RAPID COMMUNICATION

# Vagus Nerve Stimulation Activates Central Nervous System Structures in Epileptic Patients During PET $H_2{}^{15}O$ Blood Flow Imaging

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**OBJECTIVE: To determine the central areas of activation by vagal nerve stimulation (VNS) in epilepsy. VNS is a promising neurosurgical method for treating patients with partial and secondary generalized epilepsy. The anti-epileptic mechanism of action from VNS is not well understood.**

**METHODS: We performed $H_2{}^{15}O$ PET blood flow functional imaging on three patients with epilepsy in a vagal nerve stimulation study (E04 Protocol with Cyberonics). The three patients included two that had previous epilepsy surgery but continued to have frequent seizures. Seizure onset was frontal in two patients and bitemporal in the third patient. Twelve PET scans per subject were acquired every 10 minutes with a Siemens 953/A scanner. In 6 stimulus scans, VNS was activated for 60 seconds (2 mA, 30 Hz) commensurate with isotope injection. In 6 control scans no VNS was administered. No clinical seizures were present during any scan. Three way ANOVA with linear contrasts (subject, task, repetition) of coregistered images identified significant treatment effects.**

**RESULTS: The difference between PET with VNS and without revealed that left VNS activated right thalamus ($P<0.0006$), right posterior temporal cortex ($P<0.0003$), left putamen ($P<0.0002$), and left inferior cerebellum ($P<0.0009$).**

**CONCLUSIONS: VNS causes activation of several central areas including contralateral thalamus. Localization to the thalamus suggests a possible mechanism to explain the therapeutic benefit, consistent with the role of the thalamus as a generator and modulator of cerebral activity.** (Neurosurgery 39:426–431, 1996)

Key words: Epilepsy, Positron emission tomography, Thalamus, Vagus nerve stimulation

Vagus Nerve Stimulation (VNS) is a new and potentially efficacious neurosurgical treatment for medically intractable epilepsy (5, 21). Although epilepsy surgery is being performed more frequently, many patients are not good candidates and VNS may be another neurosurgical treatment option. The results of a large randomized study of high versus low intensity VNS in 114 patients found a mean reduction of seizures of 24.5% for patients with high intensity VNS and 6.15% for patients with low intensity VNS (21). There is an ongoing large multicenter double blind trial of VNS as adjunctive treatment for refractory partial epilpepsy. VNS reduces the duration of seizures induced by penicillin G and pentylentetrazole, and shortens or prevents seizures induced by maximum electroshock (10, 23).

The structures involved in the mechanism of VNS are poorly known. Naritoku recently reported increased expression of fos immunoreactivity in the habenula of the thalamus and in the locus ceruleus with VNS (11). Positron emission tomography (PET) $H_2{}^{15}O$ cerebral blood flow

(CBF) imaging is one tool which allows an understanding of which neuro-anatomic structures are recruited by VNS in human subjects. Determination of the structures activated by VNS may help elucidate the antiepileptic mechanism of VNS, possibly by identifying inhibitory pathways recruited by VNS.

## PATIENTS AND METHODS

### Patients

Three patients with medically intractable partial seizures were each implanted with left vagus nerve stimulators (NeuroCybernetic Prosthesis Model 100, Cyberonics Inc, Webster, Texas, USA) (14, 20). Two patients in this study had previous epilepsy surgery (9 and 2.5 years previous to VNS) but continued to have significant number of seizures. The patients were maintained on their anticonvulsants for the duration of study. Each patient had a three month baseline period to determine seizure frequency before VNS was started. The duration of VNS prior to $H_2{}^{15}O$ PET imaging was six, seven, and two months for patient A, B, C respectively. The patients' profiles with baseline seizure frequency (a month was defined as a 28 day month) as well followup seizure frequency with VNS (cumulative seizure frequency) up to twelve months are outlined in *Table 1*.

Patient A, a 54 year old male has complex partial seizures that began at age 33. The complex partial seizures included motor automatisms, staring, confusion and laughing consistent with gelastic epilepsy. He underwent subdural electrode seizure monitoring and had his seizures localized to the left frontal lobe. He underwent left frontal resection of the anterior and lateral polar segments nine years previously at another institution. Despite surgery he still had persistent seizures with 10.31 seizures/day during the baseline period. The seizure frequency with VNS at twelve months was 3.13 seizures/day. With VNS the character of the seizures were less intense.

