Chapter 16
Neurostimulation for Epilepsy, Including a Pilot Study of Anterior Nucleus Stimulation

Nina M. Graves, Pharm.D. and Robert S. Fisher M.D., Ph.D.

INTRODUCTION

Epilepsy is a common disorder, affecting approximately 0.7% of the population of the United States and of the world. The mainstay of therapy is medication, but only approximately two-thirds of individuals with epilepsy come under satisfactory control with medications (22). Some whose epilepsy cannot be medically controlled can be cured or substantially improved by resective surgery. However, this still leaves a substantial number of individuals whose epilepsy is intractable to existing medical and surgical approaches. Electrical stimulation of the nervous system is an attractive possible therapy for these individuals because stimulation might be expected to work by different mechanisms from those invoked by medications or focal surgery. Additionally, electrical stimulation, similar to medication therapy, is a reversible technique if it is not found to be beneficial in a particular case. Stimulation of the vagus nerve for epilepsy is now accepted therapy. However, vagus nerve stimulation was not the earliest target for stimulation therapy; rather, that distinction belongs to the cerebellum, thalamus, and caudate.

HISTORY OF DEEP BRAIN STIMULATION (DBS)

The pioneering work on brain stimulation for epilepsy was performed by the New York neurosurgeon, Irving Cooper (31). Cooper took note of the classical animal studies of Sherrington and, later, Moruzzi, demonstrating reduction in extensor tone in response to stimulation of the anterior cerebellum. On November 7, 1972, Cooper implanted the first cerebellar stimulator in a patient with epilepsy (31). The patient was reported to be free from seizures for 13 weeks after implantation, until a wire broke and seizures returned. Cooper reported his first seven cerebellar stimulation patients in a letter to LANCET in 1973, three of whom had spasticity and four of whom had epilepsy. Electrodes were placed over the cortex of the anterior cerebellum in the midline. In subsequent papers, he varied placement of the stimulators over the posterior midline or neocerebellum. Tissue was stimulated at 10 pulses per second with 10 V (1–3 mA) as 1 ms pulses. In early use, stimulation train duration was for 1 minute, alternating left and right, but the cycle time varied widely in later implantations. A report in NEUROSURGERY in 1977 (4) indicated that 18 of 32 patients receiving cerebellar stimulation for epilepsy responded with at least a 50% improvement in their seizure frequency. Cooper emphasized the importance of "biocalibration" of electrode placement with use of somatosensory evoked responses and depth recordings.

Several other neurosurgeons adopted Cooper's stimulation paradigms. A review of the literature (21) shows 11 uncontrolled series of cerebellar stimulation for epilepsy, all expressing positive results, and two controlled series, both expressing negative results. The caveat with respect to the controlled series is the small numbers of patients, with only 5 patients in the Van Buren et al. study (37), and 12 patients in the Wright et al. (50) study. In addition, the Van Buren et al. study had a calculation error unfavorable to stimulation. Some investigators continue to advocate for cerebellar stimulation (8), but cerebellar stimulation, and brain stimulation in general, was performed less often after publication of the two negative controlled studies.

Cooper also was the pioneer for thalamic stimulation for epilepsy. In 1980, Cooper and Upton (5), Cooper et al. (6), and Upton et al. (35, 36) initiated anterior nucleus stimulation, and during the next 4 years, implanted six patients, four of whom were said to have improved seizure control. Two of the patients also showed improvement in temporal hypometabolism, assessed by positron emission tomography (PET) scans (35). The exact anatomic target of Cooper's stimulation remains uncertain, because of the limited neuroimaging techniques available at the time. Sussman et al. (32) used the Cooper protocol in anterior thalamus, but with stimulation up to a frequency of 100 pulses per second, 5 to 6 V, in five patients with previously intractable seizures. In a study presented in abstract form, they reported improvement in three of the five patients.

