REVIEW

Unraveling epilepsy: Investigating stem cell approaches for innovative treatment and future cure

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Abstract

Epilepsy is a persistent neurological disorder characterized by repeated, spontaneous seizures that arise without a specific cause. These seizures result from abnormal electrical activity in the brain, leading to a range of symptoms, from brief periods of unconsciousness or minor sensory disturbances to severe convulsions. The management of epilepsy remains a significant challenge, as current treatment modalities, primarily involving antiepileptic drugs and surgical interventions to remove seizure foci, often provide adequate control for a substantial portion of patients. For this reason, stem cell therapies have become a hopeful approach because of their ability to potentially restore and renew impaired neural networks, which is particularly relevant for neurological disorders like epilepsy. This review investigates the present state of stem cell therapies in epilepsy, analyzing distinct types of stem cells, their mode of action, preclinical and clinical trials, as well as future research prospects.

Keywords: Epilepsy, treatment, neurological disorders, neural networks, seizures, stem cell

Introduction

Epilepsy, a prevalent brain condition affecting over 50 million people globally, is primarily prevalent in infants and older age groups (Miguel Sanz et al., 2023). The World Health Organization (WHO) considers epilepsy as a disorder if there are recurring seizures at least twice in 24 hours as a result of electrical imbalances between inhibitory and excitatory mechanisms of the brain (Klein et al., 2024), which necessitates a comprehensive strategy for successful treatment. Individuals afflicted with this neurological disorder experience significant adverse impacts that greatly diminish their quality of life in their social life, education, and employment. The seizures typically exert significant influence over people's lives, leaving them with little sense of living. However, there is still no efficient treatment targeting the root cause of seizures. Pharmaceutical treatments, surgeries, and certain diets are all common treatments for controlling seizures, and they are generally aimed to minimize the superficial side effects of the seizures or try to suppress them. Nevertheless, stem cell therapy emerges as a significant candidate that can target the core causes of seizures. The self-renewing and differentiating capacities of stem cells enable them to contribute to tissue repair and regeneration, potentially restoring and integrating dysfunctional neuronal circuits to a healthy state (Lybrand et al., 2020). This review discusses the present state of stem cell therapies in epilepsy as an innovative and promising approach for future treatment and cure (Wang et al., 2021).

Epilepsy is a complex and heterogeneous neurological disease with multiple underlying mechanisms. The molecular mechanism of this alteration is mainly based on the reduction of Gamma-Aminobutyric Acid (GABA) neurotransmission and the increase of glutamatergic neurotransmission (**Figure 1**). These alterations are typically due to modifications in the structure and synthesis of ion channels, the release and reabsorption of neurotransmitters, and issues with transporter and post-synaptic receptor activation. These changes are typically due to modifications in the structure and synthesis of ion channels, the release and reabsorption of neurotransmitters, and issues with transporter and post-synaptic receptor activation. Consequently, these alterations can disrupt the balance between excitatory and inhibitory neurons, destabilizing neuronal homeostasis and resulting in neuronal hyperexcitability (McNamara et al., 1999). Finally, these mechanisms generally cause one main problem, which is damaging the brain and subsequently causing changes in neuronal circuits (Patel et al., 2019). According to the underlying mechanisms, the etiology of epilepsy is divided into six groups: structural, genetic, infectious, metabolic, immune, and unknown epilepsies.

As a result of these underlying mechanisms, there are multiple epileptic seizure types that an individual with epilepsy may experience. The International League Against Epilepsy (ILAE) categorization divides epileptic seizures into three major categories: focal, generalized, and unknown (Sirven et al., 2015). Generalized seizures and focal seizures are the two types of seizures. A focal seizure occurs on one side of the brain, but can spread to both sides, causing mild or severe symptoms depending on how electrical discharges spread. Epilepsy cases categorized as focal seizures account for approximately 60% of all epilepsy cases. Additionally, generalized seizures occur simultaneously in both hemispheres of the brain. The primary cause of this type of seizure is an imbalance between the brain's excitatory and inhibitory pathways. On the other hand, around 23-35% of epilepsy cases are classified as generalized. Finally, the unknown seizures are those that do not fit into both classifications focal and generalized (Dubé et al., 2007). These seizures typically occur at random, although occasionally they can be triggered by stress, sleep deprivation, waking up, alcohol consumption, certain medications, flashing lights, or a woman's monthly period.

