

ELECTRICAL STIMULATION DEPRESSES EPILEPTIFORM ACTIVITY

Local Suppression of Epileptiform Activity by Electrical Stimulation in Rat Hippocampus In Vitro

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High frequency electrical stimulation of deep brain structures (DBSs) has been effective at controlling abnormal neuronal activity in Parkinson patients and is now being applied for the treatment of pharmacologically intractable epilepsy. The mechanisms underlying the therapeutic effects of DBSs are unknown. In particular, the effect of the electrical stimulation on neuronal firing remains poorly understood. Previous reports showed that uniform electric fields with both AC (continuous sinusoidal) or DC waveforms could suppress epileptiform activity in vitro. In the present study, we tested the effects of monopolar electrode stimulation and low-duty-cycle AC-stimulation protocols, which more closely approximate those used clinically, on three in vitro epilepsy models. Continuous sinusoidal stimulation, 50% duty-cycle sinusoidal stimulation, and low (1.68%) duty-cycle pulsed stimulation (120 μ s, 140 Hz) could completely suppress spontaneous low- Ca^{2+} epileptiform activity with average thresholds of $71.11 \pm 26.16 \mu\text{A}$, $93.33 \pm 12.58 \mu\text{A}$, and $300 \pm 100 \mu\text{A}$, respectively. Continuous sinusoidal stimulation could also completely suppress picrotoxin- and high- K^{+} -induced epileptiform activity with either uniform or localized fields. The suppression generated by the monopolar electrode was localized to a region surrounding the stimulation electrode. Potassium concentration and transmembrane potential recordings showed that AC stimulation was associated with an increase in extracellular potassium concentration and neuronal depolarization block; AC stimulation efficacy was not orientation selective. In contrast, DC stimulation blocked activity by membrane hyperpolarization and was orientation selective, but had a lower threshold for suppression.

COMMENTARY

New medications, for both clinical and experimental use, are able to control intractable seizures in only a few patients. Although temporal and extratemporal resections increasingly have become mainstream treatments for intractable seizures that are refractory to pharmacologic treatment, not all patients are candidates for resection. Moreover, ablation of neuronal tissue, even in seemingly ideal candidates, does not predictably control symptoms and may result in serious, irreversible complications.

Vagal nerve stimulation, an alternative to resection, now is clinically approved but leaves only a minority of patients seizure free. Currently, interest in direct brain stimulation to treat intractable seizures is increased, in part, because of the success of the modality for the treatment of pain and movement disorders. Promising results have been reported by some—but not all (1). In addition, intermittent stimulation, delivered only at the time of the seizure, is another treatment modality being investigated in several laboratories (2–5). The work of Liam et al., along with others just cited, supports the idea that stimulation at the time of epileptiform activity might be an effective treatment.

Liam and colleagues found that intermittent stimulation, with appropriate adjustments, approximates the efficacy of continuous stimulation. Interestingly, the investigators found that very intermittent stimulation (1.68% of the time) could be therapeutic, although less so than when the device was activated 50% of the time. One common problem with any type of implanted stimulation devices is battery life, and batteries last longer if stimulation does not have to be continuous; thus the finding eventually could have practical value. In addition, they showed that the efficacy of stimulation diminished with distance from the stimulation electrode. This finding suggests that problems could occur in developing a clinical device because it is unlikely that the “seizure focus” can be pinpointed with complete exactness, and likely that the focus is larger than would be covered by a small implanted electrode. Interestingly, Liam et al. also found that direct current (DC) stimulation offered no advantages over alternating current (AC). Because of the greater likelihood of adverse effects of DC, it is helpful to know that it is not needed.

The article also raises issues that will require further study. First, in their models, epileptiform activity eventually resumed after stimulation ended. However, the finding is not a surprise,

given the models used (epileptiform activity induced by low calcium, high potassium, or picrotoxin); after all, the epileptogenic agent was still present. Previous reports using similar models also have demonstrated efficacy in ameliorating seizure activity while stimulation was ongoing; with cessation of the stimulation, epileptiform activity resumed. If these models reflect what would occur in humans, different approaches, or modifications of this approach, would be necessary to obtain permanent seizure control (6).

Second, the effects of stimulation were restricted to the region around the electrodes. Are seizure foci in humans restricted enough in location to be controlled by stimulation through a given electrode or set of electrodes? What would happen with seizure activity that is distant from the site of stimulation? Would stimulation through several electrodes be more effective? Finally, is the epileptogenic region stable in location and spread, or would the area shift with time, particularly in response to efforts to halt the seizures by localized stimulation?

Third, the investigators used hippocampal slices, and most, but not all, deep brain stimulation has been directed toward midline structures, such as the thalamus or subthalamic nucleus. Additional work on midline structures is warranted. Furthermore, the electrodes used were smaller than those used clinically, with a greater charge density. Nonetheless, the report provides a

useful comparison of possible stimulation parameters, and the results are encouraging.

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