Anterior Thalamic Nucleus Deep Brain Stimulation

Yu et al., demonstrated that high-frequency stimulation applied to the Anterior Thalamic Nucleus desynchronizes ipsilateral hippocampal background electrical activity over a broad frequency range, and reduces pathological epileptic discharges including interictal spikes and high-frequency oscillations. Furthermore, high-frequency stimulation of the anterior nucleus of the thalamus is capable of decoupling large-scale neural activity involving the hippocampus and distributed cortical areas.

They found that stimulation frequencies ranging from 15 to 45 Hz were associated with synchronization of hippocampal local field potentials, whereas higher frequencies (>45 Hz) promoted desynchronization of ipsilateral hippocampal activity. Moreover, reciprocal effective connectivity between the anterior nucleus of the thalamus and the hippocampus was demonstrated by hippocampal-thalamic evoked potentials and thalamic-hippocampal evoked potentials. In summary, high-frequency stimulation of the anterior nucleus of the thalamus is shown to desynchronize focal and large-scale epileptic networks, and here is proposed as the mechanism for reducing seizure generation and propagation.

This data also demonstrate position-specific correlation between deep brain stimulation applied to the anterior nucleus of the thalamus and patients with temporal lobe epilepsy and seizure onset zone within the Papez circuit or limbic system. The observation may prove useful for guiding electrode implantation to increase clinical efficacy [1)].

The anterior thalamic nucleus deep brain stimulation (DBS) is a palliative treatment for drug resistant epilepsy. The long-term efficacy and the optimal target localization for AN DBS are not well understood.

The anterior nucleus of the thalamus (ANT) modulates temporal lobe and hypothalamic activities, and relays information to the cingulate gyrus and entorhinal cortex.

Only short term RCTs on intracranial neurostimulation for epilepsy are available. Compared to sham stimulation, one to three months of anterior thalamic DBS (multi)focal epilepsy), responsive ictal onset zone stimulation (multi)focal epilepsy) and hippocampal DBS (temporal lobe epilepsy) moderately reduce seizure frequency in refractory epilepsy patients. Anterior thalamic DBS is associated with higher rates of self-reported depression and subjective memory impairment. SUDEP rates require careful monitoring in patients undergoing responsive ictal onset zone stimulatio [2)].

Case series

The efficacy of anterior thalamic nuclei (ANT) deep brain stimulation (DBS) in mitigating epileptic seizures has been established. Though the neuroprotection of ANT-DBS has been illustrated, the seizure mitigating mechanism of ANT-DBS has not been thoroughly elucidated. In particular, the effect of ANT-DBS on neurogenesis has not been reported previously. METHOD:

Thirty-two male Sprague Dawley rats were randomly assigned to the following groups: sham-DBS-

healthy (HL) (n=8), DBS-HL (n=8), sham-DBS-epilepsy (EP) (n=8) and DBS-EP (n=8). Normal saline and kainic acid were injected, respectively, into the former and later two groups, and seizures were monitored. One month later, rats received electrode implantation. Stimulation was exerted in the DBS group but not in the sham-DBS group. Next, all rats were sacrificed, and the ipsilateral hippocampus was dissected and prepared for quantitative real-time PCR (qPCR) and western blot analysis in order to measure neuronal nuclear (NeuN), brain-derived neurotrophic factor (BDNF), doublecortin (DCX) and Ki-67 expressions.

A 44.4% seizure frequency reduction was obtained after ANT-DBS, and no seizures was observed in healthy rats. NeuN, BDNF, Ki-67 and DCX expression levels were significantly decreased in the epileptic rats compared to healthy rats ($P<0.01$ or $P<0.05$). Obvious increases in NeuN, Ki-67 and DCX expressions were observed in epileptic and healthy rats receiving stimulation compared to rats receiving no stimulation (all $Ps<0.01$). However, BDNF expression was not affected by ANT-DBS (all $Ps>0.05$).

(1) ANT-DBS reduces neuronal loss during the chronic stage of epilepsy. (2) Neurogenesis is elevated by ANT-DBS in both epileptic and healthy rats, and this elevation may not be regulated via a BDNF pathway [3].

2016

A retrospective review of 16 patients who underwent AN DBS.

Krishna et al selected only patients with reliable seizure frequency data and at least a 1-year follow-up. They studied the duration of the seizure reduction after DBS insertion and before stimulation (the insertional effect) and its association with long-term outcome. They modeled the volume of activation using the active contacts, stimulation parameters, and postoperative imaging. The overlap of this volume was plotted in Montreal Neurological Institute 152 space in 7 patients with significant clinical efficacy.