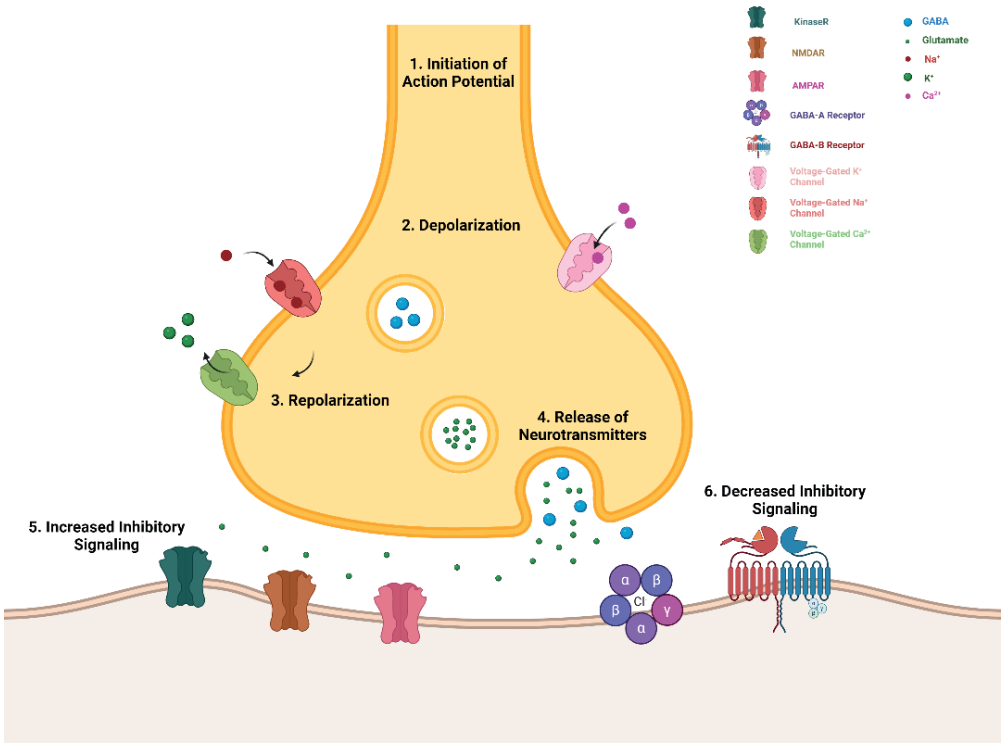

Figure 1. Mechanism of Epilepsy *(Created by BioRender)*.

Beyond seizure control, current treatments do not address the underlying neurobiological changes in the brain, such as neuronal loss and synaptic dysfunction, which contribute to the disease's progression. Stem cell therapy offers the potential to not only reduce seizures, but also to repair damaged neural circuits, promote neurogenesis, and restore normal brain function. This therapy aims to replace lost or damaged neurons, modulate abnormal neural networks, and even provide neuroprotective effects; making it a versatile option for addressing the multifaceted challenges of epilepsy (Chang & Chang, 2022). Furthermore, stem cells have the potential to release various trophic factors that support brain healing and reduce inflammation, offering a holistic approach to treatment that goes beyond symptom management (Das et al., 2019).

Current treatment methods

The World Health Organization states that epilepsy accounts for 0.3% of all deaths worldwide (Murray et al., 2012). According to current technological and scientific advancements, multiple treatment options aim to make patients seizure-free for those who try to live with severe life conditions like epilepsy. The most commonly used treatments in clinics include anti-seizure medications (ASMs) to control seizures, surgical procedures to remove the seizure focus, implantable devices like vagus nerve stimulators, and dietary therapies such as the ketogenic diet.

Pharmaceutical treatment

The first line of treatment method to treat epilepsy are pharmaceutical compounds called antiseizure medications (ASMs) or antiepileptic drugs to prevent or lessen the frequency and intensity of seizures by addressing different pathways and mechanisms in the brain that control neuronal excit-

ability and transmission (Vezzani et al., 2019). A thorough understanding of the effects and mode of action of ASMs is important, especially to be able to apply them to individual patients according to their seizure type. However, ASMs can have severe side effects, including an increased risk of birth defects, allergic skin rashes, liver or bone marrow failure, and complications involving the liver or pancreas. Additionally, a significant decrease in white blood cell or platelet counts, though not common, can occur, particularly in polytherapy, and should not be ignored (Louis et al., 2009).

