Trigeminal Nerve Stimulation: Seminal Animal and Human Studies for Epilepsy and Depression

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KEYWORDS

• Trigeminal nerve stimulation • Epilepsy • Depression
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Epilepsy affects 3 million Americans, of whom 1 million (30%) have drug-resistant epilepsy.[1,2,3,4] Drug-resistant epilepsy frequently leads to unemployment, injuries, and sudden death.[1,2,3,4] Likewise, major depression is a significant public health problem, affecting more than 17 million American adults, a significant number of whom are persistently ill despite multiple trials of antidepressant medications.[5,6,7] Given the side effects of drug therapy for both conditions (eg, sedation, cognitive impairment, behavioral side effects, weight gain and metabolic syndrome, risk for allergies, and suicide), there is a need for alternative nondrug therapies for both epilepsy and depression.

There is growing interest in neuromodulation for depression and epilepsy, including vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS) as alternatives to failed drug therapy.[8,9,10,11,12,13,14] These approaches are expensive, have modest efficacy, and can be surgically invasive. Trigeminal nerve stimulation (TNS) is an emerging neuromodulation therapy with unique advantages: it can be delivered externally, bilaterally, and at low cost.[15,16] Response during a trial of external TNS can be used to evaluate potential surgical candidates before an implantable stimulation device is inserted.[15,16] This article evaluates the anatomy of the trigeminal nerve, presents animal data, and summarizes recent developments in the application of TNS in drug-resistant epilepsy and major depressive disorder.[15,16,17]

ANATOMY OF THE TRIGEMINAL NERVE

The trigeminal nerve is the largest cranial nerve (fifth or CN V), and has extensive connections with brainstem and other brain structures.[18,19,20,21] The trigeminal nerve has 3 major sensory branches over the face, all of which are bilateral (**Fig. 1**).[18] These branches pass through 3 foramens in the skull, just lateral to the midline.[22] The nerves within these foramens also supply sensation over the facial structures, and project to the main trigeminal ganglion at the base of the skull.[18] The ophthalmic branch (V1) is ideally placed to allow bilateral stimulation using a single paired electrode placed over the forehead. **Fig. 2** details the anatomy of the ophthalmic division of the trigeminal nerve.

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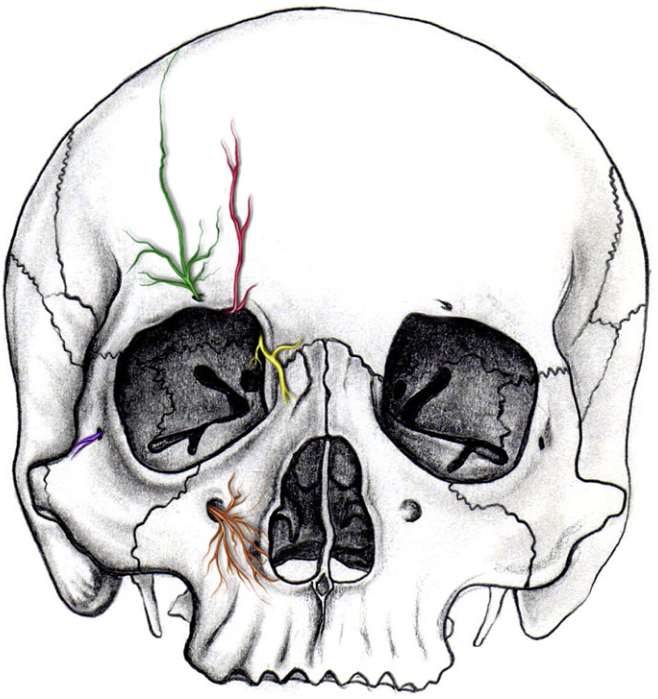

Fig. 1. Anatomy of the cutaneous branches of the trigeminal nerve: V1 and V2 are shown. (*Courtesy of* Josh Emerson.)