Several sites in brain, other than cerebellum, have been the target of stimulation to treat seizures in patients, including the caudate, locus coeruleus, brainstem, subthalamus, and thalamus. Only stimulation to the cerebellum, centromedian thalamus, and vagus nerve stimulation have been subject to completed controlled trials. Feinstein et al. (11) implanted unilateral electrodes in the region of the locus coeruleus in two patients with epilepsy, and saw possible improvement in one patient. Faber and Vladyka (10) reported benefit of locus coeruleus stimulation for epilepsy in another patient.

The mechanism of action for DBS for epilepsy is unknown. Several mechanisms have been postulated for brain stimulation for movement disorders. It is likely that some or all of these will eventually be applicable to epilepsy. For movement disorders, there are four general hypotheses: depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathological network activity (26).

ANATOMIC TARGETS

There are several review articles that discuss the history and current status of DBS for epilepsy (9, 13, 16–18, 23, 25, 34). Several anatomic targets have been explored using animal models and/or human experience. Thus far, no target has been subjected to a large-scale randomized clinical trial, thus, the scientific evidence to support one anatomic target over another is limited. In addition, stimulation paradigms (acute versus chronic; continuous versus intermittent; and contingent versus periodic), stimulation parameters, and patient selection have varied substantially, further preventing clear conclusions from the existing data. This chapter reviews the data from some of the most widely explored anatomic targets for which there is scientific literature. New information about DBS, for epilepsy and other disorders, is emerging at a rapid rate.

CAUDATE NUCLEUS

Electrical stimulation of the caudate nucleus inhibits epileptiform activity of hippocampus and cortex in several animal model systems. Chkhenkeli et al. (3) studied effects of stimulation of the head of the caudate nucleus in 57 patients with epilepsy, delivering up to 8 mA at frequencies of 4 to 8 pulses per second. Of these patients, 38 received long-term leads (23 had completely internalized neurostimulators and 15 had externalized leads). Although the duration of stimulation ranged from 1 to 25 months, the effect on seizure frequency was not reported. The authors did note, however, that high-frequency stimulation (50–100 Hz, 0.4–0.6 mA, 0.2–2 ms, 2–5 s elicited spikes and spike-wave activity in the ipsilateral hippocampus and amygdala and possibly provoked or augmented epileptic activity. Low frequency stimulation (4–6 Hz, 0.2–0.8 mA, 0.2–2 ms, 2–5 s) of certain (unspecified) areas of the ventral caudate nucleus decreased interictal focal epileptic discharges. In addition, propagating discharges were reported to abruptly

cease. Information was not provided regarding the number of patients in whom these findings were observed. On-off cycles varied. Stimulation of one caudate was observed to inhibit epileptiform discharges in bilateral cortex and bilateral hippocampi. Among 17 patients with uncontrolled, open-label, chronic stimulation of the caudate nucleus, generalized seizures were reduced to approximately 15% of baseline, and partial seizures to approximately 20% of baseline. Some patients with status epilepticus improved after caudate stimulation.

CENTROMEDIAN NUCLEUS OF THE THALAMUS (CM)

The majority of the research addressing stimulation of the CM for the treatment of epilepsy has been reported by the Velasco et al. (38–47). Most of the reported patients had generalized epilepsy. The investigators think that CM stimulation has a hyperpolarizing effect on the reticulothalamic and cortical neurons involved in initiating and propagating secondarily generalized seizures. In 1987, the group published a paper (41) in which five patients with generalized tonicoclonic seizures were implanted bilaterally, with each patient's electrodes externalized behind the mastoid bone on each side. Stimulation was delivered for 2 h/d for 3 months (bipolar, biphasic pulses, 60–100 Hz, 0.1-ms duration, 0.8–2.0 mA, delivered in 1-minute trains every 5 minutes, alternating right and left sides). All patients experienced an 80 to 100% reduction in generalized tonicoclonic seizures and a 60 to 100% reduction in complex partial seizures. Electroencephalogram (EEG) interictal spikes and slow waves also were reduced. Much of the benefit continued beyond the 2-hour period of stimulation, suggesting that the stimulation resulted in a long-term change in thalamic activity.

