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Review

Controlling Cerebellar Output to Treat Refractory Epilepsy

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Generalized epilepsy is characterized by recurrent seizures caused by oscillatory neuronal firing throughout thalamocortical networks. Current therapeutic approaches often intervene at the level of the thalamus or cerebral cortex to ameliorate seizures. We review here the therapeutic potential of cerebellar stimulation. The cerebellum forms a prominent ascending input to the thalamus and, whereas stimulation of the foliated cerebellar cortex exerts inconsistent results, stimulation of the centrally located cerebellar nuclei (CN) reliably stops generalized seizures in experimental models. Stimulation of this area indicates that the period of stimulation with respect to the phase of the oscillations in thalamocortical networks can optimize its effect, opening up the possibility of developing on-demand deep brain stimulation (DBS) treatments.

Neurostimulation for Drug-Resistant Epilepsy

Epilepsy, defined as the occurrence of recurrent, unprovoked seizures, is one of the most common neurological disorders, affecting approximately 65 million people worldwide [1,2]. The disorder can have devastating effects on one's life, not only directly as a result of clinical effects, which may include injury and hospitalization, but also due to socioeconomic effects such as social isolation, stigmatization, educational difficulties, and unemployment. These various consequences of epilepsy result in high comorbidity with psychiatric disorders and increased suicide rate [3]. Anti-epileptic drugs (AEDs), which induce considerable side effects, provide a decrease in seizure occurrence of more than 50% in ~70% of epilepsy patients [2–5]. In the remaining 30% of patients the next line of treatment is often invasive. If the focus (or foci) of the seizures can be localized, and if the tissue involved is accessible and **non-eloquent** (see Glossary), patients can be treated by neurosurgical resection [6]. If patients cannot be operated upon or show refractory epilepsy following resection, they are potential candidates for neurostimulation. This class comprises ~30% of the medication-resistant cases.

Selecting the optimal stimulation target to treat these severely affected patients is a challenging task. However, the current surge of data from various clinical trials on the impact of vagal nerve stimulation (VNS) and deep brain stimulation (DBS) in the thalamus or epileptic focus reveals that, specific neurostimulation paradigms have therapeutic value for various types of drug-resistant epilepsies (Box 1). Moreover, recent experimental evidence indicates that neurostimulation of the cerebellum can have potential therapeutic benefits [7,8]. In contrast to the cerebellar cortex, which has been probed for treatment of epilepsy since the dawn of DBS [9], the CN have rarely been targeted for seizure control in epilepsy patients [10,11]. However, the CN are in a key position to affect a wide range of thalamic nuclei (Box 2) and can therefore, in our opinion, be of potential therapeutic interest for the treatment of particular types of epilepsy. In the current review, we address why the CN should be targeted and how the impact of the CN on thalamocortical networks should be studied in experimental epilepsy models. We aim to provoke a re-evaluation of the potential use of cerebellar neurostimulation to stop epileptic seizures.

Trends

Electrical neurostimulation is commonly applied in patients with drug-resistant epilepsy, but the optimal stimulation sites for each of the type of seizures remain to be identified and may be outside the epileptic focus.

The most important issues for identifying the optimal stimulation site are its anatomical connections, its impact on the neuronal spiking patterns of downstream targets when stimulated, and its accessibility.

Emerging data from optogenetic studies in mouse models of various epilepsies indicate that controlling the cerebellar output can be effectively used to stop several types of seizures.

By selectively increasing or decreasing the spiking activity of CN neurons, the firing of downstream neurons in thalamocortical networks can be efficiently modulated so as to disrupt epileptic activity.

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Box 1. Common Neurostimulation Treatment in the Clinic

Vagal Nerve Stimulation

Regardless of the type of seizures, the first line of neurostimulation treatment for refractory epilepsy [85] is VNS. A meta-analysis on the results of VNS in thousands of epilepsy patients revealed that, on average, 50% of patients showed a 51% reduction in seizure frequency, with the important side notes that generalized seizures are more effectively treated than focal seizures and that only few patients will become seizure-free following VNS treatment [85]. The mechanisms underlying the therapeutic effect of VNS have only recently been described to rely at least partially on the prevention of hypersynchronized neuronal activity (Box 2) [86–88].

