Mechanisms of Synaptic Plasticity Disruption in Epilepsy: Advances in Understanding and Therapeutic Innovations

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Abstract:

This review provides an in-depth examination of the processes underlying synaptic plasticity disruption in epilepsy, with a focus on recent advances in understanding and treatment development. Epilepsy is a common neurological disorder affecting around 1% of the global population. It is characterised by recurrent, unprovoked seizures caused by aberrant brain activity. The condition impacts various aspects of life, including cognitive function and emotional well-being. Recent research has shown synaptic plasticity — the capacity of synapses to develop or weaken over time — as an important role in epilepsy aetiology. Aberrant synaptic plasticity, such as excessive long-term potentiation (LTP) and deficient long-term depression (LTD), contributes to the formation of hyperexcitable brain circuits and increases seizure risk.

In epilepsy, key mechanisms impacting synaptic plasticity include neurotransmitter imbalances, synaptic remodelling, inflammatory responses, and genetic and epigenetic factors. Despite the availability of antiepileptic medications (AEDs), approximately one-third of patients remain resistant to treatment, emphasising the need for innovative therapeutic methods. Current treatment approaches include AEDs, surgical procedures, metabolic therapies, and new treatments such as gene therapy and nanotechnology-based solutions.

The aim of this critical review is to comprehend and target maladaptive alterations in synaptic plasticity with the intent to develop more effective therapies. It explores innovative treatment targets, precision medicine, advanced neuromodulation techniques, and the integration of epigenetic therapies. This research addresses not only future goals but also the challenges hindering the development of novel treatments, given the complexity of synaptic plasticity and the heterogeneity of epilepsy. This will be critical for overcoming present therapy barriers and improving patient outcomes.

Key words: Epilepsy, Seizures, Antiepileptic, Cytokines, Synaptic Plasticity.

Introduction

Epilepsy is a chronic neurological disorder characterised by recurrent, unprovoked seizures due to abnormal electrical activity in the brain.[1] As of 2023-2024, the global prevalence of epilepsy is estimated to be around 1% of the population, or approximately 50 million individuals. This estimate is based on data from recent investigations[4] and global health polls. Epilepsy places a significant burden on patients, caregivers and healthcare systems.[2] Seizures vary in nature and intensity, ranging from generalised tonic-clonic seizures to focal seizures with or without impaired consciousness. The condition frequently has a dramatic influence on many aspects of life including cognitive function, emotional well-being and everyday activities.[3]

Learning and memory depend on capacity of synapses to grow or weaken over time in response to increases or decreases in activity. However, aberrant synaptic plasticity is becoming more well recognised as a critical process in the aetiology of epilepsy. Changes in synaptic connection and neuronal excitability can help to initiate and spread seizures.[4] Understanding the link between synaptic plasticity and epilepsy may provide novel targets for therapeutic intervention and improve treatment outcomes.[5]

Recent research has revealed numerous mechanisms that could influence synaptic plasticity in epilepsy.

Mechanisms that influence synaptic plasticity:

1. **Abnormal emission of neurotransmitters and receptor function:** Irregularities in neurotransmitter emission and receptor activity may disrupt excitatory and inhibitory communication, contributing to seizures.
2. **Aberrant synaptic remodelling:** Pathological anomalies in signalling pathways can result in changes to synaptic shape and density, leading to the spread of epileptic activity.
3. **Inflammatory responses:** Neuroinflammation and glial cell activation can affect synaptic plasticity by altering neurotransmitter levels and connections.
4. **Genetic and epigenetic factors:** Alterations in genes associated with synaptic function and plasticity may increase the risk of epilepsy and influence its progression.[6]

Epilepsy is commonly managed with antiepileptic medicines (AEDs) that aim to control seizures and improve quality of life. Despite the availability of multiple AEDs, approximately one-third of epileptic patients remain resistant to drug therapy. This underscores the importance of alternate treatment approaches and innovative strategies for addressing the underlying pathophysiological processes of epilepsy.[7]

The current therapeutic approaches for epilespy include: Antiepileptic drugs (AEDs)