Patient B, a 44 year old male, has the syndrome of hemiatrophy, hemiparesis and intractable epilepsy. The seizures were simple and complex partial seizures of left frontal onset. The baseline seizure frequency was 0.36 seizures /day and at nine months was 0.38 seizures/day. However, the patient reported a reduction in intensity and duration of seizures.

**TABLE 1. Patient Profile of Seizure Frequency**

| | Seizures/ month | | |
|---|---|---|---|
| | Baseline | with VNS | % change |
| Patient | | | |
| A | 288.6 | 87.6 at 12 months | - 69.6% |
| B | 10.0 | 10.5 at 9 months | + 6.2% |
| C | 12.0 | 15.7 at 6 months | + 30.8% |

Patient C, a 25 year old male, has bitemporal epilepsy (complex partial seizures) with seizure onsets confirmed by epilepsy video-telemetry. This patient had a right temporal lobectomy with a 70-80% reduction in seizure frequency. but still had frequent complex partial seizures postoperatively. The patient underwent epilepsy video-telemetry agian which showed that the seziures that persisted arose from the left temporal lobe. Since the patient had bitemporal lobe epilepsy the patient could not have surgery on both sides and VNS was offered. VNS was implanted 2.5 years after the temporal lobectomy. Despite a reported reduction in intensity of his seizures, his seizure frequency did not change after VNS (*Table 1*). His baseline seizure frequency was 0.43 seizures/day and at six months with VNS was 0.56 seizures/day.

### Imaging

Informed consent for the PET studies was obtained in accordance with the U.S.C. Institutional Review Board. In all patients, the routine therapeutic VNS was held for one hour prior to imaging. Twelve PET scans per patient were acquired every 10 minutes. For each scan, a bolus of 35 mCi of $H_2{}^{15}O$ was injected intravenously and a 90 second image was acquired. Six scans were performed without VNS (off), alternating with 6 scans with VNS (on). VNS with standard clinically used settings (2 milliamps at 30 hertz) was activated for 60 seconds concurrent with the injection of the isotope and scanning. The above intervals were chosen because the duration of the anti-epileptic effect of VNS in an animal model after constant stimulation for 60 minutes is maximal at about 3 minutes and is gone by 10 minutes (18).

Scans were obtained with the Siemens 953/A scanner (Siemens, Germany) and were reconstructed using calculated attenuation correction to an image resolution of 8 mm full width at half maximum. Arterial blood samples were not obtained, instead images of radioactive counts were used to estimate relative cerebral blood flow (3, 9). Patients were scanned with eyes and ears unoccluded in a quiet, semi-darkened room. The patients were continuously observed throughout the imaging session and no clinical seizures occurred.

### Image Analysis

Images from each subject were aligned using a within subject coregistration method (24). Scans from each subject were then transformed to the Talairach coordinate space for group statistical comparisons (19, 25). Images were then smoothed with a Gaussian filter to a final image resolution of 15 mm full width at half maximum. All images were globally normalized by proportional rescaling. A 3-way analysis of variance (ANOVA) where the 3 effects were *subject* (n=3), *repetition* (n=6) and *task* (n=2) was used

to identify significant task effects (12). A *t*-statistic, calculated on a pixel by pixel basis identified significant task effects. Only pixels reaching a threshold of $p<0.005$ were included. Pixels where CBF increased significantly with VNS were superimposed on a mean CBF image and sites of maximal significance were localized in Talairach coordinates.

## RESULTS

VNS caused increased regional cerebral blood flow in all three patients with epilepsy. The regions with the most significant increase in blood flow were in the left posterior cerebellum right middle temporal gyrus, right thalamus, and left putamen. *Table* 2 shows the localization of blood flow increases related to left vagal nerve stimulation for the three patients. Patient A, who had the best clinical response with a 69.6% seizure reduction at twelve months had the largest percentage increase of CBF in the left posterior cerebellum and right thalamus of 12.6% and 12.2%. Patient's B and C, who had the least clinical response in seizure frequency had the least amount of changes in CBF by PET.

*Figure 1* demonstrates the combined image of all three patients, where the baseline (VNS off) $H_2{}^{15}O$ PET was subtracted from activated (VNS on) $H_2{}^{15}O$ PET. Significant increase in CBF were identified in the contralateral structures (thalamus and posterior temporal neocortex) as well as ipsilateral (inferior cerebellum and putamen). Areas from which brain is missing due to previous surgery shows as black.

