
Neuromodulation Therapy: Nonmedical, Nonsurgical Treatment for Intractable Epilepsy

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<http://dx.doi.org/10.5772/57441>

1. Introduction

Neuromodulation therapy has been tried for patients with many neuropsychiatric disorders such as Parkinson's disease, tremor, obsessive-compulsive disorder, depression, intractable pain, or addiction etc [1]. In epilepsy, this kind of treatment has been applied to treat patients with intractable epilepsy for decades who are not controlled by antiepileptic drugs (AEDs) nor surgical candidates. Historically, the earliest report of the use of electrical brain stimulation to control seizures in humans showed that focal electrical cortical stimulation could stop both normal EEG rhythms and spontaneous epileptiform discharges [2].

Vagal nerve or deep brain stimulation (e.g. thalamic stimulation) is indirect neural stimulation method, which delivers high frequency electrical stimulation indirectly to the epileptic brain via vagal nerve or thalamus, regardless of seizure foci [3,4]. This kind of stimulation is called open loop system since the stimulation is delivered intermittently and regularly without external cues (e.g. seizure onset). In contrast, closed loop system has been more recently applied in which the stimulation is directly applied to the seizure focus when seizure activity actually occurs. To do this, the stimulation system is combined with early seizure detection algorithm and activated automatically to deliver the stimulation only when the seizure activity is detected [5]. Responsive neurostimulation is an example of the closed loop system, which has been tested in recent clinical trials. While these methods need surgery to implant the electrodes for stimulation, noninvasive stimulation can be tried too especially using low frequency repetitive transcranial magnetic stimulation. In this method, the stimulation has been applied directly to the seizure focus but without combining seizure detection system so far. Although the exact therapeutic mechanism is not fully understood yet, these kinds of treatments have been reported to reduce seizures in intractable epilepsy patients.

In this chapter, various kinds of neuromodulation methods are introduced with the results of treatment efficacy and side effects from previous clinical trials in intractable epilepsy patients. In addition, recent clinical and basic researches to investigate possible therapeutic mechanisms are summarized. Future study directions what should be solved to improve the therapeutic efficacy and/or reduce adverse effects are also discussed.

2. Types of neurostimulation

2.1. Open loop indirect stimulation thru the peripheral nerve: Vagal nerve stimulation

Vagal nerve stimulation (VNS) is the first and the only FDA approved neurostimulation therapy in epilepsy, which has been tried in various seizure types and epileptic syndromes [3, 4]. The most famous clinical trials using VNS are randomized controlled trials of E03 [6] and E05 [7] in 114 and 119 patients, which provided an important evidence for FDA approval of VNS therapy in 1997. The stimulation paradigm was consisted of both high and low stimulations. The high stimulation was 3.5 mA, 30 Hz, 500 μ s pulsewidth, with 30 s on time and 5 min off time, whereas the low stimulation was similar output currents with 1 Hz frequency rate, 130 μ s pulsewidth, on time of 30 s, and off time of 180 min.

Mechanism of action has been suggested based on the animal experiments and human researches using various electrophysiological and functional brain imaging studies [8]. It is believed that VNS modulates mainly subcortical neural network that influences larger cortical areas modifying synaptic connections. However, the exact mechanism of action how VNS reduces seizures is still under investigation, which needs future studies.

2.2. Open loop indirect stimulation into the brain: Deep brain stimulation

Stimulation of anterior nucleus of thalamus (ANT) in epilepsy patients was reported to have therapeutic effects earlier [9], and the results from double blind multicenter clinical trials have been reported recently in 110 epilepsy patients from 17 epilepsy centers [10]. In this, so-called, SANTE trial (Clinical Trials. Gov. NCT00101933), the efficacy showed 40.4% of seizure reduction during the 3 months of blinded phase in the treatment group, for both complex partial and secondarily generalized tonic clonic seizures, compared with 14.5% in the control group. Thirty-three patients with temporal lobe epilepsy (TLE) showed better response (44% of seizure reduction during the blinded phase compared with 22% reduction in TLE patients with standard treatment). Interestingly, the seizure reduction rate was increased over time in the open label period, which showed 41% median seizure reduction at 13 months. After 2 years of seizure follow-up, treated patients showed median 56% reduction in seizure frequency and 54% of patients obtaining more than 50% seizure reduction. Although there was a concern about depression (14.8%) or memory impairment (13.0%), DBS was generally safe without serious side effects such as intracranial hemorrhage, infection or death.

