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Control of Seizure Activity by Electrical Stimulation: Effect of Frequency

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Abstract: Epilepsy is a devastating disease of the central nervous system, affecting ~1% of the world's population. Drug therapy is effective in many patients, but 25% of the patients do not respond to anticonvulsants. Surgical resection can be an effective treatment but is associated with serious complications that can remove it as an option. Electrical stimulation has been successful to control abnormal activity such as motor disorders and current research is aimed at determining the efficacy of this method for seizure control. Several electrical stimulation frequencies and waveforms have been developed to control seizure activity. The purpose of this presentation is to review these various approaches, and to discuss their underlying mechanisms and their potential for clinical implementation.

Direct Current Membrane Polarization

Applied currents and electric fields can generate membrane hyperpolarization and increase the threshold for neuronal firing. When applied at low amplitudes these signals can control neural excitability both in-vitro and in-vivo. For example currents as low as 5 to 15 μA applied 15min/day for 14 days to amygdala-kindled animals significantly increased seizure thresholds. However, DC currents are known to generate tissue damage through nonreversible chemical reactions that take place at the electrode surface. Moreover, these currents are applied externally and must also be generate membrane depolarization that could produce side effects.

Low frequency electrical stimulation (LFS

In animal experiments, low frequency electrical stimulation can decrease neural excitability and seizure activity in both *in-vivo* and *in-vitro* models of epilepsy. Effects of stimulation such as increased inhibition and long term synaptic depression (LTD) have been proposed to explain the decrease excitability. In human patients with epilepsy, low frequency electrical stimulation (at 0.5 Hz, biphasic square waves, 2-4 mA) delivered to different ictal onset zones each day in 30 min intervals, was able to reduce seizure frequency. In addition, stimulation of the caudate nucleus at 4-8 Hz, in 57 patients suffering from intractable epilepsy, also reduced the seizure frequency. Although, activation of the ictal zones in patients with intractable epilepsy can decrease seizure frequency, one of the possible side effects of the stimulation is induction of seizures even at these low frequencies.

High frequency stimulation

High frequency train of pulses has been applied both directly in the brain (Deep Brain Stimulation) and to peripheral nerves (Vagus Nerve Stimulation) to control seizure activity. There are now over 10,000 patients per year implanted with high frequency vagus nerve stimulation systems for the treatment of epilepsy. The VN stimulator received FDA approval in July 1997. Stimulation is in the range of 30Hz and can significantly reduce the number of seizures. The mechanism of this effect is unknown. In the CNS, stimulation at higher frequencies, (120Hz) can also significantly reduce the number of seizures. Various targets for this stimulation have been tested with varying degrees of success. The anterior nucleus of the thalamus is the latest target tested in a double blind controlled study. The mechanisms of this effect are also unknown and will be discussed.

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