In 1993, the same group published a report (42) of externalized neurostimulation in 23 patients: nine with generalized tonicoclonic seizures, three with focal motor and secondary generalized seizures, five with complex partial and secondary generalized seizures, and six with generalized tonic seizures and atypical absences. The investigators found that stimulation resulted in a significant decrease in seizure frequency and paroxysmal EEG waves in the patients with tonicoclonic seizures. They also found a substantial decrease in seizure frequency and paroxysmal EEG waves in patients with simple partial motor seizures. However, no significant changes were observed in patients with complex partial seizures or generalized tonic seizures. Overall, 12 of the 23 patients had at least a 50% decrease in seizure frequency, and one patient became seizure free.

The Velasco group presented a subsequent study of five patients with predominantly generalized tonicoclonic seizures (43). Patients first underwent a 3-month period of stimulation for 2 hours per day, using externalized electrodes and a portable stimulator. This was followed by a 3-month period with no stimulation. Patients then were implanted with internalized, bilateral Medtronic Itrel Model 7424 stimulation systems and followed for 7 to 33 months. During this period of long-term stimulation, the original intent was for the patient to turn on the neurostimulator for only 2 hours per day. However, patients were inadvertently turning the stimulation on and off, so the investigators changed the protocol to reflect a fixed setting of a 1-minute train every 9 minutes, alternating between the right and left sides, with intervals of 4 minutes, for 24 hours each day.

The equipment used for short-term versus long-term stimulation had different parameter capabilities, such that the pulse duration was 0.09 ms with the completely internalized system and 1.0 ms with the externalized system; and current intensity was 440 μA with the completely internalized system and 680 to 790 μA with the externalized system. Nevertheless, both types of systems decreased the frequency of generalized tonicoclonic seizures. Other seizure types, such as complex partial seizures and tonic seizure emerged de novo, or increased when compared with baseline. Paroxysmal EEG activity also increased during long-term stimulation.

Recently, the Velasco group reported long-term use of bilateral CM stimulation (60–130 Hz, 2.5–5.0 V, and 0.21–0.45 ms) in 49 patients with intractable seizures (40). Patients were followed for at least 6 months and as long as 15 years. The investigators concluded that CM stimulation efficiently controlled generalized tonicoclonic seizures, atypical absences, and tonic seizures, but did not efficiently control complex partial seizures. The degree of efficacy observed seemed to be correlated with the extent to which the electrodes were placed accurately in the CM (39, 40). The authors noted that when the neurostimulator was turned off, a residual effect on seizure control persisted, however, they pointed out that seizures eventually returned to baseline levels when stimulation was discontinued for long periods. The authors think that the effect observed was functional (as opposed to lesional), but acknowledge that the

neurophysiological mechanisms involved remain unknown (47).

In contrast to these open-label studies, Fisher et al. (12) studied the efficacy and safety of CM stimulation using a double-blind, cross-over design with seven patients. The investigators implanted completely internalized neurostimulators (Medtronic Itrel Model 7424), which patients were instructed to turn on for 2 h/d (90 μs pulses at a rate of 65 pulses per second, delivered in 1-minute trains every 5 minutes, with voltage set to half of the sensory threshold). Stimulation was on or off for 3-month periods, separated by a 3-month washout period. Although there was a 30% mean decrease in tonicoclonic seizure frequency during the stimulation-on period versus an 8% reduction during the stimulation-off period, this was not statistically significant. The double-blind portion of the study was followed by an open-label period with stimulation continuing for 24 h/d. During this follow-up, three of six patients with generalized seizures reported at least a 50% decrease in seizure frequency.

EPILEPTOGENIC TISSUE

In an effort to control temporal lobe seizures, several investigators have studied stimulation of foci in the hippocampus or amygdala. Velasco et al. (46) used bilateral depth electrodes or unilateral electrode grids to investigate the effect of hippocampal/amygdala stimulation (130 Hz, 0.2–0.4 mA) for 2 to 3 weeks in 10 inpatients with intractable temporal lobe seizures. Of the 10 patients, seven were implanted successfully in the hippocampal formation or parahippocampal gyrus and experienced no interruption in stimulation. These seven patients were seizure-free and had a significant decrease in the number of interictal EEG spikes at the focus after 5 to 6 days of stimulation. The same investigators studied the use of hippocampal stimulation during 3 to 4 months in three patients (two unilateral, one bilateral). In these patients, long-term stimulation blocked epileptiform activity, with no negative effect on short-term memory (38).