Possible role of thalamic DBS in epilepsy is that the thalamus might be a relay station that inhibits or disrupts epileptic seizures spreading via thalamocortical neural network. Actually,

ANT is believed to desynchronize seizure discharges thus inhibit seizure spread from hippocampus or neocortex to other brain areas [11]. Animal studies have provided evidence that low frequency ANT stimulation increases synchronization of the cortical EEG by recruiting rhythmic thalamocortical activities whereas high frequency stimulation leads to desynchronize EEG rhythms that will be effective for reducing seizures [12].

2.3. Closed loop direct stimulation to the seizure focus: Responsive neurostimulation

Closed loop neurostimulation is a method that responds immediately after the seizure is detected by automated seizure detection algorithm. Early stimulation after the seizure onset is expected to stop the seizure during the early stage before the seizure propagates to remote cortical areas thus evolving to secondarily generalization. Responsive neurostimulation (RNS) is the most recently tried one, which is a combination of early seizure detection and automated neurostimulation based on detection results from real-time EEG analysis. The RNS system requires an electrode implantation to the seizure focus for both seizure detection and electrical stimulation. Once the detection algorithm detects a seizure, high frequency electrical stimulation is applied automatically to abort the seizure as early as possible.

The rationale for RNS is based on the study showing that cortical stimulation could terminate afterdischarges (ADs) during functional mapping [13]. ADs, unnecessary but inevitable events, are very similar to ictal EEG discharges during seizures although they are induced activities from high frequency electrical stimulation, not spontaneously occurred ones. Interestingly, brief bursts of electrical cortical stimulation that had induced ADs if delivered longer, could stop ADs immediately in many occasions. It worked better when the stimulation was applied briefly shorter than one second and more promptly with shorter stimulation latency within several seconds after ADs occurred [14]. After this, unblinded clinical studies were conducted in adults with refractory partial epilepsy mainly for safety and feasibility [15]. And then, a double-blind, multicenter, randomized controlled clinical trial of RNS was conducted, and the efficacy was reported recently [16].

The controlled clinical trial was performed in 191 patients from 32 epilepsy centers who were diagnosed with highly drug-resistant partial epilepsy and had one or two focal seizure foci. The stimulation parameter for RNS was the amplitude of 0.5-12 mA, the pulse width of 40-1000 μ s, and the frequency of 1-333 Hz. The average seizure frequency was significantly improved with 38% of seizure reduction in the active RNS group compared to 17% in the sham control group during the initial 12 weeks of blinded phase. During the open label period, seizure frequency was reduced in the sham control group in the initial blinded phase to the level of those in the treatment group. As with ANT stimulation, there was further progressive improvement during the open label period with median seizure reduction rate up to 50% after two years [16]. Based upon these results, RNS has been approved by FDA in November 14, 2013, for patients with drug-resistant epilepsy.

Choosing the best early seizure detection algorithm is very important for successful treatment in RNS [17]. Various EEG quantification methods have been tried for seizure prediction or early seizure detection, which include correlation dimension [18-21], correlation density [22], similarity index [23-25], phase synchronization [26-28], accumulated energy [29], complexity

or synchrony [30]. Improvement of early detection algorithm will be one of the most important requirements to make RNS more useful therapeutic option in treatment of intractable epilepsy.

More effective stimulation parameters have been tested in animal researches. Among the stimulation parameters, the frequency has been known as the most important factor to inhibit seizure activity better [31-33]. Several types of closed-loop brain computer interface systems have been tested in epilepsy animal model with improved seizure detection and reduced false detection rates [34].

2.4. Open loop direct stimulation to the seizure focus: Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is well established neurophysiologic study tool that has been used in neuroscience research and various clinical fields. TMS can be used in single, paired or repetitive trains, and repetitive stimulation [35]. Repetitive TMS (rTMS) is a safe and noninvasive method to alter neuronal functions thus applying to various clinical disorders such as stroke, pain, epilepsy etc. While other neural stimulation methods listed above need surgery to implant the electrodes for stimulation, TMS is a noninvasive stimulation without surgical intervention that is one of the greatest advantages when considered as a chronic treatment method clinically. In this method, the stimulation has been applied directly to the seizure focus but without combining seizure detection system so far.

