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Mechanisms of Epilepsy and Efficacy of Neuroplasticity-Based Treatment

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Abstract. Epilepsy is a neurological disorder characterized by the development of trauma to the nervous system and recurrent seizures. Neuroplasticity, the ability of the nervous system to reorganize its structure and function in response to trauma, plays a crucial role in the development and treatment of epilepsy. Several recent studies have mentioned the potential of treating epilepsy based on neuroplasticity, such as deep brain stimulation (DBS), neurofeedback and non-invasive brain stimulation techniques. While conventional treatments focus primarily on seizure control, neuroplasticity interventions aim to alter neural circuits, reduce seizure frequency and severity, and may ameliorate the effects caused by the sequelae of epilepsy. There are already a number of therapies for epilepsy that incorporate neuroplasticity, which provides a basis for subsequent research. This paper explores the pathogenesis of epilepsy with a focus on the role of neuroplasticity in the onset and progression of epilepsy. However, further research is needed to optimize these approaches and fully understand their therapeutic potential.

Keywords: Epilepsy; Neuroplasticity; Deep brain stimulation; Non-invasive brain stimulation; Drug-resistant epilepsy.

1. Introduction

Globally, one of the major threats to human health is neurological disorders. Death rates due to neurological disorders have risen significantly over the past 30 years[1]. Epilepsy is a neurological disorder that is characterized by recurrent seizures. It can have neurological, cognitive, psychological and life consequences for the patient. Prolonged seizures may lead to structural damage to the brain, such as affecting the hippocampus area of the brain, causing the patient to experience short- or long-term memory impairment. Or it may affect areas of the patient's language function, leading to poor speech and reduced language comprehension, and may also make it difficult for the patient to concentrate, making it difficult for them to complete their daily studies and tasks[2]. Also, epilepsy can cause the patient to fear social activities, making them more prone to stress and depressed moods. If epilepsy occurs continuously, it may even lead to brain damage, which can be life-threatening. If anti-epileptic drugs are taken for a long period of time, they may also bring about a series of side effects, such as making the patient drowsy, gaining weight, or adversely affecting liver and kidney function. The diagnosis of epilepsy requires that the patient has one or more seizures in a week. Many people with acquired neurological damage (e.g., trauma or stroke) may develop epilepsy over time because the lesions can reorganize through brain circuits resulting in abnormal epileptic discharges. The incidence of epilepsy in children is approximately ten times that of adults, and the main causes include genetic factors, metabolic disorders, central nervous system infections, febrile seizures, and head trauma. Adult epilepsy is primarily associated with brain tumors, cerebrovascular malformations, metabolic abnormalities or endocrine disorders, and systemic diseases. The highest incidence of epilepsy occurs in the elderly, usually secondary to cerebrovascular disease, neurodegenerative disease, head trauma, or brain tumors.

If someone has had one or more unprovoked epileptic episodes within a week of the injury, then epilepsy may be determined at the time of clinical diagnosis. Its development can be divided into three phases [3]: the initial triggering event, the latent period and the period of recurrent seizures, which characterize epilepsy. Common triggering events are stroke and head injury, in the case of

stroke or head injury, the molecular level of the damaged area changes [4]. Shortly after a tumor or encephalitis injury, the patient's epilepsy enters a latency period. The latency period may last for months or years until the patient begins to develop unprovoked chronic epilepsy. Recurrent seizures are often exacerbated by cellular and molecular changes caused by the injury.

Research into neuroplasticity holds profound significance for the treatment of epilepsy. Currently, around 30% of epilepsy patients are resistant to existing medications, a condition known as "refractory epilepsy." In-depth exploration of the mechanisms behind epilepsy can aid in the development of more effective treatments. By investigating neuroplasticity, we can better understand how epilepsy is triggered and propagated within the brain, offering potential new therapeutic targets. For instance, inhibiting maladaptive neuroplasticity, such as the reinforcement of abnormal neural circuits, could help prevent the escalation of seizure frequency, providing new hope for patients with refractory epilepsy.

Harnessing neuroplasticity in the treatment of epilepsy opens the door to non-pharmacological interventions, such as neuromodulation techniques and behavioral interventions. These methods, by modulating neural circuits in the brain, may reduce the reliance on medication, offering alternative options for patients who are unresponsive to drugs or experience severe side effects. As research in this area advances, we can anticipate more personalized, safer, and more effective treatments for epilepsy.