The trigeminal ganglion, located in the Meckel cave (cavum trigeminale), projects to the trigeminal nucleus, which has reciprocal projections to the nucleus tractus solitarius (NTS), locus coeruleus, and the reticular formation, structures that play an important role in inhibition of seizures.[18,19,20,21] Evidence from animals indicates that stimulation of the trigeminal nerve and its related structures inhibit seizures.[17,23,24,25,26] NTS stimulation was investigated in a cat model of epilepsy.[23] NTS stimulation delayed the onset of overt seizures induced by chronic amygdala stimulation (an animal model commonly used to produce chronic epilepsy).[23] The latency to the development of seizures was significantly delayed, and many animals never developed the expected seizures.[23] Overall, intermittent NTS stimulation prolonged or inhibited the onset of kindled seizures.[23] The trigeminal nucleus also has extensive projections to locus coeruleus and midbrain periaqueductal gray, structures involved in the production of the catecholamine neurotransmitters epinephrine and norepinephrine.[25,26] Stimulation of the locus coeruleus suppresses epileptic discharges induced by cobalt and penicillin, agents used to provoke seizures in animals.[27] The locus coeruleus plays a central role in the anticonvulsant effect of VNS and, given the projections of the trigeminal nerve to the vagus nerve via the reticular formation, the locus coeruleus may share a common role in the efficacy of both VNS and TNS.[28]

Based on animal data linking stimulation of central trigeminal pathways to an antiepileptic effect, Fanselow and colleagues[17] initiated studies of TNS using a rat model of epilepsy, and DeGiorgio and colleagues[8,15,16] initiated phase I clinical studies of infraorbital and supraorbital TNS for intractable seizures in humans. In this review, the results of these seminal studies will be presented.

ANIMAL STUDIES

Cranial nerve stimulation has been used for more than a decade to reduce seizure activity in patients with epilepsy. Specifically, the technique of VNS received US Food and Drug Administration approval in 1997 and has been implemented in tens of thousands of patients.[8,9,29] However, the mechanisms by which VNS alleviates seizures in responsive patients are not well understood, and not all patients are candidates for, or responsive to, this therapy.[30] Further, it was not previously clear whether the seizure-reduction effect of VNS was specific to the vagus nerve, or whether this effect could be generalized to other cranial nerves.

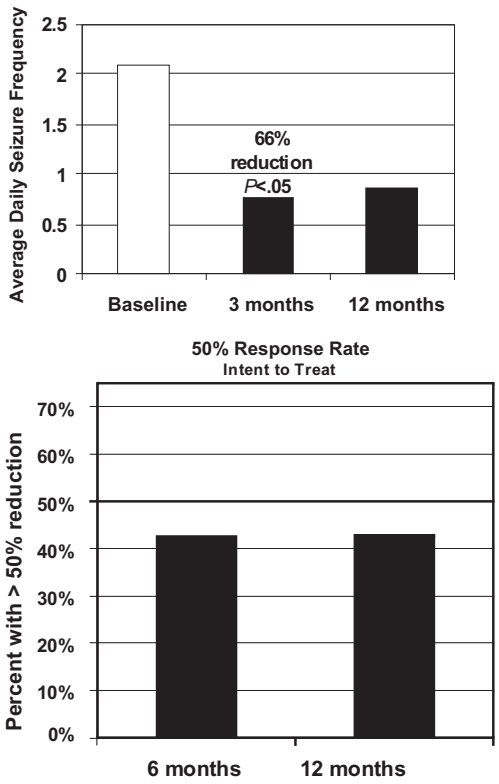

Fig. 2. Pilot feasibility trial of TNS for epilepsy. Change in average daily seizure frequency (*left*). Note that, at 3 months, the reduction in seizures was 66% of the initial therapeutic threshold (Intent to treat), *P*<.05.

