Treating Seizures With Low-Frequency Electrical Stimulation

Hippocampal Low-Frequency Stimulation Prevents Seizure Generation in a Mouse Model of Mesial Temporal Lobe Epilepsy

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Mesial temporal lobe epilepsy (MTLE) is the most common form of focal, pharmacoresistant epilepsy in adults and is often associated with hippocampal sclerosis. Here, we established the efficacy of optogenetic and electrical low-frequency stimulation (LFS) in interfering with seizure generation in a mouse model of MTLE. Specifically, we applied LFS in the sclerotic hippocampus to study the effects on spontaneous subclinical and evoked generalized seizures. We found that stimulation at 1 Hz for 1 hour resulted in an almost complete suppression of spontaneous seizures in both hippocampi. This seizure-suppressive action during daily stimulation remained stable over several weeks. Furthermore, LFS for 30 minutes before a proconvulsive stimulus successfully prevented seizure generalization. Finally, acute slice experiments revealed a reduced efficacy of perforant path transmission onto granule cells upon LFS. Taken together, our results suggest that hippocampal LFS constitutes a promising approach for seizure control in MTLE.

Commentary

One type of acquired epilepsy called mesial temporal lobe epilepsy (MTLE) is the most common form of focal, drug resistant epilepsy in adults (~20% of all epilepsies). It is thought to arise from an initial insult during childhood such as complex febrile seizures or head trauma. Mesial temporal lobe epilepsy is often associated with hippocampal sclerosis (HS, 50%-60% of cases), which is characterized by neuron loss and gliosis, and creates an epileptic focus.1 The standard of care for MTLE with HS, often called mesial temporal sclerosis, is surgical resection of the epileptic foci. This procedure has excellent outcome with about 60% of the patients becoming seizure-free and an additional 20% displaying a significant reduction of seizures, while the remaining see no improvement. However, a subset of patients cannot undergo surgery or have neurosurgical complications. There is thus a critical need to develop novel treatment options for MTLE patients with HS.

A recent treatment alternative for epilepsy that has received increasing attention is electrical stimulation, including responsive neurostimulation and deep brain stimulation, which typically involves high-frequency stimulation (HFS, 130-200 Hz) primarily in the hippocampus or the anterior thalamic nucleus. This procedure is reversible and less invasive than hippocampal resection. A few studies reported that chronic hippocampal HFS reduced seizure frequency by more than 50% in more than half of the patients (for references see the study by Lim et al2). Nevertheless, overall neurostimulation with HFS has mixed results in many patients, which may relate to disruption or damage to the neuronal network and different degrees of cell loss and gliosis. Intriguingly, a recent study in MTLE humans with HS reported that low-frequency stimulation (LFS, 5 Hz) in the hippocampus reduced seizure activity by >50% in 2 patients without implantation- or stimulation-related side effects. Clearly, more preclinical studies are needed to identify the cell types or intact networks that mediate these effects and to examine the effectiveness of different types of stimulation of these network on seizure frequency and severity. There is also a need to develop a mouse model that recapitulates the variability observed in the human population.

The present study by Paschen et al addressed some of these issues. They modified a well-accepted model of MTLE with HS, the unilateral kainic acid mouse model that recapitulates the human pathology and exhibits spontaneous recurrent, subclinical seizures. Although these mice rarely have spontaneous clinical seizures, HFS can be applied to evoke seizures that resemble spontaneous generalized seizures with typical myoclonic movements. Using different concentrations of kainic acid, animals displayed different degrees of pathological and electrophysiological severity, which recapitulates the variability in patients. Using this model, the authors applied optogenetic (with channelrhodopsin) or electrical LFS of the entorhinal afferents to induce the firing of dentate granule cell....
firing that are preserved in this model and in patients. First, they applied optical LFS (for 1 hour at 0.2, 0.5, or 1 Hz) while recording local field potentials in vivo. The 1 Hz photostimulation was the most efficient at reducing spontaneous epileptiform activity in both the ipsilateral (sclerotic) and contralateral hippocampi. Further, there were no abnormalities in the motor behavior of these animals. Importantly, seizure suppression worked as efficiently in all kainic acid (KA) conditions independent of the epileptiform and pathological severity. Second, the authors examined the impact of LFS on evoked clinical seizures. Both electrical and optical LFS applied prior to, but not after, stimulation to induce seizures decreased the probability of seizure generation and decreased the severity of the occurring seizures. These data indicate that LFS induced electrically or optically can acutely suppress seizures. The authors then examined whether daily 1 Hz LFS for several hours could stably suppress seizures over 3 weeks. They found that LFS stimulation maintained a suppressive effect on seizures over the 3-week period without desensitization. Further, intermittent LFS was also effective at reducing seizures.

Data presented here are in agreement with previous in vitro and in vivo studies. Optical or electrical 1 Hz stimulation for 3 to 15 minutes of entorhinal fibers or other fiber paths in acute hippocampal slices has been shown to reduce chemically induced epileptiform discharges.\(^3\)\(^-\)\(^5\) In addition, long-term 1 Hz LFS in the ventral hippocampal commissure or entorhinal cortex of MTLE epilepsy models (ie, amygdala kindling and pilocarpine rodent models) reduced seizure frequency and hippocampal interictal spike frequency. This effect lasted for several hours following the end of stimulation 1 Hz.\(^6\)\(^-\)\(^7\) The present study thus adds to the body of literature on LFS and importantly shows LFS efficiency in a model of MTLE with HS. The authors also attempted to assess the cellular mechanisms of seizure suppression using acute slices from the epileptic animals. Photostimulation at 1 Hz reduced the depolarization and firing probability of granule cells upon stimulation of entorhinal afferents. By contrast, the intrinsic properties of granule cells were not affected. The authors suggested that the reduced granule cell excitability likely results from decreased glutamate release from entorhinal fibers, but this needs to be further investigated. Technically, the authors used both electrical and optogenetic stimulations. The latter one allows a more precise stimulation of specific cellular targets and is advantageous for mechanistic purposes. However, optogenetics cannot yet be applied to humans. This study also highlights that 2 types of stimulation, acute prior to seizures versus chronic, would work. From a clinical perspective, it may be advantageous to apply LFS only prior to a seizure limiting exposure of the brain to electrical stimulation that could progressively alter the network. However, this requires the ability to predict the timing of seizure occurrence. This may in fact become a reality using a closed loop circuit to record electrical activity, predict seizure incidence based on machine learning (eg, the study by Daoud and Bayoumi\(^8\)), and then apply LFS based on the risk of seizures. This needs to be examined and refined in animal models.

Collectively, the findings detailed above are promising as they open a potentially new treatment option for MTLE patients with HS. The proposed LFS treatment is an attractive alternative to neurostimulation with HFS, which is an already approved therapy, although it needs to be tested in humans first using chronic electrical stimulation, ideally comparing LFS and HFS directly. Finally, this approach may also be viable for other focal epilepsies such as focal cortical dysplasia, but this remains to be further investigated.

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