This article begins by exploring the mechanisms underlying epilepsy, detailing various principles of its onset and its relationship with neuroplasticity. It then introduces the concept of neuroplasticity, highlighting current cases and the mechanisms of applying neuroplasticity in epilepsy treatment. Furthermore, the article discusses the feasibility and limitations of treating epilepsy through neuroplasticity-based approaches.

2. Mechanisms of Epilepsy

The intrinsic mechanisms of epilepsy are complex and varied, and the currently widely recognized cause is due to an imbalance between excitation and inhibition in the central nervous system. It is closely related to neurotransmitter imbalances, ion channels, glial cells, and genetic and immune abnormalities, and primarily involves abnormal neuronal firing activity. Normally, neurons transmit information through electrical signals to maintain normal brain function. However, in patients with epilepsy, some neurons exhibit abnormal, excessive electrical activity, which can lead to seizures. This abnormal discharge may be localized or spread throughout the brain, triggering various types of seizures. Causes of abnormal neuronal discharge may include increased neuronal excitability or decreased inhibition, which disrupts the normal balance of electrical signals in the brain. For example, neuronal hyperexcitability caused by excessive release of the neurotransmitter glutamate or deficient release of gamma-aminobutyric acid (GABA) can be considered as the basis for seizures [5].

Inflammation is one of the key mechanisms contributing to the development of epilepsy, and it involves reactions of tissues and cells in the bloodstream. These reactions may in some cases lead to cell damage or loss within the tissue. Studies have shown that inflammation plays a key role in the development of epilepsy, and that it may lead to lower seizure thresholds, neurodegeneration, impaired neuron generation, diminished synaptic plasticity, disturbed blood flow and cellular responses, and possible disruption of neuroplasticity and blood-brain barrier permeability. Various types of cells, such as microglia, are activated in inflammation and produce inflammatory mediators and reactive substances, such as reactive oxygen species, causing tissue damage and neurotoxicity. These processes have been linked to cognitive deficits, including oxidative stress and synaptic remodeling [6]. Another study showed that astrocytes promote central nervous system tissue repair by releasing insulin-like growth factor, which promotes central nervous system tissue repair, but also produces excessive amounts of cytokines such as IL-6 to perpetuate inflammation. This disrupts the blood-brain barrier and regulation of neuronal function, leading to abnormal excitability and thus seizures [7].

The central nervous system is able to reorganize itself in response to physiological and pathological stimuli, a process known as neuroplasticity. This is determined by the properties of the cells and molecules of the organism, and neuroplasticity is when synapses change the structure, number, and function of their connections. For example, neuroplasticity during the development of epilepsy after neuronal injury makes the brain more prone to recurrent epilepsy [8]. These alterations in neuroplasticity affect neurotransmitter-mediated neuronal signaling, including neurotransmitter transport, synthesis, or degradation, resulting in decreased inhibition and increased excitability of neurons, which leads to epileptogenesis.

Ion channel dysfunction is also an important factor in seizures. Ion channels are protein structures on neuronal membranes that regulate the movement of sodium, potassium, calcium, and other ions and directly affect the electrical activity of neurons. Ion channel dysfunction due to genetic mutations or acquired factors can destabilize the neuronal membrane potential, which can trigger seizures.

Additionally, the pathophysiology of epilepsy may involve structural or metabolic damage to the brain. Congenital brain abnormalities, brain tumors, traumatic brain injuries, cerebrovascular diseases, or brain infections can disrupt the normal function of neuronal networks, leading to abnormal discharges[9]. Metabolic disturbances, such as hypoglycemia, hyponatremia, or metabolic encephalopathy, may also induce seizures by affecting neuronal metabolism and electrical activity. Genetic factors are also a significant cause of epilepsy. Hereditary epilepsy often exhibits familial clustering and has an earlier age of onset.

Although the fundamental mechanism of epilepsy involves abnormal neuronal discharges, certain external or internal factors can trigger seizures. These factors include sleep deprivation, stress, excessive fatigue, strong light stimuli, and the use of alcohol or drugs, to name a few triggers that affect neuronal excitability and make susceptible individuals more prone to seizures.