Therefore, in the laboratory of Dr M.A.L. Nicolelis in the Department of Neurobiology at Duke University, Fanselow and colleagues[17] tested whether stimulation of another cranial nerve, the trigeminal nerve, could exert anticonvulsant effects in awake rats.

METHODS FOR STIMULATING THE TRIGEMINAL NERVE IN RATS

Initial animal studies of TNS were performed in awake, adult rats using the pentylenetetrazole-induced seizure model.[17] Rats were surgically implanted with arrays of chronic, indwelling electrodes in layer V of the somatosensory cortex and in the somatosensory thalamus.[17] These electrodes allowed for local field potential (LFP) recordings at 16 sites within each recording target. Seizures were initiated using intraperitoneal injection of pentylenetetrazole (40 mg/kg).[17] Injection of this agent induced generalized tonic-clonic seizures with a duration of about 4 seconds and a frequency of 4 per minute for approximately 2 hours.[17]

To reliably activate the trigeminal nerve in awake animals, a nerve cuff electrode, constructed in-house, was implanted around the infraorbital branch of the trigeminal nerve.[17] The nerve cuff electrode contained 2 platinum bands between which current was passed to activate fibers in the infraorbital nerve.[17] This branch of the trigeminal nerve carries somatosensory input from the whiskers on the face of the rat to the trigeminal ganglion, which subsequently projects to the trigeminal brainstem nuclei.[17] These nuclei project to the ventroposterior medial nucleus of the thalamus, which sends afferents to the primary somatosensory cortex.[18]

In these studies, trains of trigeminal stimuli were presented at varying frequencies and amplitudes.[17] Stimulus trains were presented using a continuous duty cycle of 1 minute on to 1 minute off. Seizures observed in the LFP recordings were quantified in 3 ways: (1) number of seizures, (2) seizure duration, and (3) integrated seizure activity, a measure of overall seizure activity calculated by integrating the absolute value of the LFP signals.[17]

REDUCTION OF SEIZURES IN ANIMALS DURING TNS

When TNS was applied during pentylenetetrazole administration, seizure activity was reduced in the thalamus and neocortex according to all 3 measures of seizure prevalence.[17] At a stimulus frequency of greater than 100 Hz and a stimulus intensity of 11 mA, a seizure reduction of 78% was observed across all animals.[17] In addition to a reduction in electrographic measures of seizures, as measured in the cortical and thalamic LFPs, the behavioral characteristics of the pentylenetetrazole-induced seizures (clonic jerking of the body and forelimbs) were concomitantly reduced.[17] Thus, the seizure-reduction effect was not specific solely to the somatosensory regions of the thalamus and neocortex.[17]

The seizure-reduction effect was dependent on both stimulus frequency and stimulus intensity.[17] It was necessary to stimulate at greater than 50 Hz to observe a reduction in seizure activity.[17] Increasing stimulus frequency to more than 100 Hz showed no improvement in seizure reduction and, with frequencies less than 50 Hz, there was a trend toward increased seizure duration, peaking at a stimulus frequency of 10 Hz.[17] Seizure reduction increased with increasing current levels, presumably because higher current levels activated more fibers in the stimulated infraorbital branch of the trigeminal nerve.[17] TNS had no discernable effect on heart rate, and animals did

not show distress at the levels of stimulation used in these studies.[17]

These initial experiments showed that TNS was effective at reducing pentylenetetrazole-induced seizures in awake animals. We were also interested in 2 other aspects of TNS efficacy against seizures. The first of these was the use of bilateral TNS, and the second was seizure-triggered stimulation.