In addition to all these severe side effects, 30-50% of epilepsy patients are drug-resistant; non-responsive to the properly selected and administered antiepileptic drug regimens, either alone or combined with other treatments, according to the International League Against Epilepsy (Kwan et al., 2010). A major challenge in developing new treatments for drug-resistant epilepsy is the poor understanding of the biological basis of pharmaco-resistance (Voskuyl & Clinckers, 2009). This setback with pharmacological treatments highlights the need to explore alternative or supplementary treatment approaches.

Surgical treatment

Surgical treatment is the alternative option to ASMs, especially for the drug-resistant epilepsy patients. Surgical treatment is carried out via the removal of the specific area that originates the seizures (Kwan et al., 2011). The success and suitability of this treatment method varies according to the type of epilepsy, the affected brain area, and the patient's overall health. Brain mapping is the most essential part of surgical treatment, because it is crucial to know the functions of the affected area; such as language, motor, sensory, or vision, to understand how the patient's life will be affected after the surgery. Nevertheless, surgical treatment carries risks; including paralysis, memory issues, partial loss of peripheral vision, double vision, mood disturbances, diminished motor skills, and speech impediments (Guerreiro et al., 2016; Nair et al., 2016). Moreover, although surgery can be successful for certain types of epilepsy, most patients with drug-resistant epilepsy do not qualify for this option.

Other treatments

Alternative treatment modalities, especially for drug-resistant epilepsy, comprise vagus nerve stimulation and dietary interventions, such as ketogenic diet and modified Atkins diet. Surgically implanting a device to stimulate the vagus nerve aims to decrease or prevent seizures , while dietary therapies try to induce a state of ketosis, which is believed to have an anticonvulsant effect by altering metabolic processes (Johnson, 2019, Riva et al., 2021).

There are five main device types used for vagal stimulation, each with different mechanisms and characteristics for stimulating the vagus nerve; Deep Brain Stimulation (DBS), Responsive Neurostimulation (RNS), Vagus Nerve Stimulation (VNS) Therapy, External Trigeminal Nerve Stimulation, and Seizure Alert devices (Shaefi & Harkness, 2003). Unfortunately, if a patient has concurrent health conditions such as severe asthma, breathing difficulties, sleep apnea, or certain heart problems, vagal stimulation may lead to serious complications (Liu et al., 2017). In addition, it comes with risks that can reduce the quality of life, such as voice changes, shortness of breath, and pain in the throat or neck (Kwan et al., 2010).

Dietary therapies, often employed as adjuncts to seizure medications for seizure control, include the classic ketogenic diet, the low glycemic index treatment (LGIT), the medium-chain triglyceride (MCT) ketogenic diet, and the modified Atkins diet (MAD) (Lee et al., 2018). These diets require precise weighing and measurements. Maintaining moderate calorie, liquid, and protein intake illustrates

the difficult and strict nature of these diets, particularly for children. Despite the benefits, these diets have been associated with an increased risk of serious acidosis and gastrointestinal issues, which can negatively impact a patient's daily life. Prolonged adherence to such dietary regimens can lead to severe consequences; including elevated blood cholesterol levels, kidney stones, constipation, inhibited growth, and bone fractures (Vezzani et al., 2019). Ultimately, these treatments do not cure the disease but provide only palliative care, highlighting the need for more effective and innovative solutions for epilepsy (Neal et al., 2008).

Against all recent progress, epilepsy still poses a significant challenge in terms of treatment and management (Alayli et al., 2023). Currently, epilepsy affects around 1-2% of the global population. Despite the presence of over thirty anti-epileptic medications in the market, 30% of patients continue to experience refractory epilepsy, indicating that medications alone are inadequate for seizure control (French et al., 2004). Moreover, alternative treatment modalities such as surgery and neurostimulator device implants are not universally applicable to every patient, as they offer relief to a limited subset of individuals. Even for those deemed suitable candidates, these options necessitate thorough patient evaluation and selection processes. Regarding dietary interventions, modified Atkins (MAD) and ketogenic (KD) diets are primarily utilized currently. However, neither of these options offers a comprehensive solution on its own, and they may not be suitable for every patient. Besides, these diets are not ideal for long-term use because of their strict regimen and side effects (Neal et al., 2008). Therefore, there is an urgent need for efficient treatment options and a prompt solution, as epilepsy is a severe disorder.