In a follow-up study, Velasco et al. (44) used bilateral depth or unilateral subdural electrodes to study 15 patients with intractable temporal lobe seizures. Of the 15 patients, 10 received continuous hippocampal/parahippocampal stimulation for 16 days, and five received sham stimulation. The investigators found that low-intensity, high-frequency stimulation (130 Hz, 0.21–1.0 ms, 2.5–3.5 V; approximately 200–300 μA) resulted in a highly significant decrease in both seizures and interictal spiking. Conversely, the sham stimulation had no effect.

The investigators think that the antiepileptic effect observed was at least partially caused by a physiological inhibition of the stimulated tissue, on the basis of observations related to "1) increased threshold and decreased duration, propagation, and blockage of clinical signs accompanied with the hippocampal afterdischarge; 2) flattening of hippocampal-evoked response recovery cycles, 3) single photon emission computed tomographic hypoperfusion, and 4) increased concentration of benzodiazepine receptor binding at the stimulated hippocampal region" (45). A follow-up report (7) examined γ-aminobutyric acid (GABA) tissue content, GABAA, benzodiazepine receptor levels, and neuronal density in the parahippocampal cortex of five patients who experienced spike or seizure reduction during subacute electrical stimulation (130 Hz, 450 μs, 200–400 μA) for 16 to 20 days in the parahippocampal cortex. Control tissue was brain from patients in whom electrical stimulation was not effective, from patients who did not receive stimulation, or from autopsy material from subjects without epilepsy. The patients in whom stimulation was effective had high GABA tissue levels and higher cell counts. The patients in whom stimulation was not effective showed increased benzodiazepine receptor levels. Patients who responded to electrical stimulation were younger, had a shorter seizure history, and had a lower prevalence of mesial temporal sclerosis. Therefore, the authors suggest that subacute electrical stimulation is more effective in patients with less severe epilepsy.

In contrast to the Velasco group's short-term use of depth and subdural electrodes, Vonck et al. (49) studied the efficacy of long-term amygdalohippocampal stimulation using bilateral, quadripolar DBS electrodes. The investigators followed three patients for a mean of 5 months and found that all had at least a 50% decrease in seizure frequency, with no side effects. The authors also determined that it was possible to use DBS leads (versus depth or subdural electrodes) to locate the ictal onset zone before stimulation, thus eliminating an additional surgical procedure.

A recent report by Kinoshita et al. (20) describes the effect of short-term cortical stimulation at or distant from the seizure focus in one patient. Interictal spikes were reduced after 50 or 0.9 Hz stimulation. The authors conclude that cortical stimulation has a suppressive effect on epileptic activity in human cortex.

SUBTHALAMIC NUCLEUS (STN)

Success of electrical stimulation of the subthalamic region for movement disorders generated interest in subthalamic stimulation for epilepsy. Animal work investigating the potential antiepileptic effect of STN stimulation has been published using several models, including kindled seizures (24), flurothyl seizures (24), kainic acid–induced seizures (25), and spontaneous absence seizures (48). The effect on the flurothyl seizures was frequency dependent (24). In the absence seizure model, only 130-Hz stimulation was examined and found to suppress ongoing spontaneous seizures in rats (48). In 1998 to 2000, Benabid and the group in Grenoble, France implanted electrodes in the STN of three patients with epilepsy. Benabid et al. (1) published a pediatric case study in which long-term (30 months), high-frequency STN stimulation at 130 Hz, with 90 ms pulses at 5.2 V resulted in an 80% reduction in the number and severity of seizures caused by focal cortical dysplasia. Chabardès et al. (2) reported results of STN stimulation (130 Hz, 60–90 ms, 1.5–5.2 V) of five patients (including the pediatric patient in the previous Benabid et al. study [1]), in which mean reduction of seizure frequency was 62.4% (range: 41.5–80.7%). Three of the five patients were classified as good responders, clearly benefiting from STN stimulation, one patient was classified a moderate responder (with a percentage of improvement that did not exceed 50%), and one patient was a poor responder (with no change in seizure patterns after 6 months of stimulation).

