



Deep Brain Stimulation for Epilepsy

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ABSTRACT

Novel antiepileptic drugs (AED) are now available. However, many epileptic patients still find the condition difficult to handle. Drug therapy does not work for about one-third of the cases and not all people who will benefit from surgery. The use of electric current as a treatment option has emerged since the late twentieth century. Inhibition of synapse activity is a way that low-frequency stimulation (LFS) prevents epileptic activity. It will enhance the endocytosis of AMPA-type glutamate receptors and activate calcineurin, thereby leading to long-term depression (LTD). High-frequency stimulation (HFS) also contributes to the control of epilepsy by increasing the membrane permeability of neurons. Nonetheless, the detailed mechanisms responsible for these effects are still unknown. More research is required to fine-tune electrical stimulation parameters and yield better results in epilepsy patient care.

Keywords: epilepsy, deep brain stimulation, low-frequency electrical stimulation, high-frequency electrical stimulation

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INTRODUCTION

In recent decades, despite the introduction of new antiepileptic drugs (AED) to the market, approximately 30% of seizure cases do not respond to drug treatment. Among these cases, nearly 50% are not suitable for surgery due to reasons such as multifocal seizures or primary generalized epilepsy (1). Additionally, drug therapy and surgery have significant side effects. The existing side effects of antiepileptic drugs are numerous, and they only eliminate seizures in 40% of cases, reducing seizure frequency in the remaining cases (2).

Therefore, it is essential to develop new therapeutic approaches for patients with epilepsy. Over the past two decades, the use of electrical currents has become a popular treatment strategy. Electrotherapy dates back to 46 AD when a Romanian physician named Scribonius Largus used electric fish (specifically the black torpedo

fish, which produces electricity) to treat patients with headaches, resulting in symptom improvement (3).

Application of Electrotherapy in Epilepsy Treatment

Important brain regions targeted for epilepsy treatment in both humans and animals using electrodes include the anterior and central thalamic nuclei, hippocampus, amygdala, substantia nigra, locus coeruleus, cerebellum, subthalamic nuclei, and cortical epileptic foci (1).

The thalamus establishes extensive connections with the cerebral cortex, and the cerebellum primarily has inhibitory outputs. Stimulation of these regions leads to antiepileptic effects (1). The locus coeruleus sends abundant projections to various brain areas, modulating their activity through noradrenergic signaling (3). Inhibiting subthalamic nuclei and the substantia

nigra results in increased activity of upper motor neurons in the posterior part of the midbrain, which also sends numerous inhibitory projections to the cerebral cortex (3). One crucial circuit in the limbic system related to seizure generation is the Papez circuit. It starts from the entorhinal cortex, reaches the mammillary body in the hypothalamus, and then returns to the anterior thalamic nuclei and, via the cingulate gyrus pathway, back to the entorhinal cortex. Stimulation of the anterior thalamic nuclei disrupts this circuit and produces antiepileptic effects (3). Vagus nerve stimulation, due to its extensive inputs to the thalamus, activates inhibitory nerve fibers projecting to the cerebral cortex (1).

In electrical stimulation of the mentioned brain regions, high frequencies (typically between 50 and 200 Hz) are commonly used, reducing seizure occurrence and interictal spikes (3). However, low-frequency electrical stimulation has also shown significant effects on reducing neuronal activity in various studies (4).

For seizure control, electrical stimulation is generally used in two ways: 1) targeting brain regions that affect cortical excitability and seizure threshold, and 2) direct stimulation of epileptic foci. Types of electrical stimulation used for seizure suppression include deep brain stimulation with both high and low frequencies, vagus nerve stimulation, seizure-inducing electrical stimulation, and transcranial magnetic stimulation (5–9).

Low-Frequency Electrical Stimulation

Electrotherapy using low-frequency stimulation (LFS) has antiepileptic effects in patients with epilepsy (4, 3, 10). In laboratory models, hippocampal or perforant path electrical stimulation at frequencies of 1 or 50 Hz for 2 hours reduced interictal events, but it did not affect spontaneous seizures (11). Stimulation of the mammillary body at 4–6 Hz decreased interictal spikes and stopped focal seizures (3). Low-frequency electrical stimulation in the lateral habenula suppressed seizures in three *in vitro* models of hippocampal epilepsy (models involving 4-aminopyridine, high-potassium, and magnesium-free conditions) (7).