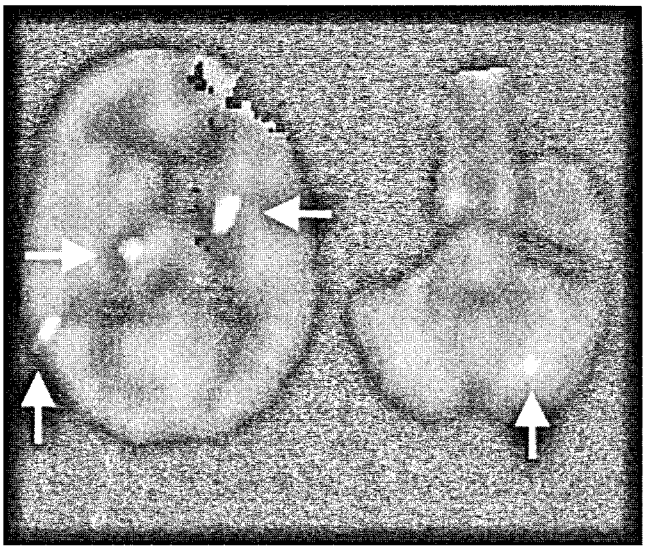

**FIGURE 1. PET scan of all three patients displayed transversely (the right image is through cerebellum, the left image is through the level of the temporal lobe). The areas of activation are highlighted by arrows.**

## DISCUSSION

The primary finding of this pilot study was that VNS, using standard clinical settings, caused a measurable and significant change in CBF. The most robust changes of increased CBF were in the ipsilateral cerebellum and contralateral thalamus. Garnett et al also were able to demonstrate that VNS causes change in cerebral blood flow with $H_2{}^{15}O$ PET (4). They found that VNS in humans causes activation of ipsilateral thalamus and cingulate gyrus which is in contrast to our finding of contralateral thalamus activation. One explanation for the difference is that two of their five subjects had electrical seizure activity during the study. Brain activity and blood flow in the interictal and ictal states are vastly different (8). This study used a total of twelve scans per patient as opposed to six used by Garnett's group which may have improved the signal to noise ratio. Nevertheless, Garnett's and our study shows VNS has measurable effect on $H_2{}^{15}O$ CBF.

The areas with increased CBF are consistent with the known anatomy of the vagus nerve. The vagus nerve carries general somatic afferents (GSA), general visceral afferents (GVA) and efferents. The majority of fibers are GVA (15). Most of the afferent fibers first project to the nucleus of the solitary tract (NST) but there are connections with the medial reticular formation of the medulla as well. Left VNS in cat with implanted cerebral micro-electrodes recorded increased cellular firing in the contralateral ventro-postero-medial nuclei of the thalamus (16). Ascending visceral afferent information from vagal stimulation in rats is relayed through the parabrachial

**TABLE 2. Localization of Blood Flow Increases to Left Vagal Nerve Stimulation**

| | rCBF (ml/min/100 gm) | | | | % Increase of rCBF per individual | | |
|---|---|---|---|---|---|---|---|
| Brain Region | VNS off | VNS on | t | P | A | B | C |
| Left Posterior Cerebellum | 69.0 ± 4.3 | 72.6 ± 1.9 | 4.52 | 0.0009 | 12.6 | 3.3 | 0.4 |
| Right Middle Temporal Gyrus | 64.5 ± 5.6 | 67.2 ± 4.5 | 4.17 | 0.0003 | 7.6 | 1.0 | 4.6 |
| Right Thalamus | 59.4 ± 3.2 | 63.0 ± 3.8 | 3.83 | 0.0006 | 12.2 | 2.3 | 4.3 |
| Left Putamen | 64.7 ± 12.4 | 67.7 ± 13.3 | 4.43 | 0.0002 | 5.6 | 3.2 | 4.4 |

nucleus to the contralateral ventral basal thalamus (15).Studies in monkeys with autoradiographic anterograde fiber-tracing and horseradish peroxidase retrograde cell labeling of the nucleus of the solitary tract found projections to the contralateral ventral posterior lateral nucleus of the thalamus, and ipsilateral parvicelluar part of the ventral posteriomedial thalamic nucleus via the central tegmental tract (1). There maybe bilateral thalamic projections from one vagus nerve, although there appears to be more evidence for the contralateral projection. This study supports the studies demonstrating contralateral thalamic projection of the vagus nerve.

The cerebellar activation by VNS found in this study is also supported by animal data. Electrical stimulation in rabbits of the vagus nerve produces field potential in the ipsilateral and contralateral nodulus and uvula of the cerebellar vermis (13). The responses from the ipsilateral vagus nerve were mediated by a mossy fiber pathway, and those from the contralateral vagus nerve by a climbing fiber pathway. The cerebellar activation by VNS may represent direct projections from the vagus nerve.