Stem cell-based therapy

In the treatment of epilepsy, stem cells have shown promise in treating a variety of neurological conditions. Stem cells are unspecialized cells that are capable of differentiating into different cell types. In stem cell therapy for epilepsy, the aim is to replace or repair damaged brain cells that play a role in the onset and progression of seizures. Prolonged or uncontrolled epileptic seizures can have wide-ranging adverse effects, including neuronal injury or death, mitochondrial dysfunction, increased reactive oxygen species, and astrocyte activation across the body. Because stem cells may regenerate, stem cell-based therapies present an appealing option for controlling long-term seizures, especially in drug-resistant epilepsy cases. This suggests that stem cell treatment holds potential as a new therapeutic strategy for treating this disease. Given their inherent capability to self-renew and differentiate into distinct cells, stem cells play a vital role in tissue regeneration. Additionally, this property offers the possibility of restoring and integrating disrupted neural circuits into a functioning condition. Stem cell therapy may play crucial roles in managing epilepsy, including inducing seizure remission, inhibiting epileptogenesis, averting the onset of chronic epilepsy, as well as enhancing cognition (Chang & Chang, 2022).

Different types of stem cells are primarily preferred by clinicians for use in treating epilepsy. Embryonic stem cells (ESCs) are undifferentiated cells obtained from embryos, and they can differentiate into numerous types of cells, notably neural cells, due to their pluripotency. Research has demonstrated their capacity to generate neurons and glial cells in order to repair the brain (Thompson et al., 2023). Nevertheless, ethical considerations and the possibility of tumor formation are substantial obstacles. Induced pluripotent stem cells (iPSCs), obtained from reprogrammed somatic cells, offer a solution to the ethical challenges faced with ESCs. Researchers are focusing on improving the differentiation efficiency of iPSCs to prevent tumorigenic properties, ensuring they mature fully before transplanta-

tion (Sayed et al., 2016). Furthermore, mesenchymal stem cells (MSCs), multipotent cells, give rise to several types of cells, including neurons. They contain anti-inflammatory and immunomodulatory effects, which can attenuate the epileptic brain environment (Huang et al., 2016). Neural stem cells (NSCs) are a promising treatment option for damaged neural networks, because they possess the ability to differentiate into both neurons and glial cells. Preclinical research NSCs have the ability to incorporate into the brain tissue of the host and decrease seizures (Xu et al., 2019). The limited availability of adult and fetal brain-derived NSCs and ethical concerns are among the issues that contribute to the scarcity of NSC treatments for epilepsy, despite their potential therapeutic advantages. Obtaining a sufficient quantity of adult brain-derived NSCs for therapeutic reasons is impossible from a living donor and difficult from the postmortem adult or fetal brain, since they are mostly found in certain locations like the subventricular zone and the hippocampus. Moreover, the act of collecting neural stem cells produced from fetal brains gives rise to ethical apprehensions about the destruction of human fetuses and the possibility of exploitation (Thodeson et al., 2018).

MSCs demonstrate the most therapeutic potential among these different stem cell types because of their beneficial characteristics, such as neuroprotection, immunomodulation, support for neurogenesis, and the ability to suppress oxidative stress damage and inflammation. MSCs exert many benefits, because they secrete diverse biologically active components like anti-inflammatory cytokines and neurotrophic factors (Milczarek et al., 2018; Vizoso et al., 2017). Research has demonstrated that these stem cells can traverse the blood-brain barrier (BBB) and target areas affected by the disease. Furthermore, MSCs have been shown to localize in the hippocampus of animal models with epilepsy; despite being given intravenously, they play a pivotal role in the treatment of the disease (Abdanipour et al., 2011). Studies have shown that administering MSCs can reduce seizure incidences (Hlebokazov et al., 2017, 2021; Milczarek et al., 2018; Szczepanik et al., 2020), enhance cognition (Fukumura et al., 2018; Milczarek et al., 2018; Wang et al., 2021) and motor control (Mohammed et al., 2014), raise the number of neurons (Abdanipour et al., 2011), and decrease oxidative stress (Salem et al., 2018). GABAergic interneurons have been shown to survive longer when MSCs were introduced (Fukumura et al., 2018; Mohammed et al., 2014).

