Deep Brain Stimulation in the Dish: Focus on Mechanisms

Long-lasting Hyperpolarization Underlies Seizure Reduction by Low Frequency Deep Brain Electrical Stimulation.


Mesial temporal lobe epilepsy (MTLE) is a common medically refractory neurological disease. Deep brain electrical stimulation (DBS) of grey matter has been used for MTLE with limited success. However, stimulation of a white matter tract connecting the hippocampi, the ventral hippocampal commissure (VHC), with low frequencies that simulate interictal discharges has shown promising results, with seizure reduction greater than 98% in bilateral hippocampi during stimulation and greater than 50% seizure reduction in bilateral hippocampi after treatment. A major hurdle to the implementation and optimization of this treatment is that the mechanisms of seizure reduction by low frequency electrical stimulation (LFS) are not known. The goal of this study is to understand how commissural fibre tract stimulation reduces bilateral hippocampal epileptic activity in an in vitro slice preparation containing bilateral hippocampi connected by the VHC. It is our hypothesis that electrical stimuli induce hyperpolarization lasting hundreds of milliseconds following each pulse which reduces spontaneous epileptic activity during each inter-stimulus interval (ISI). Stimulus-induced long-lasting hyperpolarization (LLH) can be mediated by GABA<sub>B</sub> inhibitory post-synaptic potentials (IPSPs) or slow after-hyperpolarization (sAHP). To test the role of LLH in effective bilateral seizure reduction by fibre tract stimulation, we measured stimulus-induced hyperpolarization during LFS of the VHC using electrophysiology techniques. Antagonism of the GABA<sub>B</sub> IPSP and/or sAHP diminished stimulus-induced hyperpolarization concurrently with LFS efficacy (greater than 50% reduction). Blocking both the GABA<sub>B</sub> IPSP and sAHP simultaneously eliminated the effect of electrical stimulation on seizure reduction entirely. These data show that LFS of the VHC is an effective protocol for bilateral hippocampal seizure reduction and that its efficacy relies on the induction of long-lasting hyperpolarization mediated through GABAB IPSPs and sAHP. Based on this study, optimization of the timing of LFS and LFS-induced-LLH may lead to improved outcomes from DBS treatments for human epilepsy.

Commentary

Deep brain stimulation (DBS) has emerged as an alternative therapeutic approach for the treatment of refractory epilepsies, in particular of mesial temporal lobe epilepsy, with >800 patients reported on in >50 published clinical studies to date (1). Despite its frequent and emerging clinical use and its demonstration of tolerability and efficacy in seizure prevention, the underlying mechanisms are still poorly defined. Interpretation of clinical and laboratory research data is challenging due to a multitude of stimulation protocols used, differing in stimulation frequencies and target locations.

Stimulations have been used in a wide frequency range between 0.1 and 400 Hz, and studies have shown that efficacy depends on frequency, duration, and mode of delivery (pulses vs continuous stimulation). Both low frequency stimulation (LFS; usually <12 Hz) and high frequency stimulation (HFS; usually >25 Hz) have been used clinically with opposing outcomes in different settings (2, 3). The sites of stimulation reflect different strategies to intervene with seizure generation. Modulation of the seizure network can be achieved by stimulating the cerebellum, basal ganglia, brainstem, hypothalamus, or thalamus, whereas the seizure focus may directly be targeted by stimulation of the hippocampus, amygdala or piriform cortex, entorhinal cortex, or neocortex (4). This enormous variability of approaches necessitates the need for more mechanistic studies, of which there have been surprisingly few. Key hypotheses include depression of the synaptic neuronal response and increased inhibitory neurotransmission, the generation of potassium-mediated depolarization block, and glial mechanisms (5, 6). Recent research using deep brain stimulation to treat essential tremor in an animal model of Parkinson’s disease has demonstrated that nonsynaptic mechanisms involving the increased generation of adenosine, an endogenous anticonvulsant of the brain (7), suppressed tremor activity and caused limited side effects (8).