Efficacy of Bilateral TNS

Unlike VNS, in which typically only the left vagus nerve is stimulated to avoid cardiac side effects, TNS can readily be applied to both trigeminal nerves simultaneously.[8,9,15,16] However, it was not known whether this would improve the efficacy of TNS or whether unilateral stimulation of the trigeminal nerve was sufficient to elicit the full seizure-reduction effect of TNS. Therefore, nerve cuff electrodes were implanted bilaterally on each of the infraorbital nerves along with indwelling electrodes in each of the primary somatosensory cortices.[17] Each infraorbital nerve was stimulated individually and then both nerves were stimulated simultaneously.[17] When both infraorbital nerves were stimulated simultaneously, there was a decrease in the current required to achieve maximal seizure reduction.[17] That is, with unilateral TNS, a stimulus intensity of 11 mA was required to achieve 75% seizure reduction, whereas with bilateral stimulation the same degree of seizure reduction was accomplished with 7 mA of current presented to each nerve simultaneously.[17] This result suggests that the effects of TNS increase with multiple nerve stimulation sites, which has implications for the optimization of TNS application in patient populations.[17] The electrographic (and behavioral) seizure-reduction effects were identical for each side stimulated (ie, either contralateral or ipsilateral to the neocortical recording site).[17] This is further evidence that the effects of TNS involve more than just the brain regions directly targeted by the trigeminal nerve.[17]

Closed-loop Seizure-triggered TNS

An open question about cranial nerve stimulation was whether it was better to provide stimulation on a continuous on-off duty cycle or to apply responsive stimulation only when a seizure was detected. Such a closed-loop paradigm required the development of a seizure-detection algorithm capable of detecting a seizure and promptly triggering TNS. In conjunction with Ashlan P. Reid in the Department of Biomedical Engineering at Duke University, a seizure detector was developed that triggered TNS when the LFP signal increased to more than a manually set voltage threshold.[17] When such activity was detected in the LFP, 500 millisecond trains of 500-microsecond pulses were delivered until the aberrant LFP activity was no longer detected.[17] When unilateral TNS was provided in this seizure-triggered manner, it successfully stopped seizure activity, in an average of 529 milliseconds after seizure onset.[17] This seizure-reduction effect was not observed when TNS was initiated manually after a seizure had been underway for more than 10 seconds (Fanselow, Reid, and Nicolelis, unpublished observations, 2010), so it therefore seemed to be critical to provide the stimulation early in a seizure episode. These results showed that TNS could successfully be applied in a closed-loop, seizure-triggered manner. This finding has implications for the mechanism(s) by which TNS reduces seizure activity. It is likely that, in humans, a more sophisticated seizure-detection algorithm would be required for implementation of a closed-loop stimulation paradigm, but these results serve as a proof of principle for seizure-triggered TNS.

Potential Mechanisms of TNS Seizure-reduction Effects

The mechanisms by which any type of cranial nerve stimulation reduces seizure activity are poorly understood. Multiple studies have suggested that a component of the effect of VNS on seizures is caused by involvement of the neuromodulators released from brainstem nuclei or their downstream targets. For example, Krahl and colleagues[28] showed that lesions of the locus coeruleus, the noradrenergic nucleus of the brainstem, blocked the seizure-suppression effects of VNS. Recent evidence for the involvement of norepinephrine was obtained by Raedt and colleagues[31] who showed that norepinephrine levels in the hippocampus increased during VNS. Whether noradrenergic effects are also present during TNS is not yet known. In addition, the reticular activating system, including the reticular formation of the brainstem, has been implicated in reducing seizure activity, primarily because stimulation of this region is known to desynchronize firing in the neocortex.[32]

It is likely that there are multiple mechanisms by which cranial nerve stimulation, including TNS, exerts its effects on the brain. Evidence for this comes from the different time scales on which cranial nerve stimulation can be effective. First, as discussed earlier, seizure-triggered TNS was able to abort seizures on a rapid time scale, suggesting that TNS can have immediate effects on seizure activity.[17] In support of this, there is