Preclinical and clinical studies have demonstrated the advantages of stem cell therapy (**Table 1** and **Table 2**). In addition, MSCs have been found to enhance cognitive function and learning abilities, reduce or halt seizures, decrease neuroinflammation, and increase the number of neurons in patients diagnosed with epilepsy. For instance, clinical trials in phases I and II have demonstrated the safety of administering antiepileptic medications in conjunction with one or two doses of MSCs, either intravenously or intrathecally. Although stem cell therapy has not yet been integrated into standard clinical practice, its efficacy and safety have been validated by numerous clinical studies. The results have consistently shown that MSCs can offer substantial benefits without significant adverse effects, paving the way for future applications in clinical settings. The integration of stem cell treatment into standard epilepsy treatments could significantly enhance the quality of life for patients, offering hope for a more effective and comprehensive management of this disease.

Table 1: Preclinical studies of stem cell treatment for epilepsy.

Animal Model	Stem Cell Source	Results
Chemical induction: Glutamate	MSCs	Administration of MSCs led to reduced NMDA receptor activity and decreased calcium ion influx, protecting neurons from glutamate toxicity (Papazian et al., 2018).
Chemical induction: Lithium-pilocarpine	MSCs	Systemic infusion of stem cells in rats showed migration to the hippocampus, protecting neurons and reducing epileptogenesis and neurological impairments (Fukumura et al., 2018).
Transgenic	Neuroepithelial stem cells (NESs) derived from human embryonic stem cells	Genetically modified NESs lacking ADK gene increased adenosine production (Poppe et al., 2018).
Chemical Induction: Pilocarpine, pentylenetetrazole, and picrotoxin	NSCs	NSC infusion in rats exhibited antioxidant effects (de Gois da Silva et al., 2018).
Chemical induction: Kainate	Human induced pluripotent stem cell (hiPSC)-derived MEG-like precursor cells	Transplanted cells differentiated into inhibitory interneurons, reduced spontaneous recurrent seizures, and improved cognition and mood (Upadhya et al., 2019).
Chemical induction: Pilocarpine	NSCs and NSC-derived GABAergic neurons	Reduction of seizure frequency in the hippocampus (Xu et al., 2019).
Chemical induction: Pilocarpine	MSC-derived exosomes	Administration to hippocampal astrocytes reduced epilepsy-induced astrocyte alterations, neuroinflammation, and improved cognitive function (Xian et al., 2019).
Chemical induction: Kainate	hMSCs	Intranasal injection of hMSC-derived EVs resulted in neuron incorporation in hippocampal regions, providing neuroprotection and reducing chronic symptoms of epilepsy (Kodali et al., 2019).
Transgenic	Interneuron graft and periventricular endothelial cells	Enhanced migration of interneurons and reduced behavioral impairments in an experimental model (Datta et al., 2020).
Chemical induction: Kainic acid	Adipose-derived stem cell	Transplantation of stem cells enhanced learning and memory in a rate model (Wang et al., 2021).
Chemical induction: Scopolamine and pilocarpine	Olfactory mucosa MSC	Stem cell treatment ameliorated the neural network and inhibited inflammation in a mouse model (Liu et al., 2023).

Table 2: Clinical Studies of stem cell treatment for epilepsy.

Clinical Trial ID	Study Phase	Stem Cell Source	Route of administration	Results
NCT02497443	2	MSCs	Intravenous injection	Autologous MSC treatment in drug-resistant epilepsy patients reduced seizure frequency, with some patients becoming seizure-free or responsive to AEDs (Hlebokazov et al., 2017).
NCT00916266	1	Bone marrow mononuclear cells (BMMCs)	Intra-arterial injection	Intra-arterial delivery in MTLE patients led to seizure remission, improved cognition, and no adverse effects (DaCosta et al., 2018).
NCT03676569	1	Adipose-Derived Regenerative Cells (ADRCs)	Intrathecal infusion	Intrathecal delivery in autoimmune refractory epilepsy patients enhanced cognition and motor control (Szczepanik et al., 2020).