The putamen and middle temporal gyrus were also activated by VNS but the significance of these areas is less well known. There is a paucity of known anatomical connections between the vagus nerve and these structures. The putamen and temporal gyrus activation may represent projections from the thalamus.

Activation of thalamus and cerebellum may not only reflect the anatomy of the vagus nerve, but also the mechanism of action. Both the thalamus and cerebellum have been implicated in modulating seizures ( 7). Anterior thalamic stimulation in humans may have an antiepileptic effect (17). The centro-median nuclei of the thalamus on both sides were implanted with electrodes and stimulation produced significant reduction in seizures (2, 22). Cerebellar stimulation in humans with epilepsy has deomonstrated some efficacy in reducing seizures (7). The sample size for direct cererbellar and thalamic stimulation , which is more invasive than VNS, were small. and the benefit is still controversial. VNS may provide an indirect method for stimulating these same structures for it's possible anti-epileptic effect.

These pilot data raise a number of interesting questions. It will be valuable to determine if there is a correlation between the magnitude of blood flow increases in thalamus or cerebellum and the effectiveness of VNS in reducing seizures? Does varying the intensity of stimulation recruit different structures? Since the vagus nerve stimulator is implanted on the left vagus nerve and appears to activate the right thalamus, is the VNS more effective in reducing seizures that arise from the right hemisphere than the left? Is there a different response to VNS between patients with temporal lobe epilepsy compared with frontal lobe epilepsy? We believe further study of VNS in a larger series with $H_2{}^{15}O$ PET in order to confirm these findings and answer these questions is warranted.

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## REFERENCES

1. Beckstead RM, Morse JR, Norgen R: The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. **J Comp Neurol** 190(2):259-282, 1980.
2. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M: Placebo controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. **Epilepsia** 33:841-851, 1991.
3. Fox PT, Mintun MA, Raichle ME, Herscovitch P: A non-invasive approach to quantitative functional brain mapping with H2 (15)O and positron emission tomography. **J Cereb Blood Flow Metabolism** 4:329-333, 1984.
4. Garnett ES, Nahmias C, Scheffel A. Firanu G, Upton ARM. Regional cerebral blood flow in man manipulated by direct vagal stimulation. **PACE** 15:1579, 1992.
5. George R; Salinsky M; Kuzniecky R; Rosenfeld W; Bergen D; Tarver WB; Wernicke JF. Vagus nerve stimulation for treatment of partial seizures: 3. Long-term follow-up on first 67 patients exiting a controlled study. **Epilepsia** 35(3):637-43, 1994.
6. Juhasz G, Detari L, Kukorelli T: Effects of hypnogenic vagal stimulation on thalamic neuronal activity in cats. **Brain Res Bull** 15(5):437-41, 1985.
7. Krauss GL, Fisher RS: Cerebellar and thalamic stimulation for epilepsy, in Orrin Devinsky, Alexander Beric, and Michael Dogali (eds.):*Electrical and Magnetic Stimulation of the Brain and Spinal Cord,*. New York, Raven Press, 1993; pp. 231-245.
8. Kuhl DE, Engel J, Phelps ME, Selin C: Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of (18)FDG and (13)NH(3). **Ann Neurol** 8:348-360, 1980.
9. Mazziotta JC, Huang SC, Phelps ME, Carson RE, MacDonald NS, Mahoney K: A noninvasive positron computed tomography technique using oxygen-15-labeled water for the evaluation of neurobehavioral task batteries. **J Cereb Blood Flow Metabolism** 5:70-78, 1985.
10. McLachlin RS: Suppression of interictal spikes and seizures by stimulation of the vagus nerve. **Epilepsia** 34:918-923, 1993.
11. Naritoku DK, Terry WJ, and Helfert RH: Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. **Epilepsy Res.** 22: 53-62, 1995.
12. Neter J, Wasserman W, Kutner MH: *Applied Linear Statistical Models*. Boston: Irwin, 1990.