evidence that neuronal firing is suppressed during TNS in rats as soon as the nerve stimulation begins.[33] Second, in humans, VNS and TNS are typically provided on a continuous fixed-duty cycle, and, in animal studies, it has been shown that there is a period of increased seizure threshold after termination of each On cycle.[17,34] Therefore, there may also be effects of cranial nerve stimulation that last from tens of seconds to minutes and outlast the period of nerve stimulation. In addition, there seem to be long-term effects of cranial nerve stimulation, in which seizure frequency and severity are observed to decrease in the course of months to years.[8,35,36,37] This finding suggests that TNS could potentially cause long-term alterations in the brain that could depend on genetically mediated changes in brain function, as has been shown for VNS.[8,35,36] None of these seizure-reduction mechanisms are mutually exclusive, and they could operate concurrently to reduce seizure activity.

CONCLUSIONS FROM ANIMAL STUDIES OF TNS, AND FUTURE DIRECTIONS

Animal studies showed that TNS was effective for reducing seizure activity, that bilateral trigeminal stimulation was more effective than unilateral stimulation, and that TNS was effective when delivered in a closed-loop, seizure-triggered paradigm. These studies prepared the way for subsequent studies of TNS in human subjects, as discussed later. Future animal studies will investigate the cellular-level/circuit-level mechanisms by which TNS exerts its effects, and, based on this information, explore ways to optimize stimulus parameters to maximize the seizure-reduction capabilities of TNS in patients with epilepsy.

Pilot Feasibility Trials in Humans with Epilepsy and Depression

Epilepsy

Beginning in 2001, subjects with severe epilepsy with a minimum of 3 seizures per month were enrolled in an open-label pilot feasibility study of external infraorbital and supraorbital TNS in Los Angeles (CA). Thirteen subjects entered a 1-month pretreatment baseline and, after 1 month, were treated with TNS with a duty cycle of up to 30 seconds on to 30 seconds off.[15,16]

Subjects were initiated with infraorbital TNS, but external infraorbital TNS proved awkward. Subjects were then converted to receiving TNS delivered via supraorbital electrodes, which allowed for bilateral stimulation using a sustainable and well-tolerated platform. Initial studies focused safety and feasibility issues, such as on the effect of TNS on pain, stimulation intensity studies, and the effects of TNS on heart rate and blood pressure. TNS was well tolerated. Side effects were infrequent and mild, but included skin irritation, which improved by reducing stimulation to 12 to 16 hours/d, or through application of 1% hydrocortisone cream.[15,16] Tingling, forehead pressure, and headache were reported, but improved with reduction of current.[15,16] Extensive monitoring of pulse and blood pressure were performed acutely after initial exposure to TNS, and chronically for at least 1 year.[16] No effect was identified on electrocardiograph, heart rate, or systolic or diastolic blood pressure.[16] With regard to therapeutic effects, at 3 months, the mean seizure frequency was reduced by 66%, from a pretreatment baseline of 2.1, to 0.71 seizures/d ($P<.05$).[16] At 12 months, the mean seizure frequency was 0.86 seizures/d (59% reduction, $P = .058$).[16] Five subjects experienced greater than 50% reduction at 6 and 12 months, and 1 subject had greater than 90% reduction.[16] Replacing the electrodes daily, TNS can be used for years, and some patients have used the device for up to 5 years[16] **Figs. 1** and **2** shows the acute and long-term efficacy at 3 and 12 months, as well as responder rates at 6 and 12 months of long-term follow-up. In this pilot trial, responder rates using intent-to-treat analysis (which does not inflate response rates caused by dropouts) showed efficacy that favorably compares with responder rates of VNS, DBS, and renal nerve stimulation. This finding requires confirmation in future controlled clinical trials.[8,9,10] In light of the positive results from the pilot feasibility study, and the absence of any adverse effect of TNS on heart rate and blood pressure, a randomized, phase II, controlled clinical trial of high versus low TNS was begun at 2 sites in Los Angeles (CA) to evaluate TNS in double-blind controlled conditions. Fifty subjects were enrolled. Initial results are promising, and the study results should be available by early 2012, and will inform a larger pivotal trial of TNS.

