Brain stimulation for intractable epilepsy: Anterior thalamus and responsive stimulation

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ABSTRACT

Despite medications, resective surgery, and vagal nerve stimulation, some patients with epilepsy continue to have seizures. In these patients, other approaches are urgently needed. The biological basis of stimulation of anterior thalamic nucleus and epileptogenic focus is presented. Results from two large randomized controlled trials Stimulation of Anterior Nucleus of Thalamus for Epilepsy (SANTE) and Neuropace pivotal trial are discussed. Neuromodulation provides effective treatment for a select group of refractory epilepsy patients. Future investigations into the mechanism underlying ‘response’ to brain stimulation are desired.

Key words
Anterior thalamic nucleus, brain stimulation, epilepsy, neuromodulation, responsive neuromodulation

Introduction

The management of epilepsy patients with drug-resistant epilepsy who are not candidates for resective surgery remains challenging and a large proportion of these patients continue to have seizures adversely affecting their quality of life. Several targets have been investigated in hopes to treat these patients with neuromodulation. Stimulation of both the anterior nucleus (AN) of thalamus and of presumed epileptogenic areas has been studied in large-scale randomized trials in the past decade. The European regulatory bodies have approved neurostimulation of the AN of the thalamus for treatment of patients with medically refractory epilepsy. Brain stimulation at other sites is currently under investigation. In the following section, we discuss the biological basis and clinical results of thalamic and extrathalamic stimulation. For details regarding the rationale and available clinical outcomes from stimulation of other targets, the reader may refer to comprehensive reviews published elsewhere.

Thalamic Stimulation

The anterior thalamic nucleus is the most well-studied target for stimulation in epilepsy with other reported thalamic targets being centromedian (CM) nucleus and reticular nuclei.

Why anterior nucleus of thalamus?
AN of the thalamus forms an integral part of the Papez’s circuit and has been implicated in the memory pathway. The input to this nucleus is mainly from the hippocampus and entorhinal cortex via the fornix and the mammillary bodies. AN in turn projects to a variety of cortical regions including cingulate gyrus, posterior parietal/insular region, and lateral temporal cortex. The role of this pathway in initiation and propagation of seizures has been extensively studied. Mirski et al., first reported their results of mammillothalamic tract lesioning in seizures induced by pentylenetetrazole (PTZ) in guinea pigs. Lesioning the mammillothalamic tract resulted in significant protection against both electrographic and clinical seizures, whereas lesioning of the surrounding nuclei (due to higher current settings) was not beneficial. In a follow-up study, the authors studied the effect of electrical stimulation of the mammillary nuclei in rat model of PTZ-induced seizures. The high-frequency (100 Hz) stimulation but not low-frequency (8 Hz) stimulation resulted in protection from PTZ-induced clonic seizures but failed to abolish the electrographical cortical response associated with PTZ administration. Their group further refined the stimulation target to AN and reported significant protection from PTZ-induced clonic seizure threshold as well as cortical response associated with it.
Several anatomical characteristics make AN a powerful target for stimulation.\[8,9\] This nucleus receives afferents from the hippocampus and the mesial temporal region, which are known to be highly epileptogenic. The other major afferent to AN is derived from bipolar projections from mamillary body, the other projection being the midbrain.\[9\] The AN projects diffusely to the cortex, especially the cingulate cortex, insula, and medial temporal lobe. Finally, the inhibitory influence by the reticular nuclei on the thalamocortical circuitry in the AN-cortical projections is rather scarce compared with that present in other thalamic nuclei.

**Technique of AN Targeting**

Patients with medically refractory seizures undergo evaluation by a multidisciplinary epilepsy team. Suitable candidates with what is deemed to be unresectable epilepsy are considered for implantation of anterior thalamic nucleus stimulator. Patients undergo frame placement followed by a magnetic resonance imaging (MRI). Direct targeting of the AN is carried out using standard stereotactic planning software.\[10\] As depicted in [Figure 1], AN of the thalamus can be visualized posterior to a distinct sagittally oriented mammillothalamic tract. The AN can be seen separated from the more posterior dorsomedian (DM) nucleus. We plan the trajectory in such a way that the most proximal electrode (contact three of Medtronic 3387 stimulating lead having a 10.5-mm span across four electrode contacts) sits well within the boundaries of AN. The bottom two contacts invariably reside in the DM nucleus. The implantation of electrodes is carried out under local or general anesthesia. Microelectrode recording can be used to study the neurophysiologic attributes of these thalamic neurons, though this is not essential [Figure 2].

