ISSN: 2538-5887; Pathobiology Research. 2024; 27 (4): 39-43

Brief review of deep brain stimulation anticonvulsant mechanisms in epilepsy

ARTICLE INFO

Article Type:
Review

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ABSTRACT

Deep Brain Stimulation (DBS) has been developed as a new therapeutic manner for the treatment of neurological disorders, offering a reversible and adjustable alternative to traditional lesion-based surgeries. By delivering targeted electrical stimulation to specific brain regions, DBS modulates neural circuits and restores dysfunctional networks. Beyond its established role in movement disorders like Parkinson's disease, DBS has shown remarkable efficacy in managing epilepsy. Its therapeutic effects are mediated through complex mechanisms, including neurotransmitter modulation, ion channel regulation, and alterations in the brain's microenvironment. This article explores how DBS leverages these multifaceted processes to revolutionize neuromodulation and offers insights into its expanding potential for treating epilepsy.

Keywords:

Deep Brain Stimulation, Epilepsy, Anticonvulsant, Seizure.

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1. Introduction

Deep brain stimulation (DBS) has been a recognized neurosurgical technique since the 1990s, with over 160,000 patients treated globally. This procedure involves the implantation of electrodes into specific subcortical regions of the brain during stereotactic surgery, allowing for the delivery of chronic low-level electrical currents to modify neural activity therapeutically. DBS is primarily used to manage movement disorders such as Parkinson's disease (PD) (1,2), various types of tremor (3), and dystonia (4). It is also indicated for conditions like treatment-resistant epilepsy (5) and obsessive-compulsive disorder (OCD) (6).

Prior to DBS, surgical interventions for movement disorders typically involved ablative techniques that created lesions using radiofrequency. Common procedures included thalamotomy (7) and pallidotomy (7), particularly before levodopa became available for PD treatment. To assess the potential outcomes of creating lesions, surgeons employed high-frequency stimulation in the ventral intermediate nucleus of the thalamus, which produced immediate and reversible tremor relief (8). This led to the innovative concept of using electrical stimulation to modify neuronal function instead of destroying tissue. Consequently, fully implantable DBS systems were developed, featuring dual electrodes linked to an implantable pulse generator, functioning similarly to a cardiac pacemaker, to provide continuous long-term therapy.

Today, DBS is categorized under neuro-modulation therapies that alter neural function through electrical stimulation. Its effects are generally immediate, reversible, adjustable, and can be titrated without permanently injuring neural tissue. Unlike lesioning techniques, DBS can be applied bilaterally with minimal severe side effects in movement disorder surgeries. The realization that high-frequency stimulation could mimic the effects of ablative surgeries led to the hypothesis that DBS suppresses neuronal activity in the targeted nucleus, effectively creating a functional lesion (9) through depolarization blocks (10,11). While functional inactivation and depolarization play roles in its efficacy, research suggests that DBS impacts cellular, electrical, molecular, and network levels far beyond what lesions achieve. The prevailing theory posits that dysfunctional neuronal circuits or circuitopathies can be treated with DBS, enabling electrical stimulation to restore these circuits to a normal physiological state (9,11–14).

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2. Effects of DBS application on neurotransmitters and neuromodulators

One of the most important mechanisms involved in the anticonvulsant action of DBS is the "changes neurotransmitter and neuromodulators" hypothesis. There are a lot of reports in which the researchers showed changes in the activity of neurotransmitters. Here we mentioned only some of the most important neurotransmitters that may be involved in anticonvulsant action of DBS. DBS of the anterior nucleus of the thalamus (ANT) exerts significant effects on neurotransmitter systems, particularly serotonin, adenosine, and dopamine, which are crucial for its antiepileptogenic effects. Serotonin (5-HT) plays a crucial role in increasing seizure thresholds, making the serotonergic system a key focus in epilepsy research. In PTZ-treated rats, high-frequency stimulation (HFS) of the ANT elevated levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) without impacting norepinephrine or dopamine levels (15).Additionally, the seizure-delaying effects and electrographic changes observed following PTZ administration were replicated by administering the serotonin 5-HT7 receptor agonist 5-carboxamidotryptamine (5-CT) directly to the ANT (16). However, these anticonvulsant effects were diminished in PTZ-treated animals given high doses of the 5-HT antagonist methysergide (16). As pre-ictal epileptiform bursts were reduced by both 5-CT and methysergide, but remained unchanged by DBS, it was suggested that while the serotonergic system contributes to the anticonvulsant effects of ANT-DBS, it is not the sole mediator (16).

Adenosine signaling is another critical pathway affected by ANT DBS. The stimulation appears to downregulate adenosine kinase (ADK), an enzyme responsible for degrading adenosine. This downregulation leads to increased levels of adenosine in the brain, which has potent anticonvulsant properties. Adenosine acts on A1 receptors to inhibit neuronal excitability by reducing cAMP levels and opening potassium channels, resulting in hyperpolarization of neurons and decreased neurotransmitter release. This enhanced adenosine signaling contributes to a reduction in seizure frequency and severity, highlighting its importance in the therapeutic efficacy of this neuromodulation technique (17–19). Another study indicated that DBS of the anterior nucleus of the thalamus significantly inhibits spontaneous recurrent seizures in a rat model of epilepsy by increasing extracellular adenosine levels and decreasing the expression of adenosine-regulating enzymes Equilibrative nucleoside transporters-1 (ENT1) and ectonucleotidases (CD39, CD73) (20). Additionally, increased adenosine levels can exert neuroprotective effects during seizure activity by mitigating excitotoxic damage (17).

