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Mechanisms of Neurostimulation for Epilepsy

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Abstract
This review discusses the use of neurostimulation therapies for epilepsy treatment, including vagal nerve stimulation, responsive neurostimulation, and deep brain stimulation. Different therapeutic strategies and their underlying mechanisms are explored, with a focus on optimizing parameters for seizure reduction. The review also highlights the paradigm shift toward a more diverse and multimodal approach to deep brain neuromodulation.

Keywords
neuromodulation, electrical stimulation, seizure, suppression

Neurostimulation Therapies in Clinical Practice

Epilepsy, one of the world's most common neurological diseases, is a syndrome in which brain networks are altered to repeatedly produce seizures within dynamic seizure cycle consisting of the following stages: low seizure risk, high seizure risk, seizure, and relative brain suppression.[1-4] Neurostimulation, coined electrotheraputics,[5] is the frontier of epilepsy treatment and can target phases of the seizure cycle. Neurostimulation therapies, including vagal nerve stimulation (VNS),[6,7] responsive neurostimulation (RNS),[8-10] and deep brain stimulation (DBS),[11-13] have benefits of being reversible and adjustable,[14,15] with better neuropsychological outcomes than resection,[16,17] in addition to potential for cognitive rehabilitation or memory enhancement.[18-20]

Vagal nerve stimulation was approved for epilepsy in 1997 and depression in 2005.[6] Thirty percent of patients have >50% seizure reduction and 50% of patients have >40% seizure reduction.[21] Empirical optimization of frequency, duty cycle, or incorporating closed-loop systems to deliver stimulation closer to seizure onset may improve outcomes.[7] Responsive cortical neuro-stimulation (NeuroPace) is another FDA-approved option for patients with medically refractory epilepsy who are not prime surgical candidates that has been available since 2013. The NeuroPace trial was a multicenter, double-blind, randomized controlled trial in which 191 adults with medically intractable partial epilepsy were implanted with a responsive neurostimulator connected to depth or subdural leads placed at 1 or 2 predetermined seizure foci. Of all, 37.9% seizure reduction was observed in the treatment group compared to 17.3% reduction in the sham group (n = 94). There were significant improvements in overall quality of life ($P < .02$).[8,22] The newest approved deep brain electrical stimulation (DBS) treatment for epilepsy results from the Stimulation of Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial. This was also a multicenter, randomized, double-blind trial in which 110 implanted patients with refractory partial or secondarily generalized seizures received stimulation by the Medtronic implantable programmable pulse generator. Patients had 29% greater reduction in seizures than controls. No group differences in cognition/mood were found, although participants in the stimulated group were more likely to report depression or memory problems as adverse events.[13,23]

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It becomes evident that the optimal parameters for seizure reduction are undetermined with considerations spanning location (thalamic, cerebellar, cortical foci, basal ganglia, and white matter), frequency (0.1 to 400 Hz), duration (ms to days), and open or closed loop delivery.[24] Furthermore, the delayed therapeutic effects that emerge over several weeks to years suggest large network targeting and remodeling. Additionally, while gray matter effects have been historically focused on, direct involvement of axonal fibers rather than gray matter underly neurostimulation effects in on Parkinson's disease, pain, obsessive-compulsive disorder, and epilepsy.[25] Harnessing the potential of neurostimulation for epilepsy requires understanding of the complex, overlapping, and sometimes paradoxical mechanisms of its effect. After all, a therapy that affects multiple types of epilepsy with different underlying pathophysiology over variable time spans must employ multimodal mechanisms.[26,27]

Approach to Categorizing Neuromodulation for Epilepsy

In this review, we compare neurostimulation effects to physiological phenomena of seizure termination or prevention that occur in patients with epilepsy. We provide a simplified framework for categorizing how neuromodulation reduces seizures by grouping mechanisms into those that promote network connection versus disconnection in immediate (seizure suppression) or chronic (seizure prevention) time frames. Seizures are generated by diverse and overlapping mechanisms and therefore they are effectively reduced by several possible pathways. Neurostimulation can differentially impact functional network assembly depending on when on the seizure cycle it is delivered. Therapeutic strategies can be applied during seizures to stop ongoing seizures from developing or spreading by terminating them (Suppression therapy) or between seizures during low- or high-risk periods to increase the seizure threshold (Prevention therapy). While the underlying mechanisms are complex and diverse, we consider them in terms of bolstering network connections (Connection therapy) or disrupting network interactions (Disconnection therapy).