13. Nisimaru N, Seiji Katayama: Projection of cardiovascular afferents to the lateral nodulus-uvula of the cerebellum in rabbits. **Neuroscience Research** 21:343-350, 1995.
14. Reid SA : Surgical technique for implantation of the neurocybernetic prosthesis. **Epilepsia** 31(Suppl 2):S38-S39, 1990.
15. Rutecki P: Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. **Epilepsia** 31(suppl 2):S1-S6, 1990.
16. Saleh TM, Cecehtto DF: Peptides in the parabrachial nucleus modulate visceral input to the thalamus. **Am J Physiol** 264:R668-75, 1993.
17. Sussman NM, Goldman HW, Jackel RA, Kaplan L, Callanan M, Bergen J, Harner RN: Anterior thalamic stimulation in medically intractable epilepsy. Part II. Preliminary clinical results. **Epilepsia** 29:677, 1988 (abstr).
18. Takaya M, Terry WJ, Naritoku D: How Long does the anticonvulsant effect of vagus nerve stimulation last? **Epilepsia** 36(suppl 3):S34, 1995 (abstr).
19. Talairach J, Tournoux P: *Co-planar Stereotaxic Atlas of the Brain*. New York: Thieme Medical Publishers, 1988.
20. Terry R, Tarver WB, Zabara J: An implantable neurocybernetic prosthesis system. **Epilepsia** 31(Suppl 2):S33-S37, 1990
21. The Vagus Nerve Stimulation Study Group: A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. **Neurology** 45:224-230, 1995.
22. Velasco F, Velasco M, Ogarrio C, Fanghanel G: Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. **Epilepsia** 28:421-430, 1987.
23. Woodbury JW, Woodbury DM. Vagal stimulation reduces the severity of maximal electroshock seizures in intact rats: Use of a cuff electrode for stimulating and recording. **PACE** 14:94-107, 1991.
24. Woods RP, Cherry SR, Mazziotta JC. Rapid automated algorithm for aligning and reslicing PET images. **J Compt Assist Tomogr** 115:565-587, 1992.
25. Woods RP, Mazziotta JC, Cherry SR. Automated image registration. **Ann Nuclear Medicine** 7 (suppl):S70, 1993 (abstr).

## COMMENTS

Vagus nerve stimulation (VNS) as a treatment for epilepsy seems to be effective in some patients, although the mechanism of action is unknown and there are no clear indications for this alternative treatment. If the data reported in this article can be reproduced in a larger population of patients, they may provide insights into the anatomic substrates of any stimulation-induced antiepileptic effects, and metabolic patterns might predict which patients are likely to benefit from VNS. Although an understanding of the central connections of the vagus nerve are clearly important in understanding patterns of activation produced by intermittent stimulation, the ultimate effects may involve more than expected. Because vagal efferents are stimulated antidromically, this will produce action potentials in the efferent collaterals, with a much wider distribution of synaptic activation than is generally considered. It is, therefore, surprising that the areas of increased metabolism in this study are so few and so discrete.

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Although it has been known for many years that there are patients who can abort their seizures by sensory stimulation, the mechanism of this phenomenon is unknown. VNS may also reduce seizure frequency by either sensory or motor stimulation. The initial theoretical mechanisms proposed that the nucleus of the solitary tract and brain stem reticular centers were stimulated and hence would have a diffuse effect resulting in electroencephalographic desynchronization (1). These activation positron emission tomographic studies by Ko et al., as well as those by Garnett et al. (2) do not show diffuse brain stem increases in cerebral blood flow (CBF). The two studies are very dissimilar in their positive findings, with Garnett et al. (2) reporting ipsilateral thalamic and anterior cingulate cerebral blood flow increases during VNS, and Ko et al. demonstrating contralateral thalamic and posterior temporal cortical increases and ipsilateral putamen and cerebellar increases in CBF. There are many possible explanations for these differences because of study designs, patient selection, etc., but the differences in activated CBF patterns raise a concern that these patterns may vary with the stimulation parameters, with the individuals, or for unknown reasons.

Garnett et al. (2) studied five patients who were not well characterized beyond that they experienced medically intractable seizures. VNS stimulation parameters were not indicated. Two of the five patients had electrical evidence of seizure activity during the positron emission tomography scan. Ko et al. provide a far better characterization of their patients; however, only one of these patients has demonstrated a decreased frequency of seizures in response to VNS. Two of these patients underwent prior cerebral resections of frontal or temporal lobes, and the third patient has hemiatrophy, suggesting that all of these patients have abnormal brains. Areas of resection clearly cannot be activated by VNS, and it is possible that such resections might alter regional CBF activations at other sites. Furthermore, although no clinical seizures were observed, subclinical seizures could easily have been overlooked because electroencephalographic monitoring was not performed.

