



Neurostimulation for Epilepsy: Do We Know the Best Stimulation Parameters?

Effect of Stimulus Parameters in the Treatment of Seizures by Electrical Stimulation in the Kainate Animal Model.

Rajdev P, Ward M, Irazoqui P. *Int J Neural Syst* 2011;21:151–162.

Preliminary results from animal and clinical studies demonstrate that electrical stimulation of brain structures can reduce seizure frequency in patients with refractory epilepsy. Since most researchers derive stimulation parameters by trial and error, it is unclear what stimulation frequency, amplitude and duration constitutes a set of optimal stimulation parameters for aborting seizure activity in a given patient. In this investigation, we begin to quantify the independent effects of stimulation parameters on electrographic seizures, such that they could be used to develop an efficient closed-loop prosthesis that intervenes before the clinical onset of a seizure and seizure generalization. Biphasic stimulation is manually delivered to the hippocampus in response to a visually detected electrographic seizure. Such focal, responsive stimulation allows for anti-seizure treatment delivery with improved temporal and spatial specificity over conventional open-loop stimulation paradigms, with the possibility of avoiding tissue damage stemming from excessive exposure to electrical stimulation. We retrospectively examine the effects of stimulation frequency (low, medium and high), pulse-width (low and high) and amplitude (low and high) in seizures recorded from 23 kainic acid treated rats. We also consider the effects of total charge delivered and the rate of charge delivery, and identify stimulation parameter sets that induce after-discharges or more seizures. Among the stimulation parameters evaluated, we note 2 major findings. First, stimulation frequency is a key parameter for inhibiting seizure activity; the anti-seizure effect cannot be attributed to only the charge delivered per phase. Second, an after-discharge curve shows that as the frequency and pulse-width of stimulation increases, smaller pulse amplitudes are capable of eliciting an after-discharge. It is expected that stimulation parameter optimization will lead to devices with enhanced treatment efficacies and reduced side-effect profiles, especially when used in conjunction with seizure prediction or detection algorithms in a closed-loop control application.

Commentary

Under ideal circumstances, basic science research precedes clinical adoption of a technology. The reverse path has tended to prevail with deep brain stimulation (DBS) for epilepsy. After pioneering work in use of DBS for psychiatric conditions by Heath and Delgado, the New York neurosurgeon Irving Cooper was the first to use the technology to treat clinical epilepsy (1). Two recent multicenter clinical trials provided Class I evidence of efficacy for direct brain stimulation of anterior thalamus (2) and at the seizure focus (3).

Having been involved in discussions to establish the clinical parameters of stimulation in one of these trials, I can lament the lack of guidance from basic science as to the best stimulation parameters. Variables to be considered are prodigious, including anatomic site of stimulation, pulse width, pulse frequency, delivery as constant current or constant voltage, intensity of stimulation, whether to ramp intensity up

over time and if so what time intervals, bipolar local stimulation versus stimulation to a distant reference, initial polarity negative or positive, and cycling of stimulation by a clock setting (how long on and off?) versus continuous stimulation or responsive stimulation (responsive to what?). The combinatorial possibilities are overwhelming, amounting to many thousands of possible choices. For the clinical trials, educated and rather arbitrary guesses were made, locking the protocol into parameters that might be far from optimal. The anterior thalamic DBS study stimulated at 5V, 0.9 ms pulses, at 145 pulses per second, on for 1 minute and off for 5 minutes. Some of the parameters imitated those of pilot trials from Cooper and the Velascos (4). Upper limits to the amount of current per pulse can be derived from studies of stimulation-induced tissue damage (5). Experience with movement disorders, where tremor can be assayed rapidly upon changes of stimulation settings, generated the concept that low-frequency stimulation was less effective than high-frequency. Although stimulation for movement disorders is usually done continuously, experience with intermittent vagus nerve stimulation and the desire to preserve battery life persuaded investigators in the thalamic DBS study to use intermittent stimulation. Respon-

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sive neurostimulation is initiated only when an algorithm detects preprogrammed features of the EEG.

Modern neurosurgeons employ stereotactic neurosurgery and neuroimaging to place electrodes with millimeter accuracy. Much less precise, however, is the amount of tissue stimulated by direct brain stimulation leads. Medtronic DBS leads typically comprise four contacts spaced either 0.5 or 1.5 mm apart. Current flow modeling (6) suggests that bipolar stimulation of adjacent contacts distributes current over a smaller area. Bipolar stimulation of leads at the proximal and distal ends of the DBS lead may, in turn, only produce local current flow close to each lead and not across the entire region of interest (personal communication, Mark Rise of Medtronic). A larger region can be stimulated by stimulation with one contact in the brain and another at a distance reference, such as the stimulator case in the chest wall. However, such stimulation may extend beyond the nucleus of interest, particularly if the nucleus is not spherical. Stimulation of adjacent brain might produce unwanted side effects or even increased seizures.

In context of all of these uncertainties, the study by Rajdev and coworkers is most welcome. These investigators implanted dentate gyrus of hippocampi of rats with recording and stimulating electrodes. When a seizure induced by intraperitoneal kainic acid was detected visually in the electrocardiogram, a 5-second constant-current bipolar train of charge-balanced square waves was delivered to the hippocampus. Stimulation frequency was 5, 60, or 130 pulses per second (pps); pulse width was either 60 or 240 μ s; amplitude was 150 or 300 μ A. The dependent variables were time for seizure to stop after stimulation, amplitude of local hippocampal field potentials, and intervals between interictal spikes. Without any stimulation, mean seizure duration was 88.7 ± 7.5 seconds, and with stimulation 18.9 to 67.5 seconds. The 5 pps stimuli were most effective at shortening seizures, but 130 pps were most effective in reducing spike amplitude. An upper therapeutic limit was noted, in that pulses of the highest amplitude

reduced after-discharge thresholds, which might be expected to facilitate seizures.

Stimulation at 5 pps, most effective in this laboratory study, is very different from the parameters used in hippocampal stimulation clinical trials, with 130 pps (4, 7) or 190 pps (8). Although the differences could be reflective of features specific to the kainic acid model, it must be said that no clinical study has in fact shown that high-frequency stimulation is optimal in epilepsy patients.

We need more studies like this to better define optimal stimulation parameters for clinical neuromodulation, and to close the current gulf between the scanty experimental data and limited clinical experience. Please keep the laboratory studies of neuromodulation coming.

by Robert S. Fisher, MD, PhD

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