Major Depression

Given the anatomy of the trigeminal nerve, and its projection to structures associated with mood regulation, Drs Lara Schrader and Ian Cook initiated an exploratory study of TNS in major depression. Five adults ages 31 to 59 years with nonpsychotic unipolar major depressive disorder were studied in an 8-week open-label outpatient trial at University of California, Los Angeles.[38] Entry criteria included duration of illness of at least 4 months, persistent depressive symptoms despite at least 1 antidepressant at acceptable doses during the current episode, pharmacotherapy

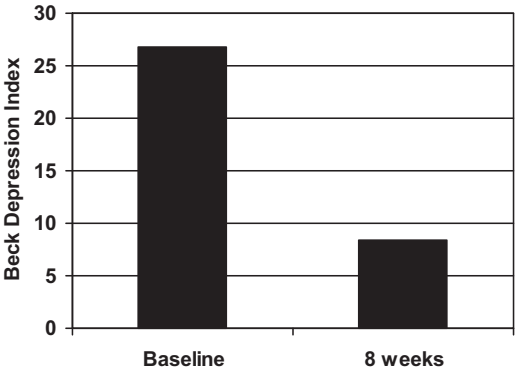

Fig. 3. TNS in major depression. Results from the First Pilot Feasibility Trial. The change in Beck Depression Index was significant: 2-tailed *t*-test, $P = .0004$. (*Data from* Cook IA, DeGiorgio CM, Miller PM, et al. Noninvasive neuromodulation with trigeminal nerve stimulation: a novel treatment for major depressive disorder. Poster presented at the NCDEU Annual Meeting. Boca Raton (FL), June 14–17, 2010.)

with at least 1 antidepressant in at least 6 weeks during the current episode, and concomitant use of at least 1 antidepressant at study entry.[38] All had prominent depressive symptoms, with a mean entry score on the 17-item Hamilton Depression Rating Scale (HDRS-17) of 16.2 (standard deviation [SD]3.3).[38] Subjects placed stimulating electrodes over the supraorbital branches of the trigeminal nerve for at least 8 hours per day (primarily while asleep), with current adjusted to maximal comfortable levels.[38]

Overall, TNS for major depression was well tolerated. No serious side effects occurred in the 8-week treatment period, and no adverse effect on blood pressure or heart rate was detected. Responses on the Beck Depression Inventory (BDI) declined significantly, from a baseline mean BDI of 26.8 (SD 8.1) to 8.4 (4.9) at 8 weeks (2-tail *t*-test, $P = .0004$). **Fig. 3**[38] summarizes the acute response in the 8-week acute treatment period. Depressive symptoms improved whether assessed with a self-rated (BDI) or clinician-rated (HDRS-17) instrument.[38] Overall, the preliminary data indicate an early and robust response of TNS for major depression.[38] These findings are now being confirmed in a larger cohort, and a randomized, phase II, double-blind trial is underway to evaluate the efficacy of TNS using a double-blind controlled design.

SUMMARY

TNS is a new method to treat both epilepsy and major depression. The unique ability to stimulate bilaterally, extracranially, and noninvasively represents a significant advantage to existing neuromodulation therapies. In humans thus far the technique has been applied noninvasively, termed external TNS. If external TNS is effective, it could lead to the development of a more convenient implantable device for patients who are responders to external TNS. The potential to predict responders to an implantable TNS devise using noninvasive means would be a significant benefit compared with other currently available implantable neuromodulatory devices.

We are completing O^{15} positron emission tomography studies, which will shed light on which structures are being activated or inhibited by TNS. This work will advance the understanding of mechanisms of action for this novel neuromodulation therapy. In addition, phase II randomized clinical trials are near completion for both epilepsy and depression, and larger phase III trials are in the planning stages. TNS represents an exciting addition to existing invasive neuromodulation therapies for epilepsy and depression.

DISCLOSURES

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