Loddenkemper et al. (25) studied STN stimulation in five patients with medication-resistant partial-onset seizures. Two of the patients experienced an 80% seizure-rate reduction after 16 months of therapy; however, the other three did not improve. Recent experience at the Cleveland Clinic was reported in 2004. In four patients (33), two improved and two showed little change in seizure frequency.

Gonzalez-Martinez et al. presented the results of STN stimulation in four patients at the AANS meeting in 2002, reporting that stimulation was successful in three of the four patients. One patient had an 82% reduction in seizures, another had a 61% reduction, and the third had a 30% reduction. In the fourth patient, stimulation had no significant effect on seizures.

Chapter 16, Neurostimulation for Epilepsy, Including a Pilot Study of Anterior Nucleus Stimulation (continued)

PILOT STUDY OF STIMULATION OF THE ANTERIOR NUCLEUS (AN) OF THE THALAMUS IN PATIENTS WITH EPILEPSY

Rationale for AN Stimulation

Animal work done after Cooper's clinical studies has tended to support the anterior nucleus as a reasonable target for electrical stimulation. Mirski and Ferrendelli mapped metabolic activation in guinea pig brain during seizures induced by pentylenetetrazol (28). Particularly active were the posterior hypothalamus in the region of the mammillary bodies and the anterior thalamus via its connection by the mammillothalamic tract (27). Lesions of the mammillothalamic tract increased the threshold for inducing seizures. Mirski and Fisher (29) used electrical stimulation of the posterior hypothalamus as a functional method of inhibition. The threshold for pentylenetetrazol-induced clonic convulsions was doubled in the presence of such stimulation. Effects of stimulation could be imitated by injection of the inhibitory GABA agonist, muscimol. Because the mammillary bodies were considered a difficult (although not necessarily impossible) stereotactic target, attention was directed to the AN, which are strongly linked to the posterior hypothalamus. Bilateral stimulation of the AN in rat inhibited cortical epileptiform EEG discharges after systemic administration of pentylenetetrazol (30). High-frequency stimulation in the range of 100 pulses per second was effective, whereas low-frequency stimulation of less than 10 pulses per second did not inhibit seizures when delivered either to the posterior hypothalamus or to the AN. Stimulation of the anterior thalamus also could inhibit seizures generated by the excitatory amino acid drug, kainic acid, given by systemic injection. Hamani et al. (14) recently

published animal work in a pilocarpine model of seizures in which the animals were subjected to unilateral or bilateral AN thalamotomies or unilateral or bilateral AN stimulation. The control animals received bilateral implants, but received no stimulation. After pilocarpine administration, 67% of the control animals developed status epilepticus within 15.3 ¡À 8.8 minutes. Bilateral stimulation significantly prolonged the latency to status epilepticus development, whereas no animal with bilateral thalamotomy developed seizures after pilocarpine administration. Unilateral stimulation or lesions produced effects that were no different from controls. On the basis of these results in animal model systems and of Cooper's early work in patients, a decision was made to further investigate stimulation of the AN as a treatment for clinical epilepsy.

Pilot Study

In 1998, a group of investigators began collaboration on the design of studies to explore the use of neurostimulation of the AN in patients with uncontrolled seizures. Each investigator wrote a feasibility study to be implemented through an investigator-sponsored investigational device exemption (IDE) or an institutional research study. Because the studies addressed similar patient populations, used similar device systems, and used similar methods in the collection of efficacy information (seizure counts from patient diaries), the results are presented collectively in this chapter. Investigators have presented their individual findings at recent American Epilepsy Society meetings and have individually published some of this data (15, 19).