Seizure Suppression

We first discuss mechanisms of immediate seizure termination, or suppression.

Mechanisms of Seizure Suppression by Enhancing Network Communication

Increasing network communication can suppress seizures in an immediate time frame when it enhances inhibition and decreases excitation. Low-frequency neurostimulation (LFS) of gray or white matter suppresses epileptic signals by pacing or synchronizing inhibited/refractory periods.[28] Generalized seizures may naturally quelch themselves by similar mechanisms that result in severe inhibition during postictal suppression.[29] Low-frequency neurostimulation of fiber tracts such as the ventral hippocampal commissure has been shown to reduce seizures both in rodents and humans.[30] The stimulation frequency is quite low (between 1 and 10 Hz) but does not involve synaptic long-term depression. Instead, experiments show that LFS in fiber tracts triggers long-lasting inhibitory potentials generated by slow afterhyperpolarization (sAHP) and slow inhibitory $GABA_B$ potassium channels[19] which serve to synchronize, or connect, the network. This network enhancement may be what enables concurrent improvement in endogenous function where this paradigm is applied, as seen in boosted memory performance along with seizure risk reduction.[20] Similar results have been obtained in the cortex whereby focal cortical seizures could be suppressed more effectively by low-frequency stimulation of corpus callosum fibers innervating the epileptogenic zone than high-frequency stimulation (HFS).[31,32]

Mechanisms of Seizure Suppression by Disconnection Across Networks

In contrast, seizures can be suppressed in an immediate time frame by disrupting pathological network communication that contributes to seizures buildup. This is evident in disconnection via dispersion of pathological beta signals from other phase-locked brain signals that results from application of high-frequency neurostimulation (HFS) in movement disorders or epilepsy and correlates with symptom improvement.[33] HFS can break up high-frequency oscillations, which underly ineffective cortical computations in patients with epilepsy.[34] Terminating or lesioning this ineffective connection with high-frequency stimulation can yield symptom relief.[35] Physiologically, high-frequency signal dispersion occurs when seizures naturally stop. HFS, when applied at frequencies paralleling seizures, can recruit innate seizure-termination mechanisms, including glutamate depletion and buffering, activation of GABAergic inhibition, adenosine release, potassium currents with membrane shunting to increase excitatory threshold, and ATP-energy failure.[36] The net inhibitory effect could be the result of indirect synaptic inhibition by retrograde activation of the incoming axons (jamming), or of neurotransmitter depletion in the outgoing axons (synaptic fatigue) due to extensive high-frequency synaptic firing.[37] Seizure termination by disconnection from high-frequency neurostimulation can occur via sustained depolarization of neural membranes, inactivating sodium channels and resulting in axonal depolarization block that prevents initiation or propagation of action potentials, which may disrupt or desynchronize neural transmission.[38,39] The net effect of axonal stimulation depends on whether the stimulated fibers synapse onto an excitatory or inhibitory neurons. Adding complexity, axonal and neuronal cell body responses to stimulation can be decoupled, leading to hyperpolarization of the neuron with depolarization of the axon, which also results in disconnection of the target structure from the network.[40]

Seizure Prevention

Chronic effects of neurostimulation occur during treatment with delayed onset as well as posttreatment completion. In fact,

hippocampal seizure reduction has been shown to persist after post-traumatic wire-disconnection of a bilateral hippocampal neurostimulation device.[41] Therefore, we next focus on how seizure initiation is prevented in the short and long-term as a result of neurostimulation. Physiologically, brains of patients with epilepsy develop protective mechanisms to "fight off" some seizures by raising the seizure threshold relative to its pathologically low set point.[36,42] Like seizure suppression, prevention also modulates networks and can be categorized as enhancing or disrupting network communication.