3. Neuroplasticity

Neuroplasticity can be broadly defined as the ability of the nervous system to change its ability to respond to internal and external stimuli by reorganizing its structure, function at molecular, cellular, neural and behavioral levels [10]. The key in neurological disease research is the precise regulation of neural activity, reorganization of neural network structures, and restoration of neural function. In some neurological diseases, neuronal damage or death due to various internal and external factors further impedes neural regeneration and repair. Treatment for these diseases often requires neuroregulation to suppress abnormal neuronal excitation [11]. Thus, the process of repairing neural damage can be referred to as neuroplasticity [12]. The modulation of neuroplasticity can repair neural damage and restore normal neural function, becoming an important therapeutic target for various neurological diseases.

In epilepsy, the theory of neuroplastic changes is considered a major pathological basis. Structural anatomical studies of the brain in epileptic patients reveal various structural plastic changes in the hippocampal dentate gyrus, including significant increases in neurogenesis, new axonal branch growth or sprouting, and synaptic reorganization. These changes affect neuronal signal conduction and disinhibition, leading to seizures [13]. Additionally, post-seizure changes also induce alterations in the expression levels of neuroplasticity-related molecules, including significant increases in various neurotrophic factors and molecules associated with synaptogenesis. These changes contribute to the pathological features of epileptic abnormal discharges.

3.1. Feasibility of Neuroplasticity-Based Therapies

In 2009, a symposium organized by the National Institutes of Health's Blueprint for Neuroscience Research convened 27 leading scientists to identify promising intervention mechanisms for promoting neuroplasticity changes [12]. In neurology, there is a lack of effective animal models for studying the therapeutic mechanisms of neuroplasticity in neurological disorders, with a few notable exceptions.

For addictive disorders, multiple models are available for research. These studies conclude that drug abuse represents a maladaptive behavior driven by the intractable plasticity of subcortical reward circuits, making it difficult to establish new behaviors.

Neuroplasticity varies in intensity at different developmental stages. Neuroplasticity peaks early in development, which means that its effects are more active in children than in adults. This effect can be both beneficial and detrimental. For example, the recovery of language and motor function after hemispherectomy for intractable epilepsy is better for the younger the patient. Reorganization of language and motor function occurs in the remaining hemispheres, with the greatest potential for reorganization in children under 6 years of age [14].

Neuroplasticity also changes during neurodegeneration and aging. In general, the level of neuroplasticity decreases in patients with neurodegenerative diseases. A number of pathologic factors can directly affect synaptic neuroplasticity. For example, in one study, researchers purified beta-amyloid dimer from postmortem tissue of Alzheimer's patients and injected it into rodents. The results showed that this substance can affect synaptic plasticity, providing a possible cellular mechanism for pathology-induced brain circuit plasticity [15]. Normal aging in combination with neurodegenerative diseases further reduces neuroplasticity. Enhancing neuroplasticity could play a role in mitigating the effects of aging, with potential interventions including pharmacotherapy or non-invasive brain stimulation.

A case study involving a 6-year-old child with intractable focal motor epilepsy revealed that limited resection of the lesion was performed to prevent language function impairments. At the age of 17, a tumor was detected, potentially leading to language deterioration, necessitating a craniotomy. In this instance, electrical stimulation of the lesion was applied to enhance the neuroplasticity of the brain's language areas, ensuring better protection and promoting postoperative recovery of language functions. Researchers employed craniotomy and cortical stimulation mapping (CSM) to identify the language areas, administering continuous electrical stimulation at 130 Hz, 1 ms, with a maximum of 10V, increasing by 2V daily, alongside language training exercises. Results showed that the patient’s language abilities improved continuously over six days, ultimately achieving comprehension and expression under maximum stimulation. More than a year post-surgery, the patient remained seizure-free, resuming normal academic and social activities. This case demonstrates that direct cortical stimulation techniques combined with prehabilitation for language functions can significantly enhance neuroplasticity, particularly in patients with long-term lesions where intrinsic neuroplasticity has already commenced[16].