Low frequency rTMS (less than 1 Hz) is known to inhibit cortical excitability [36,37] while high frequency rTMS (5-20 Hz) increases cortical excitability [38]. Low frequency rTMS, especially using 1 Hz stimulation, has been tried for refractory epilepsy. In a randomized clinical trial in 21 epilepsy patients with cortical developmental malformation, 1 Hz rTMS significantly reduced the number of seizures in the active group compared to the sham control group for at least 2 months [39]. A meta-analysis showed that low frequency rTMS has favorable antiepileptic effects, especially in patients with cortical dysplasia or neocortical epilepsy, with an effect size of 0.71 and 95% confidence interval at 0.30-1.12 [40]. Another established form of rTMS protocol is theta-burst stimulation (TBS), a burst of three 50-Hz pulses in trains repeated at 200-ms intervals. Continuous TBS (cTBS) consists of burst trains for 20-40 s that has an inhibitory effect on corticospinal excitability. On the other hand, intermittent TBS (iTBS), burst trains with a duration for 20-40 s for about 190 s, repeated in every 10 s, has a facilitating effect on corticospinal tract [41]. TBS is known to have longer effects than conventional rTMS paradigms that can be useful for clinical application, possibly including epilepsy, that will need further verification in controlled clinical trials.

3. Unsolved questions and future direction

In this chapter, various kinds of neuromodulation methods are introduced with a review of previous clinical trials and basic researches. We have reviewed important findings from previous clinical trials and other basic researches that contribute to our understanding of possible therapeutic mechanisms of neuromodulation for epilepsy treatment, as well as recent

technical notes to improve accurate and prompt seizure detection. Several important issues remain to be solved, however, such as ideal targets and stimulation parameters, and the optimization in each seizure type and/or epileptic syndrome. Investigation of the underlying therapeutic mechanisms requires more translational studies in the future that link basic researches to relevant clinical trials.

3.1. Targets for neurostimulation

Several targets have been tried to treat focal or generalized epilepsy patients who are refractory to medical or surgical treatment, including vagus nerve, ANT, hippocampus, and various cortical locations according to epileptic foci. Targeting the hippocampus sounds reasonable in mesial temporal lobe epilepsy, which has been tested mostly in the form of RNS [17,42].

Other brain structures have been tried as well to control seizures; for examples, the centro-median nucleus of thalamus, the subthalamic nucleus, the substantia nigra reticulata, the caudate nucleus, the cerebellum, the posterior hypothalamus, and the caudal zona incerta [43]. Subthalamic nucleus, cerebellum, and trigeminal nerve stimulations have been considered as possible targets for intractable epilepsy especially for generalized epilepsy patients. The subthalamic nucleus has been tested clinically mainly for movement disorders so far, but it is also known as a relay station in the nigral system for epilepsy control that involves in seizure propagation and secondary generalization in animal researches [44,45], which has been the rationale to suggest its usefulness in epilepsy. The cerebellar stimulation was tried earlier [46], and reevaluated recently in a double-blind, randomized controlled pilot study on five patients with medically refractory motor seizures, that showed its beneficial effects especially for generalized tonic-clonic seizures [47]. The trigeminal nerve is one of the cranial nerves that connects to the large subcortical brain areas. Early studies suggesting potential clinical benefits of trigeminal nerve stimulation for epilepsy patients have been reported [48,49].

3.2. Stimulus parameters

Optimization of stimulus parameters is very important to improve the efficacy of seizure control by neuromodulation. In animal experiments, low frequency electrical stimulation can decrease neural excitability and seizure activity in both in-vivo and in-vitro models of epilepsy and stimulation effects increase synaptic inhibition via long-term depression (LTD). In epilepsy patients, low frequency electrical stimulation applied to ictal onset zones reduced seizure frequency. Low frequency electrical cortical stimulation was reported to have an inhibitory effect on epileptic focus in mesial temporal lobe epilepsy [50]. However, unwanted seizures may occur as side effects of stimulation, which needs to be solved in the future studies.