DBS for Partial Seizures

Apart from VNS, various other neurostimulation trials have been conducted to treat refractory epilepsy of various types [89]. The SANTE study aimed to treat frontal and temporal lobe partial seizures in patients with drug-resistant epilepsy by stimulating the anterior nucleus of the thalamus (ANT) [90]. High-frequency stimulation effectively lowered seizure frequency by ≥50% in 43% of patients during the first year, and by 69% in 68% of patients in the fifth year of stimulation [91]. These results indicate that continuous, in other words non-responsive, ANT stimulation is to some extent effective in treating patients with an epileptic focus in the frontal and temporal lobes.

In addition to this open-loop approach, responsive neurostimulation has also been tested in patients with refractory partial seizures. Patients enrolled in the 'Neuropace' study received patient-tailored electrical stimulation in the epileptic focus upon the onset of epileptogenic activity patterns in frontal or temporal lobe [92]. The recently published findings revealed a stable level of seizure reduction up to 66% [80]. Together these data indicate that partial seizures originating from the frontal or temporal lobes may be adequately treated using responsive focal stimulation and continuous stimulation of the interconnected anterior thalamus nucleus.

Thalamic DBS for Primarily Generalized Seizures

Another form of refractory epilepsy is primarily generalized epilepsy. Neurostimulation treatment for these types of seizures requires a structure that projects to wide areas of the cerebral cortex. The centromedian (CM) thalamic region projects diffusely to agranular layers of cerebral cortices as well as to subcortical structures [93–95]. A recent single-blind study on the effects of high-frequency CM stimulation reported that all six patients with generalized epilepsies showed reduced occurrence of seizures [96], which was in line with earlier findings of the Velasco group on dozens of patients [97–101].

Glossary

Closed-loop optogenetic stimulation: light-sensitive ion-channels in the neuronal membrane, which can manipulate action potential firing, can be automatically activated following GSWDs detection with a computer algorithm.

Diffusion tensor imaging (DTI): magnetic resonance imaging based sequence that allows visualization of white matter tracts.

Generalized spike and wave discharges (GSWDs): representation of epileptic thalamocortical oscillations in EEG or electrocorticographic (ECoG) recordings reflecting a synchronous burst of activity in cortical neurons (spike) followed by a pause in firing (wave).

Kindling: chemical or electrical manipulation that initially evokes limited neuronal responses that evolve into epileptic seizures.

Non-eloquent brain region: areas in the central nervous system that, if removed, will not result in loss of sensory processing or linguistic ability, or paralysis.

Given the outcome of this evaluation we propose that single-pulse stimulation of CN should be considered for novel **closed-loop** approaches that refine on-demand seizure control.

Cerebellar Stimulation – The Cortex

From the first half of the 20th century, electrophysiological recordings have revealed that, in addition to the thalamus and cerebral cortex, the cerebellum also shows oscillatory neuronal activity during generalized epileptic seizures (Boxes 3,4). Following the work of Moruzzi in the 1940s on the regulatory effect of cerebellar stimulation on clonic motor behavior [12], several studies were undertaken to investigate the potential use of stimulation of the cerebellum to stop epileptic seizures of various types in rats, cats, and monkeys, yielding mainly positive results (as reviewed in [13]). Subsequent studies on electrical stimulation of the cerebellum in epileptic patients indicated that stimulation of the cerebellar cortex could effectively stop psychomotor, generalized tonic-clonic, myoclonic, partial, or focal seizures (Table S1 in the supplemental information online) [9,14–21]. Nevertheless, two of three subsequent and independently conducted double-blind studies on the effects of cerebellar cortical stimulation in epilepsy patients reported a much more limited and inconsistent effect, shifting the general opinion away from cerebellar cortex stimulation [22–24]. In these studies, the efficacy of stimulation treatment appeared to depend on many factors, such as the location and size of cerebellar cortical stimulation sites, and the type and severity of seizures involved.

There are several reasons that could underlie the variable and inconsistent effects of cerebellar cortex stimulation on epileptic seizures. First, the overall density and complexity of the deeply penetrating foliation of the cerebellar cortex, and the pronounced convergence of the inhibitory Purkinje cell projections to CN neurons, complicate the entrainment of CN firing by cortical stimulation (Figure 1) [25,26]. These limits prevent effective reduction of oscillatory firing in the