements of VNS settings might improve the clinical effects, with better cost savings on reductions of concomitant medications.

Rationale for Studying VNS in Mood Disorders

In addition to the neuroanatomic considerations, several additional lines of evidence provided the background for studying whether VNS might have antidepressant effects in treatment-resistant depression, culminating in the first implant for this indication in July 1998 at the Medical University of South Carolina in Charleston (Rush et al 2000), a decade after the first human epilepsy implant (Penry and Dean 1990). These hints were 1) mood effects of VNS observed in patients with epilepsy, 2) evidence by positron emission tomography (PET) scans that VNS affects the metabolism (and therefore the function) of important limbic structures, 3) the role of anticonvulsant medications in mood disorders, and 4) neurochemical studies in both animals and humans revealing that VNS alters concentrations of monoamines within the central nervous system (CNS).

Mood Effects in Epilepsy Patients

Initial uncontrolled clinical observations and, more recently, a prospective study (Harden et al 1999) and a retrospective data analysis (Elger et al, unpublished data, 1998) suggest that VNS reduces depressive symptoms in patients with epilepsy—reductions that are not entirely accounted for by reduced seizure activity. During the clinical trials of VNS for epilepsy (Ben-Menachem et al 1994; Handforth et al 1998) several investigators noted mood improvements in their patients. Although decreased seizure frequency likely accounted for some of these improvements, the clinical impression was that they went beyond those attributable to improved seizure control alone. For example, some patients with minimal or no improvement in seizure frequency also reported substantial improvements in mood. Improved quality of life was also seen, and without seizure frequency changes in some patients. Thus, while no specific measures of depressive symptoms were obtained during the epilepsy trials, these repeated reports from independent investigators suggested that VNS might be associated with significant mood improvement. This is reminiscent of the "psychotropic" effects reported in epilepsy patients treated with carbamazepine, which led to the clinical trials in mood-disordered patients (Ballenger and Post 1980). In a recent prospective study of patients with epilepsy ($N = 34$), a trend toward mood improvements was seen in the 14 who received VNS, based on the Cornell Dysthymia Rating Scale ($p < .1$; Harden et al 1999). The significant improvement in seizure frequency found in the VNS group was not related to mood changes on an individual basis. The authors suggested that VNS might improve mood independent of seizure frequency reduction.

PET Studies of Limbic Activation

In 10 patients with epilepsy who received VNS, PET measurements were taken three times before and then during VNS (Henry et al 1998). The results demonstrated increased brain blood flow from rest to during VNS in the rostral medulla, thalamus, hypothalamus, insula, and postcentral gyrus, with greater activation on the right side (contralateral to the device). In contrast, blood flow was significantly decreased during stimulation bilaterally in the hippocampus, amygdala, and cingulate gyrus. The cingulate gyrus has been repeatedly implicated in imaging studies of depression pathogenesis, and a decline in cingulate activity with antidepressant response has been seen in numerous studies (sleep deprivation [Ebert et al 1994; Wu et al 1992], selective serotonin reuptake inhibitor treatment [Mayberg et al 1997], symptom provocation with drugs [Bremner et al 1997]). Thus, VNS changes in activity of the brainstem, limbic system, and other CNS areas are compatible with antidepressant activity.

Anticonvulsants as Mood Stabilizers

A third reason for considering the role of VNS in the treatment of mood disorders is the substantial evidence that anticonvulsant medications have mood-stabilizing effects (Goodwin and Jamison 1990; Post et al 1992). Within the last 20 years, several anticonvulsants have found a role in mood stabilization (carbamazepine [Ballenger and Post 1980; Okuma et al 1973], valproic acid [Calabrese and Delucchi 1989; Swann et al 1997]) or as antidepressants in (depressed phase) bipolar disorder (lamotrogine; Fatemi et al 1997). Further, it is well established that our most effective antidepressant treatment, ECT, has powerful anticonvulsant effects (Sackeim 1999; Sackeim et al 1983). Thus, it is reasonable to hypothesize that an effective antiepileptic device might also have antidepressant or mood-stabilizing effects.

Neurochemical Changes

The basic mechanisms of action of VNS are unknown. However, both clinical and animal studies indicate that VNS likely results in changes in serotonin (Ben-Menachem et al 1995), norepinephrine (Krahl et al 1998), GABA, and glutamate (Walker et al 1999)—neurotransmitters implicated in the pathogenesis of major depression. Vagus nerve stimulation in animals activates the LC, the main source of CNS norepinephrine-containing neuronal cell bodies (Naritoku et al 1995). In patients with epilepsy, VNS appears to increase cerebrospinal fluid 5-hydroxyindoleacetic acid—a metabolite of serotonin (Ben-Menachem et al 1995). Since many of the currently available therapies are believed to work using the same neurotrans-

mitters (serotonin or norepineprine), it was hypothesized that VNS might also have antidepressant activity.