Mechanisms of Seizure Prevention by Enhancing Network Connectivity

Open loop or chronic electrical stimulation delivered when seizures are not occurring can create short- and long-term states that stabilize networks from recruitment into or initiation of seizures. In the short-term (neurostimulation delivery between seizures), connectivity of low-frequency signals, such as theta oscillations associated with memory, may be preferentially enhanced. This can be mediated by entrainment of synchronous action potentials with coordinated inhibition or refractory periods that prevent spontaneous signals while allowing coordinated signals.[28] Enhancing baseline thalamic connection via open-loop scheduled thalamic stimulation may prevent seizure initiation entraining a pattern that turns off seizures.[43] Furthermore, LFS enhances potassium chloride cotransporter 2, which protects against epileptogenic reversal of GABAergic or glycinergic neurotransmission from inhibitory to excitatory signals.[44] Stabilizing networks against pathological excitation in this way prevents the development of kindled mirror foci in patients with epilepsy. Applied between seizures, synchronous open loop high-amplitude low-frequency stimulation, on the order of about 1 Hz, paces networks by entraining low-frequency action potentials that are protective against intrusion of high-frequency epileptiform signals between activation bursts. This effect is mediated by sAHP and metabotropic $GABA_B$ receptors that cause inhibition lasting hundreds of milliseconds and persists posttreatment due to network entrainment.[28] In the long-term, neurostimulation can also enhance network communication by remodeling from recruitment of progenitor cells. ATP and glutamate-mediated transmission may be modulated by astrocyte recruitment near a stimulating electrode in the medium-term and by progenitor cell development in the stimulating location as well as functionally connected locations in the long term. To this end, progenitor cells in the hippocampi have resulted from thalamic stimulation.[45]

Mechanisms of Seizure Prevention by Disconnection Across Networks

Along with bolstering of inhibitory networks to increase seizure threshold described previously, chronic seizure prevention by neurostimulation disrupts excitatory brain networks involved in ictogenesis. Analysis of brain networks in patients who received chronic neurostimulation revealed fractionation of network pathways exposed to chronic low- or high-frequency electrical stimulation.[46] Signal transmission across brain regions is mediated by oscillations, often in the high-frequency beta and gamma ranges, that can be phase-locked to underlying lower frequency theta oscillations. Previously, immediate disruption of pathological high-frequency oscillations by breaking or shortening from neurostimulation was described. Chronic exposure to neurostimulation downregulates that pathway, reducing the oscillations produced overall. It is postulated that this occurs after desensitization or compensation to repeated increases in action potentials from HFS resulting in reduced input resistance and increased extracellular excitatory neurotransmitter (glutamate) concentration. Decoupling that pathway reduces spindle wave oscillations. This not only disrupts immediate functional connection between brain regions, but results in downregulation of that connection over time.[47] High-frequency stimulation enduringly disrupts spindles via glutamate-mediated activation of a hyperpolarization-activated current. Phase synchrony can also be disrupted with LFS, thus reducing cortical excitability. 1 Hz stimulation at the epileptic focus reduces phase synchronization of high-frequency bands (alpha, beta, gamma, and high gamma).[48]

Endogenous Neurostimulation of the Seizure Cycle

It may be helpful to compare applied neurostimulation to analogous parts of the seizure cycle to understand short- and long-term effects. Inhibition or hyperpolarization may reset the system similarly to postictal suppression following seizures. High-frequency stimulation may have effects akin to a developed seizure of transient network disconnection. Low-frequency stimulation may provide broad pacing like interictal discharges that can be protective during baseline states[49] and ictogenic during high-risk states provided during baseline states might confer.[49] Consideration of where on the seizure cycle each of these are applied can impact the effect derived.

The Mechanistic Frontier of Neurostimulation Therapy for Epilepsy

Epilepsy is a neurological disorder characterized by seizures that can occupy up to 1% of a patient's lifetime, and neurostimulation is a frontier treatment for it. Neurostimulation therapies such as VNS, RNS, and DBS have benefits such as being reversible and adjustable, with better neuropsychological outcomes than resection. The underlying mechanisms of neurostimulation are complex and diverse, and neurostimulation can differentially impact functional network assembly depending on when on the seizure cycle it is delivered. There are different strategies of neuromodulation for epilepsy, including connection and disconnection therapies. With the use of primarily empirical approaches to neurostimulation over the last 20 years, therapies have burgeoned. The next frontier for treatment optimization is mechanistic. A network-based approach, including long-term changes as the brain creates a new homeostasis

incorporating the perturbation from neuromodulation, is essential to nudge the system in the desired direction at the right time in the seizure cycle. Therefore, mechanistic studies of neural networks undergoing high or low frequency applied or endogenous stimulation should be a high research priority for advances in the treatment of epilepsy with electrical stimulation.

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