The duration of stimulation used in Ko's study was twice as long as that for therapeutic VNS, and patients receiving therapeutic VNS have individualized current levels that are not often as high as 2 mA. It is therefore possible that CBF patterns activated by VNS may vary with stimulation parameters. Because the investigators chose parameters that differed from therapeutic VNS, their findings may be more relevant to central projections of vagal nuclei but not necessarily indicative of which structures mediate the therapeutic effects of VNS.

Finally, both studies have used too few patients to identify the very small nuclei in the brain stem that could have been activated by VNS. Clearly, the nucleus of the solitary tract or the motor nucleus of X should have been activated. There is enough ambiguity in both of these studies to question whether a diffuse or a specific pathway is the mechanism for the decrease in seizure activity. Although I can accept a potential thalamic mechanism, the statement by the authors that cerebellar stimulation "showed some efficacy in reducing seizures" has not held up to more rigorous double-blind studies (3, 4). I would, however, agree with the authors that the most important finding is that there are indeed significant changes in CBF with VNS. It remains for future studies to determine exactly how, when, and why the activated CBF patterns change and what significance these may have for the control of seizure activity.

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1. Chase MH, Nakamura Y, Clemente CD: Afferent vagal stimulation: Neurographic correlates of induced EEG synchronization and desynchronization. **Brain Res** 5:236-249, 1967.
2. Garnett ES, Nahmias C, Scheffel A, Firnau G, Upton ARM: Regional cerebral blood flow in man manipulated by direct vagal stimulation. **PACE** 15:1579-1580, 1992.
3. VanBuren JM, Wood JH, Oakley J, Hambrecht F: Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. **J Neurosurg** 48:407-416, 1978.
4. Wright GD, McLellan DL, Brice JG: A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. **J Neurol Neurosurg Psychiatry** 47:769-774, 1984.

The role of VNS for the treatment of epilepsy remains unclear, in part because it has an inconsistent effect. When it does have an effect, it most commonly is mild. Perhaps some of this is because the patients who respond best to this treatment are not yet clearly identified. As a consequence, better understanding of the mechanism of action would be helpful, just as a clearer understanding of the mechanism actions of certain drugs improves their application to certain forms of epilepsy. For this reason, work as described in this article can be extremely useful in understanding putative effects of VNS.

It has been known for years that many of the epilepsias have a higher probability of interictal electroencephalographic spikes and seizures during periods of non-REM sleep and/or inattention. Put another way, some patients commonly have fewer seizures during periods of increased alertness when the electroencephalography shows relative desynchronization. From animal studies (1), it has been shown that focused attention causes increased interneuronal desynchronization and, on the single neuron level, a decrease in epileptic birth firing patterns. Intracellular single neuronal studies show that pyramidal tract cells hyperpolarize during reticular stimulation. Given these findings, and given the present findings that VNS increases blood flow to the reticular formation and thalamus, it is not difficult to understand a mild anticonvulsant effect for some patients with epilepsy solely on the above basis. The problem is extrapolating experimental data to the situation in humans and extrapolating blood flow changes in neuronal behavior. Nonetheless, studies of this nature will help to clarify the effects of VNS on epilepsy.

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1. Wyler AR, Fetz EE, Ward AA Jr: Firing patterns of epileptic and normal neurons in the chronic lumina focus in undrugged monkeys during different behavioral states. **Brain Res** 98:1-20, 1975.

This article by Ko et al., evaluates three patients with medically intractable epilepsy who had left vagal nerve stimulators placed and positron emission tomographic scans obtained with and without VNS. All three of the patients studied had structural abnormalities of the brain. One had undergone left frontal resection, one had David-Offdyke-Mason syndrome, and the third had undergone right temporal lobectomy. The first of these three patients experienced improvement in his seizure frequency with VNS. The other two did not. Using positron emission tomography, the authors found that the left vagal nerve stimulation activated the right thalamus, right posterior temporal cortex, left putamen, and left inferior cerebellum. These findings differ from previous reports.

The literature and most people's experience with VNS demonstrate that it can decrease seizure frequency in some patients but rarely cure patients. Therefore, it has not been used as an alternative to medication or surgery, but rather has been used in patients who have been proven medically intractable and are either not candidates for surgery or have failed resective surgery. There are a number of theorectical reasons why VNS can help to decrease seizure frequency in selected patients; however, none of these are evaluated in this article. It will be important to evaluate more patients with vagal nerve stimulators so that confounding factors, such as structural abnormalities of the brain, whether the stimulator was helpful, the lobe of seizure onset, etc., can be more clearly understood.

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