Further, there is a long history of autonomic nervous system dysfunction in depressed patients, which is mediated by the vagus nerve. These abnormalities include differences in heart rate variability (for review, see Glassman 1998). Thus, if depressed patients have abnormalities in brain regions that control the vagus nerve (top-down regulation), then stimulating the vagus nerve might theoretically engage this dysfunctional circuit (a bottom-up approach).

Summary

Several lines of evidence pointed toward the possible benefit of VNS as an antidepressant or mood-stabilizing treatment. These included clinical observations in epilepsy patients, anatomic afferent connections of the left vagus nerve to the CNS and to structures relevant to mood regulation, the anticonvulsant activity of VNS taken in the context of the role of anticonvulsant medications or ECT in treating mood disorders, neurochemical studies indicating VNS effects on key neurotransmitters involved in mood regulation, and evidence that VNS changes the metabolic activity of key limbic system structures. This evidence led to the initial open trial described in the companion article in this journal (Rush et al 2000).

Other Areas of Potential Research or Clinical Promise with VNS

Work to date has established that VNS is an effective anticonvulsant. Recent work suggests that VNS may have antidepressant properties. The vagus nerve is an important route of information into the CNS. Several theories of the anxiety disorders posit either a faulty interpretation of peripheral information into the CNS or erratic availability of same (Gray 1982; James 1884; Watkins et al 1998). It is conceivable that altering the flow of this information with VNS could have therapeutic potential in anxiety disorders (e.g., generalized anxiety disorder, panic disorder) or irritable bowel syndrome.

Similarly, the vagus contains information about hunger, satiety, and pain. Potential studies in the areas of treatment-resistant obesity, addictions, and pain syndromes are also theoretically justified. Moreover, the NTS sends fibers into the dorsal raphe and areas that are known to control levels of alertness. Thus, VNS might be considered as a potential treatment for some disorders of sleep or alertness like coma or narcolepsy. For example, a recent study in 10 epilepsy patients found that high-intensity, high-frequency VNS reduced total time in rapid eye movement sleep, and such sleep was less fragmented (Vaugh and D'Cruz 1999). Therefore, in addition to advancing our understanding of the pathophysiology of various neuropsychiatric disorders, VNS may have other therapeutic applications, which are guided by the known anatomy of vagus connections.

A recent study by Clark and colleagues hints at the potential for VNS to be used to investigate brain circuits involved in memory and learning (Clark et al 1999). These researchers examined word-recognition memory in 10 patients enrolled in a clinical study of VNS for epilepsy. Vagus stimulation administered after learning and during memory consolidation caused intensity-dependent enhancement of word recognition relative to sham stimulation. Other work has shown that vagotomy attenuates the memory-enhancing properties of amphetamine.

Further Refinements in the Use of VNS

At present, the delivery of VNS involves a surgical procedure that includes exposure and manipulation of the carotid artery, as well as the cosmetic and other inconveniences of having a generator in the chest wall. As a consequence, the NCP System is typically used in those patients who have not responded to other therapies. In both epilepsy and depression, some patients will receive little to no benefit, despite having had surgery. The development of less invasive ways of delivering VNS or predicting which patients will benefit would likely expand the clinical potential of VNS. Preliminary attempts at externally stimulating the vagus nerve via a transcranial magnetic stimulator have not been successful, in part due to the difficulty of finding a reliable indication of whether TMS has activated the vagus (H. Sackeim et al, unpublished data, April 1998). Another possibility might be to develop a temporary percutaneous method of stimulation.

Yet a different approach would be to identify the subset of patients who are most likely to benefit from VNS, by using functional neuroimaging or other measures. In this context, a recent PET study in adults with epilepsy found that increased blood flow in the right and left thalamus during the initial VNS stimulation correlated with decreased seizures over the next few weeks (Henry et al 1999). This finding suggests that one could use functional imaging, combined with VNS, to select patients most likely to benefit from this therapy.

Finally, VNS can be delivered at different amplitudes and frequencies and with different pulse widths, all at various duty cycles (ratio of "on" time to "off" time). More basic work would advance this area through an understanding of how varying combinations of these parameters affect different brain regions or influence different neuropsychiatric conditions. It seems logical to suggest that VNS delivered with parameters different from

those commonly used for epilepsy might produce different CNS effects that would in turn broaden the clinical indications.

Conclusion

Vagus nerve stimulation, one of the newest methods to physically alter brain function, builds on a long history of investigation of the relationship of autonomic signals with limbic and cortical function. Vagus nerve stimulation is already established as a clinically useful anticonvulsant in patients with resistant epilepsy and may have promise as an antidepressant treatment. The known anatomic projections of the vagus nerve suggest that VNS might also have other neuropsychiatric applications. Further research is needed to clarify the mechanisms of action of VNS and the potential clinical utility of this intriguing new somatic portal into the CNS.

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