High frequency electrical stimulation has been applied both indirect stimulation to the epilepsy network via both VNS and DBS, and direct stimulation to the seizure focus via RNS [4,5]. For VNS, stimulation around 30 Hz is effective to reduce seizures. For DBS, higher frequency stimulation about 120 Hz was also reported to reduce seizures. Various stimulation frequencies between 1 and 333 Hz have been used for RNS.

Intermittent versus continuous stimulation also has been discussed. Interestingly, intermittent stimulation around 1.68% of the time was reported to be effective although less than when the device was activated 50% of the time [51].

Standardization of stimulation parameters is also needed for individual seizure types and/or specific epileptic syndromes. Future studies in both basic and human researches to improve treatment efficacy based on therapeutic mechanisms will be mandatory for practical use of neuromodulation therapy in intractable epilepsy patients.

3.3. Unveiling therapeutic mechanism

Epileptic seizure is characterized by a brief, transient increase of abnormally excitable and synchronized activities in neural network. Interestingly, and somewhat paradoxically, the activity can be eliminated by neurostimulation, often using very high frequency especially in the VNS, DBS, and RNS.

From the observation that electrical stimulation suppressed ADs and seizures throughout the course of kindling, that indicates a strong antiepileptogenic effect. While the kindling seems very similar to long-term potentiation (LTP), electrical stimulation acts like LTD or depotentiation, which might explain how neuromodulation controls epilepsy in terms of the mechanism of action. Interestingly, LTP and kindling have many similarities although cellular mechanisms are different in many respects. On the other hand, prolonged electrical stimulation can elicit LTD that can be opposite phenomenon to LTP where the synaptic transmission is reduced. That is, electrical stimulation can depotentiate synapses that underwent LTP already. However, electrical stimulation can induce enhancement of synaptic strength like LTP, which needs further studies to verify stimulation parameters based on the therapeutic mechanisms [52].

Long lasting hyperpolarization was also suggested as a possible mechanism to reduce seizures in low frequency deep brain electrical stimulation, mediated via GABA_B inhibitory postsynaptic potentials and/or slow after-hyperpolarization [53]. High frequency sinusoidal fields were reported to suppress epileptiform activity in rat hippocampal slices, which was associated with potassium efflux and following depolarization block [54].

The rationale behind chronic intermittent stimulation is to modulate the background brain activity so that epileptic seizures are less likely to occur. This could be either reducing network hypersynchronization or modulating specific pathways involving epileptic network [5]. The mechanisms are expected to be distinct from those of antiepileptic drugs in which the antiepileptic effects are mediated by alterations of cellular and/or synaptic functions. Interestingly, many clinical studies using VNS, DBS, and RNS showed that the stimulation effects were improved over time for up to two years. These observations suggest the possibility that acute seizure inhibition mechanism might be different from chronic prevention or antiepileptogenic mechanism, which is actually an ideal goal of any antiepileptic treatments.

4. Conclusion

Recent progress of technological and methodological advances in neuromodulation leads to high possibilities for using these methods more widely to treat intractable epilepsy. These technological advances have been introduced to generate more practical ways of neuromodulation methods for chronic use in clinical fields. One of the remarkable advances is the combination of neuromodulation with early seizure detection algorithm. Along with results from basic researches in animals and humans, the underlying therapeutic mechanisms have been investigated as well. In addition, studies have been performed to improve the therapeutic efficacy by optimizing stimulation parameters, and accuracy of early seizure detection.

Advances in the field of neuromodulation reviewed here, as well as general advances in neuroscience, would provide us a new insight in the treatment of intractable epilepsy. Furthermore, advances in neuromodulation in epilepsy therapy could allow us progress in related neuroscience and clinical fields, especially to investigate and modulate complex neural network based on normal and abnormal brain functions.

Acknowledgements

This work was supported by the Ewha Global Top 5 Grant 2011 of Ewha Womans University and by the Korean Science and Engineering Foundation (KOSEF) Grant funded by the South Korean government (MOST) (R01-2007-000-11080-0), and by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology [R01-2011-0015788 and KRF-2009-006-5721].

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