1. AEDs used to regulate neuronal excitability and synaptic transmission. Newer AEDs and medication combinations are being investigated to improve effectiveness while minimising negative effects.
2. For drug-resistant epilepsy, surgical interventions such as excision of epileptogenic brain tissue or neurostimulation techniques (e.g., vagus nerve stimulation, responsive neurostimulation) may provide relief.
3. Metabolic treatments, such as the ketogenic diet can help people with certain epilepsy disorders.
4. Novel therapies including gene therapy, immunotherapy, and targeted molecular treatments, are being studied to address the underlying mechanisms of epilepsy.[8]

Future epilepsy research and treatment are expected to increasingly focus on synaptic plasticity. Understanding how erroneous synaptic alterations contribute to seizure development enables researchers to design targeted therapies that aim at restoring normal synaptic function.[9]

Future research & treatment focus in synaptic plasticity includes:

1. **Mechanistic insights:** Further research into how synaptic plasticity causes epileptic activity may provide novel therapeutic targets.
2. **Innovative therapies:** Developing treatments that directly influence synaptic plasticity such as nanotechnology-based techniques may result in more effective options, particularly for drug-resistant epilepsy.
3. **Precision medicine:** Tailoring treatments to an individuals' synaptic profiles, influenced by genetic and epigenetic variables can result in more personalised and successful epilepsy therapy.
4. **Advanced neuromodulation:** Using approaches that directly impact synaptic activity such as brain stimulation may offer new possibilities for seizure management.
5. **Integrative Approaches:** Combining insights from synaptic plasticity with other therapeutic strategies may support holistic treatment approaches, improving overall patient outcomes.[10]

This review paper provides an in-depth analysis of bridging the gap between synaptic plasticity and epilepsy, which is critical for improving our understanding of the condition and developing effective therapies. Ongoing research into the mechanisms of disruption, together with novel treatment options, offers hope for improved management and, eventually, a better quality of life for individuals with epilepsy.

Pathophysiology of epilepsy

Epilepsy is a complex neurological condition characterised by repeated seizures resulting from aberrant, excessive, or synchronised neuronal activity in the brain. The pathophysiology of epilepsy is diverse, involving a range of pathways that can generally be categorised as genetic, molecular, cellular and network disorders.[11]

Genetic factors: Epilepsy can be induced by mutations in genes related to ion channel function, neurotransmitter release and synaptic organisation. These mutations lead to an imbalance between excitatory and inhibitory impulses in the brain. Genetic epilepsy, including certain types of idiopathic generalised epilepsy is frequently linked to mutations in voltage-gated sodium channels (e.g., SCN1A) or gamma-aminobutyric acid (GABA) receptors.

Cellular and molecular mechanisms: Epilepsy leads to malfunctions in ion channels, neurotransmitter imbalances (particularly GABA and glutamate), and disruptions in synaptic plasticity. Abnormalities in these processes can cause neural networks to become hypersensitive and hypersynchronised, resulting in seizures. Epilepsy is also associated with dysregulation of the mammalian target of rapamycin (mTOR) pathway in addition to neuroinflammatory processes.[13]

Synaptic and network abnormalities: The development of epilepsy is significantly influenced by synaptic plasticity and network abnormalities. Long-term potentiation (LTP) and long-term depression (LTD) are synaptic plasticity mechanisms that can become dysregulated in epilepsy, resulting in erroneous synaptic connections and excitability. Similarly, network-level abnormalities, including alterations in cortical and subcortical channels, contribute to amplification of seizures.[14]

Neuroinflammation: Neuroinflammation plays a significant role in epilepsy. Activated microglia and astrocytes generate pro-inflammatory cytokines, including interleukin-1-beta (IL-1β) and tumour necrosis factor alpha (TNF-α), which can influence neuronal excitability and trigger convulsions.[15]

Epigenetic modifications: Epigenetic modifications, involving deoxyribonucleic acid (DNA) methylation, histone modifications, and non-coding ribonucleic acid (RNA) expression, may regulate gene expression patterns in epilepsy. These modifications might impact neural plasticity, inflammation, and other processes involved in epileptogenesis.[16]

Synaptic plasticity: an overview

Synaptic plasticity refers to the ability of synapses (neuronal connections) to adjust their strength or effectiveness in response to rising or decreasing activity levels over time. Synaptic plasticity is often disturbed in epilepsy, contributing to the onset and duration of seizures.[17] These disruptions can include increased excitatory transmission, reduced inhibitory transmission, or aberrant synaptic remodelling all of which can heighten neuronal excitability and the risk of seizure development and propagation. Understanding these maladaptive changes in synaptic plasticity is essential for developing novel treatment ways therapeutic strategies to manage and potentially prevent epilepsy.[18]