By modulating the dopaminergic system, DBS can improve symptoms in conditions such as depression, Parkinson's disease, substance use disorders, epilepsy, and obsessive-compulsive disorder (OCD). DBS of the bed nucleus of the stria terminalis- nucleus accumbens area improves depression and anxiety by reducing D2 receptor binding in various brain regions, suggesting dopaminergic regulation (21). DBS can also treat substance use disorders by preventing cocaine-induced dopamine increases in the nucleus accumbens (22). Tonic stimulation of the Ventral tegmental area (VTA) reduces seizure severity in mice by activating D2-like receptors, making it a potential anticonvulsant approach (23). For OCD, nucleus accumbens DBS decreases dopamine D2/3 receptor availability and increases plasma homovanillic acid levels, correlating with symptom improvement and compensating for defective dopaminergic neurotransmission (24). Medial forebrain bundle DBS has anti-depressant effects by evoking dopamine responses. Significant dopamine response induced at 130 Hz and 60 Hz with 100 μs pulse width (25).

3. Effects of DBS application on ion channels

Chronic DBS promotes alterations in ion channel expression or function that contribute to sustained changes in neuronal excitability and synaptic transmission (9,26). These effects on ion channels play a critical role in determining the overall impact of DBS on neuronal circuits and their ability to respond to stimulation. DBS significantly impacts ion channel activity within neuronal membranes. The electrical stimulation modifies neuronal excitability by affecting voltage-gated sodium and potassium channels. Study results showed that both high-frequency and low-frequency DBS induced depolarization of the membrane voltage of neurons without

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suppressing the spike rate. 140 Hz DBS evoked stronger membrane depolarization than 40 Hz DBS. Both frequencies also entrained the neurons' membrane voltage at their respective stimulation frequencies. This membrane depolarization interferes with individual neuron's ability to process inputs, creating informational lesions (27). Additionally, ANT DBS in a rat model of temporal lobe epilepsy modulates the expression of genes linked to ion channel activity, including those for gated, cation, ligand-gated, and voltage-gated channels (28).

4. Effects of DBS application on Microenvironment

DBS also significantly alters the local microenvironment surrounding the electrode, influencing glial cell activity and overall neurotransmitter dynamics. The electrical stimulation affects astrocytes and microglia, leading to changes in their release of neurotrophic factors and cytokines that can modulate neuronal health and neurotransmitter signaling (29). For instance, activated astrocytes can enhance their uptake of excess neurotransmitters like glutamate, preventing excitotoxicity while supporting neuronal survival (30). While most studies on the mechanisms of DBS focus on neurons (13,31,32), astrocytes also play a crucial role in neural signaling (33) and can influence neuronal activity through their interconnected networks (34,35). This makes astrocytes strong candidates for mediating DBS effects on seizures. Astrocyte membranes host a variety of neurotransmitter receptors, particularly G protein-coupled receptors (36). High-frequency stimulation (HFS) triggers a rapid rise in astrocytic Ca^{2+} levels (37), leading to the release of gliotransmitters like glutamate, D-serine, and ATP, which interact with pre- and postsynaptic receptors (38,39). Since ATP is not released synaptically, astrocytes are believed to mediate its increased extracellular levels, where it is quickly converted to adenosine. Furthermore, astrocytic gap junctions and hemi-channels facilitate the spread of Ca^{2+} waves beyond the stimulation site (34,35,37), potentially disrupting synaptic transmission.

Additionally, DBS modifies extracellular ion concentrations critical for maintaining synaptic function. Changes in potassium and calcium levels can affect how neurotransmitters are released and how effectively they signal across synapses (40,41). The modulation of glial cell function not only supports neuronal health but also contributes to a more favorable environment for effective neurotransmission (42). This interplay between DBS and the microenvironment underscores its role as a neuromodulatory therapy that extends beyond direct neuronal effects, including glial interactions and support mechanisms.

5. Conclusion

Deep Brain Stimulation has emerged as a transformative therapeutic approach for epilepsy, offering precise modulation of neural activity through its multifaceted mechanisms. By influencing neurotransmitter systems such as serotonin, adenosine, and dopamine, DBS effectively alters excitability and enhances seizure thresholds. Additionally, its impact extends to ion channels, where DBS modulates membrane potentials and gene expression, as well as extracellular ion balance. These combined effects highlight the intricate interplay between neuronal components in achieving therapeutic outcomes. As research continues to uncover the depth of these mechanisms, DBS holds promise not only for optimizing epilepsy treatment but also for expanding its applications to other neurological and psychiatric disorders.

Acknowledgment

We thank researchers of the Department of Physiology at Tarbiat Modares University for their scientific comments.

Conflicts of interest

The authors report no conflicts of interest.

Funding

This study was conducted without any external financial support.

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