The study by Toprani and Durand was designed to test the effects of low frequency electrical stimulation on the induction of long-lasting hyperpolarization in hippocampal pyramidal cells as a candidate mechanism for seizure reduction by LFS. The authors used a functionally connected bilateral hippocampal slice preparation and LFS stimulation of the ventral
hippocampal commissure (using a frequency range of 1 to 10 Hz) in combination with intra-extracellular recordings from both hippocampi (from CA1 and CA3). Seizures were induced by 4-aminopyridine, a blocker of voltage-activated K+ channels, by magnesium-withdrawal, or by bicuculline methiodide, an antagonist of GABA_A receptors.

Toprani and Durand first demonstrated that LFS reduced 4-AP-induced epileptiform activity in their bilateral hippocampal slice preparation. Several putative mechanisms for the antiepileptic effect of LFS were subsequently addressed. First, long-term depression (LTD) was discarded as a putative mechanism because (a) seizure reduction by LFS was observed within 30 seconds after onset of stimulation, a time course not compatible with LTD and (b) the evoked potentials did not significantly change in amplitude during LFS nor did the number of action potentials recruited per stimulus. Second, a contribution of glial cells was excluded based on the lack of voltage shifts in response to LFS. Third, a contribution of GABA_B receptors and the sAHP in epileptic and nonepileptic hyperpolarization was diminished by antagonists of both the potassium channel, because the LFS-induced long-lasting hyperpolarization (sAHP) thought to be mediated by a small conductance potassium channel, which protected cells from seizure activity. This long-lasting hyperpolarization depended on (a) GABA_B inhibitory post-synaptic potentials (IPSPs) and (b) the slow after-hyperpolarization (sAHP) thought to be mediated by a small conductance potassium channel, because the LFS-induced long-lasting hyperpolarization was diminished by antagonists of both the GABA_B receptors and the sAHP in epileptic and nonepileptic slices. GABA_B or sAHP antagonists reduced the therapeutic efficacy of LFS in the slice model. When both mechanisms were blocked, the seizure reduction by LFS was abolished.

In conclusion, the study of Toprani and Durand shows that LFS of a white matter tract that connects both hippocampi reduced chemically induced epileptiform activity in a bilateral hippocampus preparation. Seizure activity was suppressed by LFS-induced long-lasting hyperpolarization in the inter-stimulus intervals, which in turn was mediated by GABA_B IPSPs and the sAHP. A strength of the current study is that major competing putative mechanisms were nicely excluded by specific experiments.

Several aspects of this study warrant further discussion. Whereas GABA_B-mediated mechanisms are well-studied and plausible, the contribution of sAHP to LFS-induced seizure reduction are of interest, because the molecular identity of the channel underlying the sAHP (likely a small conductance potassium channel) is currently unknown and a specific blocker for this channel has been developed just recently. Of note, sAHP plays a major role in the regulation of memory retrieval (9); therefore, enhancing sAHP by LFS may lead to defects in memory retrieval, an adverse effect that might be problematic for patients with mTLE who suffer from cognitive impairment. Further limitations of the study include the use of an in vitro model of chemically induced seizures, which do not reflect pathogenic processes underlying temporal lobe epilepsy, the major target population for DBS. It remains to be determined whether the mechanisms identified here are likewise applicable to a more realistic model of spontaneous recurrent seizure activity. A recent study from the same group (10) demonstrated efficacy of LFS in a rat model of temporal lobe epilepsy triggered by status epilepticus. In that study, LFS of 1 Hz significantly reduced both the excitability of the neural tissue and the seizure frequency. These results further support the hypothesis that LFS of fiber tracts can be an effective method to suppress spontaneous seizures. The mechanistic findings provided here could lead to the development of new therapies for patients with temporal lobe epilepsy.

by Detlev Boison, PhD

References

Disclosure of Potential Conflicts of Interest

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