**Clinical outcomes after high frequency AN stimulation**

The initial results from several small open label studies were encouraging and formed the basis of larger Stimulation of Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial.\[3\] The SANTE trial was a multicenter randomized controlled trial involving 110 participants who suffered from medically refractory partial seizures (including secondary generalized seizures). It enrolled patients between 18-65-years age who reported between 6-10 seizures per month and failed at least three different antiepileptic medications. The participants were required to be on between 1-4 seizure medications at the time of enrollment. All patients underwent implantation of leads in the AN of thalamus using stereotactic technique and placement confirmed with postoperative MRI. The electrode most central within the AN was chosen as anode and the battery case as cathode. One month after implantation, the participants were assigned either to 5 V or 0 V (no stimulation) stimulation for a 3-months blinded period. An assessment of change in seizure frequency recorded on daily diaries at the end of blinded phase served as the primary endpoint. Finally, stimulation was initiated for all participants and the unblinded cohort was observed for 9 month. Secondary outcomes included changes in seizure severity, quality of life, and detailed neuropsychological testing. The median percent decrease in seizure frequency at the end of blinded phase was 40.4% in stimulation group and 14.5% in the control group. The adjusted mean percent difference in the seizure frequency between the two groups was 29% after 3 months of blinded observation. During the long-term unblinded evaluation, this cohort experienced a 56% reduction in median seizure frequency as compared with baseline corresponding to a 50% responder rate of 54%.

**Nucleus-specific activation of cortical regions — implications for precise electrode positioning**

Our group has previously studied the specific cortical responses after stimulation of various thalamic nuclei using low-resolution

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**Figure 1:** Stereotactic atlas demonstrating the anterior and dorsal location of AN in a parasagittal section. Note the DM nucleus is ventral and posterior in location. AN = Anterior nucleus, DM = Dorsomedian

**Figure 2:** Intraoperative microelectrode recordings from anterior nucleus of thalamus (a) and the DM nucleus (b). Note the difference in bursting frequency between the two locations. AN = Anterior nucleus, DM = Dorsomedian
brain electromagnetic tomography (LORETA).[11,12] Bipolar low-frequency stimulation was administered to AN, DM, and CM nucleus.[13] A time-locked nucleus-specific pattern of cortical activation was observed with AN and DM nucleus stimulation. AN stimulation activated the ipsilateral cingulated gyrus, insular cortex, posterior parietal cortex, and lateral temporal neocortex. On the contrary, DM nucleus stimulation resulted in activation of ipsilateral orbitofrontal cortex, mesial and lateral frontal areas, and mesial temporal region. The stimulation of CM nucleus resulted in diffuse ipsilateral cortical stimulation. In a later analysis, we observed that stimulation within the AN might affect the pattern of cortical activation depending on the lead location (medial versus lateral).[10] An anodic stimulation of more medial and deeper contact (3−, 2+) resulted in more hippocampal and mesial temporal activation in contrast with a cathodic (3+, 2−) stimulation. These findings highlight the specific topographic representation of different cortical regions within thalamic nuclei. These observations, although preliminary, raise the possibility of potentially tailoring the site of thalamic stimulation according to the region-specific origin of seizures in each individual patient. More work is desired in this area to further confirm and substantiate these findings.

Direct stimulation of epileptogenic focus using responsive neurostimulation

The induction of seizure by direct electrical stimulation of epileptogenic cortical focus is well known. However, continuous cortical stimulation has been shown to inhibit the generation of after discharges and seizures. Direct cortical stimulation may increase seizure threshold by alterations of limbic circuits, representing a possible additional benefit of stimulation.[9] More studies are required to study whether these mechanisms are essential for successful seizure control with neuromodulation. Patient-reported seizure frequency continues to be gold standard outcome for epilepsy trials. Self-reported seizure frequency is unreliable.[14] Improved methods for electrographic detection and prediction of seizures shall enhance our ability to accurately study the treatment effects in future.

Neuromodulation has a proven track record for safety and efficacy in a variety of neurological disorders. The reversibility, ability to adjust, and tailor treatment make it an attractive treatment option for refractory epilepsy. The results of neuromodulation in epilepsy from large multicenter randomized trials are encouraging. With the recent regulatory approval, widespread treatment of larger numbers of patients with careful study of long-term efficacy shall establish it as a viable option for these patients. The long-term information recorded from the implanted electrodes provides an exciting research opportunity to study epileptogenesis in greater details in future.

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