Nine patients reported a decrease in seizure frequency immediately after electrode insertion (insertional or microthalamotomy effect). The duration of insertional effect varied from 2 to 4 months. However, 1 patient had a long-term insertional effect of 36 months. Altogether, 11 patients reported >50% decrease in seizure frequency with long-term stimulation. The most common pattern of seizure control was immediate and sustained stimulation benefit (n = 8). In patients with long-term stimulation benefit, the efficacious target was localized in the anteroventral AN in close proximity to the mammillothalamic tract.

AN DBS is efficacious in the control of seizure frequency in selected patients. An insertional effect is commonly observed (56%). The most efficacious site of stimulation appears to be the anteroventral AN [4].

2008

In a open-label pilot study of Electrostimulation of the ATN, Lim et al investigated four cases of intractable epilepsy (one man with generalized seizure, and three woman with partial seizure and secondary generalization; age range, 18-45 years), with a follow up of 2 years. Under the indication of

bilateral or nonlocalized epileptic foci, each patient underwent stereotactic implantation of a quadripolar stimulating electrode in the bilateral ATN, guided by single-unit microelectrode recording. The stimulator was turned on after a sham period of 2-4 weeks. Seizure frequency was monitored and compared with the pre-implantation baseline. Twenty-one similar cases reported in the literature during the past 20 years were reviewed.

Insertion into and stimulation through electrodes implanted in the ATN decreased seizure frequency, with a mean reduction rate of 49.6% in the current series. Two patients had seizure reductions of > or = 60%, with complete remission achieved in one patient. These findings were consistent with those in four other investigations of intractable epilepsy, which showed an overall rate of 45-55% in seizure reduction. One of our patients suffered a small frontal hemorrhage, and a second patient had extension erosion over the scalp; however, no resultant major or permanent neurological deficits were observed.

Based on the study results and literature review, it appears reasonable to conclude that long-term ATN stimulation is a safe and effective treatment for seizure reduction in patients with intractable epilepsy [5)].

2007

Four patients underwent stereotactic implantation of quadripolar stimulating electrodes in the bilateral ANT, guided by single-unit microelectrode recording. Electrode location was confirmed by postoperative magnetic resonance imaging (MRI). The stimulator was activated 2-4 weeks following electrode insertion; initial stimulation parameters were 4-5 V, 90-110 Hz, and 60-90 micros. Seizure frequency was monitored and compared with preimplantation baseline frequency. Intelligence quotient (IQ) test and auditory P300 response were performed before and after implantation of electrodes.

Four patients (one man with generalized seizures, and three women with partial seizures and secondary generalization) aged 18-45 years old were studied with mean follow-up period of 43.8 months. The four patients demonstrated a sustained effect of 49% (range, 35-76%) seizure reduction to ANT stimulation. Simple insertion of DBS electrodes (Sham period, no stimulation) produced a mean reduction in seizures of 67% (range, 44-94%). One patient was seizure-free for 15 months with anticonvulsant medications. One patient had a small frontal hemorrhage and a second patient had extension erosion over scalp; no resultant major or permanent neurological deficit was observed. Preoperative IQ index and auditory P300 were not significantly different with those after electrodes implantation.

Implantation of electrodes in the ANT and subsequent stimulation is associated with a significant reduction in seizure frequency. However, the study could not differentiate whether the implantation itself, the subsequent stimulation or postimplantation drug manipulation had the greatest impact. These experimental results prompt further controlled study in a large patient population [6)].

2004

Kerrigan et al report an open-label pilot study of intermittent Electrostimulation of the anterior nucleus of the thalamus in five patients (three men, two women; age range, 24-47 years), with follow-up between 6 and 36 months. All patients had intractable partial epilepsy. Four of the five patients also had secondarily generalized seizures. Stimulation was delivered by bilateral implantable,

programmable devices by using an intermittent, relatively high-frequency protocol. Stimulation parameters were 100 cycles per second with charge-balanced alternating current; pulse width, 90 ms; and voltages ranging between 1.0 and 10.0 V. Seizure counts were monitored and compared with preimplantation baseline.

Four of the five patients showed clinically and statistically significant improvement with respect to the severity of their seizures, specifically with respect to the frequency of secondarily generalized tonic-clonic seizures and complex partial seizures associated with falls. One patient showed a statistically significant reduction in total seizure frequency. No adverse events could clearly be attributed to stimulation. None of the patients could determine whether the stimulator was on or off at these parameters.

Electrostimulation of the ANT appears to be well tolerated. Preliminary evidence suggests clinical improvement in seizure control in this small group of intractable patients. Further controlled study of deep brain stimulation of the anterior nucleus is warranted [7)].

1)
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