Key concepts of synaptic plasticity in epilepsy

LTP and LTD: LTP is often associated with synapse bolstering, which is essential for memory retention. However, in epilepsy, prolonged or dysfunctional LTP can lead to hyperexcitability in neuronal circuits, triggering seizure initiation and propagation.[19] LTD, on the other hand, involves breakdown of synapses. Abnormal LTD processes may disrupt the balance between excitatory and inhibitory electrical signals in the brain, thereby lowering the threshold for seizure activity.[20]

Hyperexcitability and synaptic remodelling: In epilepsy, synaptic plasticity can lead to pathogenic alterations in the brain's neuronal networks. These alterations include the reorganisation of synaptic connections, which can lead to hyperexcitable circuits more prone to generating seizures.[21] This synaptic remodelling can affect both excitatory and inhibitory synapses, with excitatory synapses becoming excessively potentiated and inhibitory synapses diminished, tipping the balance towards hyperexcitability.[22]

Role of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) Receptors: NMDA and AMPA receptors play a crucial role in synaptic development. In epilepsy, changes in the function or expression of these receptors may stimulate excitatory synaptic transmission, leading to the formation of epileptic foci. Overactivation of NMDA receptors, in particular, may trigger excitotoxicity, a process in which excessive calcium influx damages or kills neuronal cells, thereby deteriorating seizure activity.[23]

Homeostatic plasticity: Homeostatic plasticity mechanisms within the brain modify synaptic strength to safeguard stability in neural pathways. However, in epilepsy, these networks may become dysregulated. Instead of adjusting for erroneous activity, they could inadvertently contribute to the persistence and intensification of seizures.[24]

Neuroinflammation and synaptic plasticity: Inflammatory processes in the brain, commonly observed in patients with epileptic seizures, can have profound effects on overall synaptic plasticity. Neuroinflammation may influence synaptic function through several mechanisms, including alterations in neurotransmitter levels, such as increased glutamate or reduced GABA, leading to an excitatory-inhibitory imbalance in the neural network.[25] Furthermore, neuroinflammation can impact receptor expression, for instance, by upregulating NMDA and AMPA receptors or downregulating GABA receptors, thereby increasing neuronal excitability. These changes may also affect synaptic connections by promoting structural remodelling of synapses and dendritic spines, creating a more favourable environment for hyperexcitability and seizure propagation.[26] This inflammatory milieu not only contributes to the initiation and maintenance of epileptic activity but may also exacerbate the progression of epileptogenesis, potentially worsening long-term outcomes.[27]

Genetic and epigenetic factors: Individuals may be susceptible to epilepsy due to inherited defects or epigenetic shifts that influence proteins involved in synaptic plasticity. These disturbances may hinder normal synaptic activity, increasing the incidence of seizures and the likelihood of persistent deterioration of the illness.[28]

Synaptic plasticity and Epileptogenesis: Bridging the Gap

Synaptic plasticity and epileptogenesis as a bridge refers to the idea that processes underpinning synaptic plasticity which entail modulating and adapting synaptic strength and connection play an important role in the development and progression of epilepsy. This bridge demonstrates how the same processes that are required for normal brain function, learning, and memory, when interrupted or altered, contribute to the pathophysiological changes that cause epilepsy.[29] Understanding how aberrant or maladaptive synaptic plasticity leads to the formation of epileptic networks functions as a bridge between these principles. For example, excessive or uncontrolled synaptic strengthening (known as excitatory synaptic plasticity) or impaired inhibitory synaptic plasticity can both contribute to hyperexcitability and seizure production. By analysing this bridge, researchers are interested in investigating how disturbances in normal synaptic plasticity pathways may initiate or intensify epileptic disorders, as well as identify novel treatment targets to restore balance and prevent seizures.[30]Therapeutic Targets in Synaptic Plasticity

Understanding the role of synaptic plasticity in epilepsy has led to the identification of multiple attainable therapeutic targets for preventing or treating seizures by modifying synaptic activity. These goals focus on processes that govern synaptic

plasticity, such as LTP, LTD, homeostatic plasticity, and structural modification.[31] Here, we provide a more detailed discussion of therapeutic targets and approaches based on these frameworks.