3.2. Interventions to Promote Neuroplasticity

Current techniques to promote neuroplasticity include several non-invasive brain stimulation techniques, the most prominent of which is TMS. TMS uses an external magnetic coil to generate induced currents in areas of the cerebral cortex. In contrast, transcranial direct current stimulation (tDCS) attaches two electrodes to the scalp and delivers a low-amplitude direct current that penetrates the brain and alters membrane potentials, thereby affecting neuronal excitability without triggering neuronal depolarization. Low-amplitude continuous stimulation inhibits cortical excitation, while high-amplitude intermittent stimulation promotes cortical excitation [17]. The optimal stimulation protocols and methods to promote neuroplasticity require further research

DBS is a method of altering neuroplasticity through electrical stimulation. By implanting electrodes and delivering programmable electrical currents to deep brain structures, DBS can modulate neuroplasticity by activating networks of neurons connected to the stimulated area or repairing neuronal damage [18].

Pharmacological interventions can affect some of the cellular structures associated with neuroplasticity. Certain drugs, such as HDAC inhibitors, mTOR inhibitors, and trkB activators, can manipulate cellular and synaptic pathways to enhance neuroplasticity [19]. These drugs may be more

effective in promoting neuroplasticity when combined with specific behavioral therapies such as cognitive-behavioral therapy, for example, to treat depression.

Physical rehabilitation training can also improve neuroplasticity, and some include robotic assistance. This approach requires further research to adapt and optimize it so that it is effective for different patient populations. In addition, physical rehabilitation can be used as a complement to pharmacologic interventions. Aerobic exercise can benefit neurological function by promoting neuroplasticity in the brain and mitigating the effects of aging and dementia [20]. Cognitive training, a derivative of physical rehabilitation, consists of well-designed exercise programs that can affect dysfunctional nociceptors and thus improve the condition.

Real-time functional magnetic resonance imaging (rtfMRI) technology enables real-time monitoring of changes in activity in specific brain regions, making targeted therapy possible. This method allows subjects to learn new ways to regulate brain function. Data have shown that this technique allows subjects to learn to control specific brain regions, such as the prefrontal lobe [21]. Another study has shown that both healthy subjects and chronic pain patients can learn to control the activation of brain regions associated with pain perception. This can be trained with rtfMRI, through which patients can reduce their perception of pain[22].

4. Conclusion

Epilepsy is not only a neurological disorder, it can have a significant impact on all aspects of a person's life. It can impair brain function, lead to mental health problems, social discrimination, and a reduced ability to lead a life, a set of issues that make people with epilepsy need comprehensive medical, psychological, and social support to cope with these challenges. Medications bring about treatments that make the condition better but have certain side effects, and we need to pioneer new treatments to reduce the harm caused to patients during treatment. In recent years, studies have illuminated several mechanisms underlying epilepsy, including abnormal neuronal discharges in the brain, dysfunctional ion channels, functional and structural brain damage, and impairments in neuroplasticity. Neuroplasticity, the brain's ability to repair neural damage, has become a major focus of recent research. By artificially influencing neuroplasticity, it is possible to achieve therapeutic effects. Neuroplasticity therapies are most effective in children, with a lesser impact on patients suffering from neurodegenerative diseases. While there have been cases of treating epilepsy by enhancing neuroplasticity, such cases are rare. For instance, as mentioned earlier, craniotomy and CSM have been used to bolster neuroplasticity, thereby reducing postoperative epileptic seizures. There are various methods to enhance neuroplasticity, such as DBS and pharmacological interventions, and more related approaches are still under investigation. Currently, different methods have been developed to treat epilepsy, but most of them target the seizure itself rather than the underlying process. Neuroplasticity therapies aim to suppress seizures during the developmental phase, addressing epilepsy at its root. Although there are cases where neuroplasticity has been applied to treat epilepsy, research into these techniques remains incomplete. It is essential to explore additional methods that promote neuroplasticity and to develop new drugs to achieve better outcomes in both the prevention and treatment of epilepsy. The significance of this research lies in its potential to shift epilepsy treatment from symptom management to addressing the underlying mechanisms of the disorder. This approach could provide more individualized, targeted therapies that reduce reliance on drugs and improve patient outcomes. Large-scale clinical trials are critical to validate the efficacy of neuroplasticity interventions, but we currently have little experience with them. Future research should focus on refining these techniques for promoting neuroplasticity and exploring new ways to utilize neuroplasticity to provide safer and more effective epilepsy treatments.

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