The reduction in spike activity due to low-frequency electrical stimulation suggests modulation of synaptic activity. Reports indicate that changes in synaptic activity resulting from electrical stimulation tend to weaken excitatory movements (4). Another method, transcranial magnetic stimulation, has been used for epilepsy treatment. Notably, the best antiepileptic effects were observed at a frequency of 1 Hz (12).

High-Frequency Electrical Stimulation

In addition to LFS, high-frequency electrical stimulation can also have antiepileptic effects. In animal models of kindling, HFS (high-frequency stimulation) at 130 Hz increases the threshold and reduces the subsequent discharge duration (13, 14). rTMS (repetitive transcranial magnetic stimulation) at 20 Hz improves the post-discharge threshold by 55% compared to the control group (15). Animals that received HFS immediately before kindling stimuli did not fully kindle in 78% of cases, remaining similar to stages zero to three (16). In human studies, HFS in the anterior thalamic nucleus (including anterior-ventral, anterior-dorsal, and anterior-medial nuclei) is a potential target for seizure control (17, 13, 18).

Cellular Effects of Low-Frequency Electrical Stimulation

Low-frequency electrical stimulation affects neuronal membrane permeability postsynaptically through NMDA receptors or voltage-gated calcium channels, leading to increased calcium influx. Inside the neuron, calcium binds to a protein called calmodulin. The calcium-calmodulin complex activates a phosphatase protein called calcineurin. Calcineurin dephosphorylates the GluR1 subunit of AMPA-type glutamate receptors, enhancing their endocytosis from the postsynaptic membrane (19). Additionally, calcineurin activates protein phosphatase-1 (PP-1). PP-1 inhibits calcium-calmodulin-dependent kinase II (CaMKII) (20). This mechanism contributes to processes like long-term depression (LTD) and depotentiation.

The antiepileptic mechanisms of low-frequency electrotherapy likely resemble those involved in LTD and post-tetanic depression (21).

After low-frequency neuronal electrical stimulation, these changes in synaptic plasticity have been observed both in vivo and in vitro (22). LTD refers to a decrease in synaptic efficacy below baseline levels. To induce LTD, a frequency of 1 Hz with 900 pulses in the perforant path of Wistar rats produces the most effective LFS parameters, resulting in long-lasting effects for up to one week (4), although another study found that electrical stimulation at frequencies of 1 and 3 Hz in the perforant path failed to induce LTD (23).

Depotentialion occurs when the efficacy of a synapse weakens after prior potentiation. Electrical stimulation at 5 Hz in the perforant path permanently induces depotentialion three minutes after long-term potentiation (LTP) (23). Similarly, depotentialion has been observed in lateral branches of the Schaffer collateral pathway at a frequency of 1 Hz (24).

To generate LTD through low-frequency electrical stimulation, various receptor types are necessary, including metabotropic glutamate receptors, AMPA receptors, and kainate receptors, as well as dopamine, beta-adrenergic, and adenosine receptors.

Cellular Effects of High-Frequency Electrical Stimulation

In the thalamus, following high-frequency electrical stimulation (100 to 333 Hz), prolonged inhibition (lasting more than 10 seconds) occurs in most neurons surrounding the stimulation electrode. This inhibition typically precedes short bursts of calcium spiking activity and is observed in neurons with bursting activity patterns. It is suggested that neurons become hyperpolarized during high-frequency stimulation, although whether this phenomenon is due to GABA release or other mechanisms remains unclear (25).

CONCLUSION

The treatment of epilepsy is challenging due to cases of epilepsy that cannot be treated by drugs. There are prospects for utilizing electrical stimulation both at high and low frequencies. LFS influences the synaptic activity unlike HFS which affects synaptic metabolism; improving parameters will make it possible for better

outcomes among patients with epilepsy through further research.

DECLARATION

The authors report no conflicts of interest.

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