Modulation of NMDA receptors

NMDA receptor antagonists: NMDA receptors are essential for the formation of LTP, which, if dysregulated, can lead to epileptic hyperexcitability. NMDA receptor antagonists aim to inhibit excessive LTP and seizure activity.[32] Memantine, an NMDA receptor antagonist, has shown promise in reducing seizure frequency in preclinical models and clinical studies. However, the challenge remains to achieve selectivity and prevent cognitive adverse effects associated with NMDA receptor blockade.[33]

Selective NMDA receptor subunit modulators: Targeting expected NMDA receptor subunits may offer a more selective strategy. For example, selective antagonists of the NR2B subunit are being studied, as NR2B-containing NMDA receptors are crucial in synaptic plasticity and epileptic activity. These selective modulators are designed to minimise negative effects while efficiently reducing hyperexcitability.[34]

Enhancing LTD pathways

Modulators metabotropic glutamate receptors (mGluR): mGluRs mediate LTD, and altering these receptors may help restore the balance between excitation and inhibition. Positive allosteric modulators of mGluR2 and mGluR3, which are implicated in LTD, are being investigated as potential therapeutic agents. These chemicals may improve LTD in hyperexcitable circuits and reduce seizure activity.[35]

Endocannabinoid system modulation: The endocannabinoid system mediates LTD through CB1 cannabinoid receptors. Enhancing endocannabinoid signalling or utilising synthetic cannabinoids that activate CB1 receptors can induce LTD while potentially lowering seizure susceptibility. The aim is to develop cannabinoids that specifically target brain circuits implicated in epilepsy without producing intoxicating effects.[36]

Restoring homeostatic plasticity

Brain-derived neurotrophic factor (BDNF) and Tropomyosin receptor kinase B (TrkB) receptor modulation: BDNF and its receptor, TrkB, are essential for homeostatic plasticity. Increasing BDNF signalling can help restore synaptic balance and minimise hyperexcitability. Small compounds or gene therapies that boost BDNF expression or activate TrkB receptors are under investigation. However, precise management of BDNF levels is necessary to avoid undesirable effects on neurogenesis and synaptic formation.[37]

TNF-α inhibitors: TNF-α regulates synaptic strength and is elevated in epilepsy. Inhibiting TNF-α or its signalling pathways may improve homeostatic plasticity and decrease seizure frequency. Etanercept, a TNF-α inhibitor, is being studied for its potential to alter neural plasticity and enhance seizure control.[38]

Structural plasticity modulation

Targeting dendritic spine remodelling: In epilepsy, aberrant dendritic spine remodelling can lead to network hyperexcitability. Strategies to normalise spine density and shape are being investigated. Compounds that modify cytoskeletal dynamics, for example, have the potential to reverse aberrant structural plasticity and reduce seizure activity.[39]

Ion channel modulators: Ion channels play a significant role in synaptic development and are potential targets for structural modification. Ion channel modulators, including those targeting voltage-gated sodium and calcium channels, have the ability to modulate synaptic strength and network excitability. Agents that selectively target these channels to correct aberrant plasticity may have therapeutic value.[40]

Epigenetic modulation

Histone deacetylase inhibitors (HDACi): Epigenetic changes, such as histone acetylation, play a crucial role in regulating gene expression, which directly impacts synaptic plasticity and the process of epileptogenesis. HDACi work by preventing the removal of acetyl groups from histone proteins, promoting a more open chromatin structure that facilitates gene transcription. By this mechanism, HDACi can alter the expression of genes involved in synaptic plasticity, potentially restoring normal synaptic function and counteracting the pathological changes contributing to epilepsy.[4]

DNA methylation modifiers: DNA methylation influences both gene expression and synaptic plasticity. Modifiers that alter DNA methylation patterns have the potential to repair the abnormal plasticity associated with epilepsy. Research on chemicals that precisely target DNA methylation in neurons may lead to novel treatment strategies.[42]

Advanced Drug Delivery Systems

Nanoparticle-based delivery: Nanoparticle-based drug delivery systems can target medications to specific brain areas. These systems are designed to bypass the blood-brain barrier and deliver medications that regulate synaptic plasticity directly to affected regions. This method can enhance treatment effectiveness while minimising systemic side effects.[43]