The study designs prescribed intermittent high-frequency electrical stimulation of the AN in patients with intractable epilepsy. Bilateral programmable electrical stimulation devices (Medtronic ITREL II or Soletra) were implanted over the anterior chest wall, with bilateral stereotactic implantation of the multi-contact stimulation wires into the AN. Stimulation parameters were allowed to vary.

The patients (seven men, seven women; age range, 19¨C47 yr) were from four clinical sites and have been followed for at least 12 months. All patients had medically intractable epilepsy (see Table 16.1 for demographics). Patients returned for visits at intervals prescribed by each protocol, and seizure counts were monitored with the use of a patient diary. For purposes of this analysis, common time points were calculated and the results are presented for 12 weeks (3 months), 24 weeks (6 months), and 48 weeks (1 year) of follow-up. Changes in seizure frequency were assessed relative to a preimplantation (baseline) seizure frequency.

Three other patients from a single center (for which raw data was not available) also participated in this pilot study. One patient from this center experienced a subdural hemorrhage during the DBS implantation procedure and later had an intracerebral hemorrhage leading to increased intracranial pressure. As a follow-up, the patient underwent an evacuation of the subdural hemorrhage and a right frontal resection. The patient was hemiparetic and obtunded at 1-week after the event.

Primary Results

At 3-months of follow-up, the median reduction in total seizure frequency in the 14 patients was 63.8% (Table 16.2). Eight of the 14 patients (57.1%) experienced a ¡Ý50% reduction in their seizures (defined as responders). The magnitude of seizure reduction was similar at 3 months and 6 months of follow-up (63.8 versus 63.3%, respectively). At 6 months, the proportion of patients showing ¡Ý50% reduction in seizures remained stable at 57.1%. In a subgroup

of patients (n = 9 of 14) with seizures involving the temporal and/or frontal lobes, the median percent change in seizure frequency at 3 months was ¨C78.8% (standard deviation (SD), 40.8%; Table 16.3). In this subgroup, 77.8% were responders, and, at 6-months, the median change in seizure frequency was ¨C64.6% (SD, 65.2%; 66.7% responders). The smaller reduction in seizures (and associated increase in SD) observed at the 6-month follow-up can be attributed to a single patient, who exhibited a large temporary increase in seizure frequency during this period of treatment. During a 12-month period, the median reduction in total seizure frequency was -58.6% (Fig. 16.1). The responder rate was observed to be 66.7%. None of the patients could determine whether the stimulation was on or off at the parameters used for treatment. No patient became seizure-free for the full duration of follow-up, but several patients had elimination of seizures of the type leading to falls (19).

Thirteen of 14 patients experienced related adverse events, none judged to be serious (but note the serious adverse hemorrhagic event in one patient not followed by the pilot study). All events in the pilot study patients resolved, the majority with changes to medications or stimulation settings or spontaneously without corrective actions. The patients in the pilot study exhibited typical device-related adverse events: one patient had a lead fracture leading to a device explant; four patients had minor pain at the site of a device component; three patients complained of nonpainful tingling. Therapy-related events included a head laceration, depression (two patients), and increased irritability (two patients).

CONCLUSION

Electrical stimulation of the AN seems to be well tolerated; however, past experience with DBS implantation suggests some risk for serious adverse events, including hemorrhage and infection. In a review of DBS therapy for movement disorders, Loddenkemper et al. (25) compared the estimated risk of significant morbidity and mortality for electrode placement using stereotactic minimal invasive surgery (less than 2%) with the estimated risk of mortality in patients with uncontrolled seizures (0.5% per year). Preliminary evaluation of our epilepsy pilot study suggests clinical improvement in seizure control in this small group of patients, extending over a 12-month period. Because there was no control group, it is not known what proportion of the observed reduction in seizure frequency was caused by a placebo effect or a microlesion effect from the electrode implantation. A randomized, double-blinded, placebo controlled, parallel design study of AN stimulation is currently ongoing in the United States, and should serve to clarify the safety and efficacy of DBS for epilepsy.

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Fig. 16.1 Percent seizure reduction in the AN pilot patients. Blue bars indicate those patients with a presumed frontal or temporal lobe seizure focus origin.