Gene therapy: Gene therapy aims to directly influence the expression of genes involved in synaptic plasticity. For example, releasing genes that encode synaptic plasticity modulators or fix pathogenic alterations may provide a more tailored approach to treating epilepsy. Advances in viral vectors and delivery technologies make gene therapy for epilepsy more feasible.[44]

Future Directions

Personalised medicine: Developing tailored treatment approaches based on the distinctive synaptic plasticity processes damaged in each patient's epilepsy may enhance results. Advances in genetic, genomic and proteomic technology may allow for more precise characterisation of specific epilepsy subtypes and help select targeted treatments.[45]

Development of selective modulators: Future research should focus on designing selective modulators that target abnormal aspects of synaptic plasticity while preserving normal functioning. For instance, developing drugs that selectively modify certain subtypes of NMDA receptors or signalling pathways involved in LTP and LTD could minimise off-target effects.[46]

Integration of epigenetic therapies: Epigenetic modulation delivers an innovative approach to influence synaptic plasticity. Epigenetic drugs, such as HDAC inhibitors and DNA methylation modifiers, may lead to novel treatments for epilepsy by correcting abnormal plasticity. Understanding how epigenetic changes impact synaptic plasticity and epileptogenesis is an ongoing area of research.[47]

Advancements in neuroimaging and electrophysiology: Technological advances in neuroimaging and electrophysiology can help us better understand synaptic plasticity and how it changes in epilepsy. High-resolution imaging tools, such as functional MRI (fMRI) and optogenetics, may allow us to visualise and alter synaptic changes in real-time, improving our knowledge of their role in epilepsy and directing therapeutic development.[48]

Exploration of novel drug delivery systems: Innovative drug delivery technologies, such as nanoparticle-based systems or targeted gene therapy, may enhance the accuracy and efficacy of therapies for synaptic plasticity disorders. These technologies could potentially administer medicines directly to the afflicted brain areas, reducing systemic adverse effects and improving therapeutic outcomes.[49]

Challenges

Epilepsy, a complex neurological condition, poses significant challenges due to its numerous origins, clinical presentations, and the considerable burden it places on individuals and healthcare systems. Central to its pathophysiology is the disruption of synaptic plasticity processes, which, while essential for normal brain function, become pathogenic in epilepsy. This disruption complicates the development of tailored therapies, as interventions must precisely regulate these pathways while preserving cognitive functions like memory. The heterogeneity of epilepsy, with its multiple subtypes and distinct underlying causes, complicates treatment, necessitating personalised therapeutic approaches rather than a one-size-fits-all strategy. Furthermore, medicines targeted at regulating synaptic plasticity may have unanticipated adverse effects such as cognitive impairments, highlighting the importance of balancing therapeutic efficacy with safety. Identifying reliable biomarkers to reliably diagnose and monitor the condition remains a challenge but is essential for personalising treatments and assessing their effectiveness. Despite promising preclinical research, translating these findings into effective clinical therapies is challenging, underscoring the need for better preclinical models and a better understanding of therapeutic applicability. Furthermore, the long-term effectiveness and safety of these therapies are major issues since sustained benefits with minimal side effects are required for their successful usage in clinical practice.

Conclusion

This review provides a comprehensive examination of synaptic plasticity and its implications for epilepsy. Synaptic plasticity, defined as the ability of synapses to change strength and efficiency over time, is vital for neuronal adaptation to new experiences and environments. However, in epilepsy this mechanism is dysregulated, which contributes to the disorder's onset and progression. In epilepsy, aberrant synaptic plasticity is characterised by excessive LTP and deficient LTD, leading to an imbalance between excitatory and inhibitory signals. This imbalance fosters hyperexcitable neuronal networks, resulting in spontaneous seizures. Abnormalities in homeostatic plasticity further exacerbate the condition. Despite advances in understanding these pathways, several challenges remain, such as the intricacy of synaptic plasticity, the variability of epilepsy, and the risk of treatment-related adverse effects. Future research should focus on personalised medicine approaches, selective modulators that target pathological synaptic alterations, and advancements in neuroimaging, epigenetics and drug delivery systems. Addressing these obstacles through collaborative research, longitudinal investigations, and continuous education will be critical for developing effective personalised treatments. Continued investigation into these mechanisms is essential for translating findings into better medicines and improving epilepsy care.

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