Mechanisms of action of stem cell treatment

Neuroprotection refers to the preservation and defense of the nervous system from damage or degeneration. Stem cells can secrete neurotrophic substances, which serve to safeguard neurons from harm. For instance, it has been shown that MSCs secrete neurotrophic factors that assists neuronal survival and adaptation like brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) (Das et al., 2019). **Neurogenesis** refers to the process of generating new neurons. Research suggests that stem cells can differentiate into fully functional neurons, replacing the neurons that are destroyed due to epilepsy. ESCs, iPSCs, and NSCs are notable for their neurogenic potential, as they have the ability to generate new neurons (Bond et al., 2015; Hirose et al., 2020; Wesselschmidt et al., 2012). **Synaptic modulation** involves altering the strength or efficacy of synaptic connections between neurons. Transplanted stem cells have the ability to improve synaptic connection, hence repairing broken networks. NSCs, specifically, have demonstrated the ability to regulate synaptic activity, which reduces the seizures (Xu et al., 2019). **Immunomodulation** refers to the process of modifying or regulating the immune response in the body. Inflammation plays a key role in the epileptic brain, contributing to the onset and development of seizures. Stem cells, particularly MSCs, have the ability to alter the inflammatory environment, which may reduce the intensity of seizure activity (Jiang et al., 2020). MSCs also secrete neurotrophic substances, which serve to safeguard neurons from harm like BDNF and GDNF (Das et al., 2019). **Figure 2** shows the advantages of stem cells for the treatment of epilepsy.

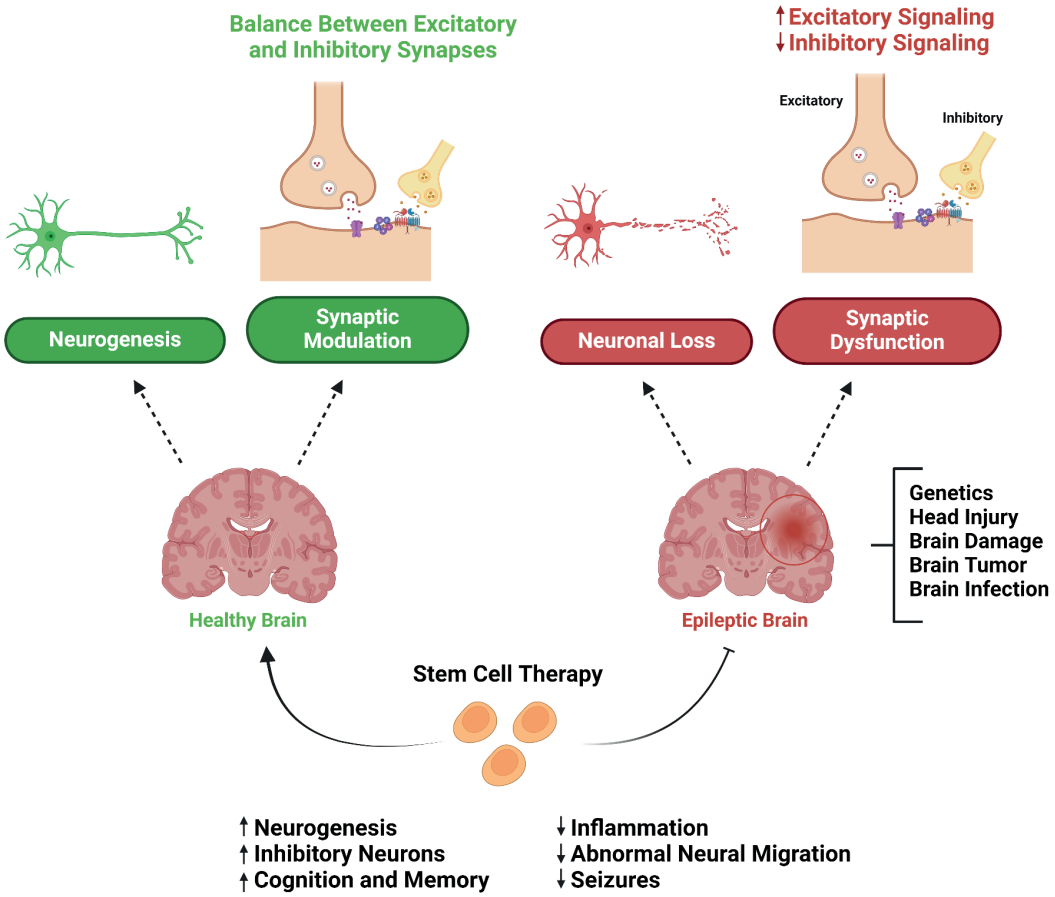

Figure 2. Mechanism of stem cell therapy in epilepsy *(Created by BioRender)*.

Conclusion

The application of stem cell therapy in clinical settings encounters various obstacles, such as enhancing the acquisition of cells, expanding production capacity, guaranteeing long-term safety, and resolving ethical dilemmas. Immunogenicity, cell viability, and incorporation into the host tissue are all supplementary challenges that require careful consideration.

This study is an important resource document for those working in the field, as it presents a comprehensive literature review on epilepsy; one of the most common neurological disorders today. In addition, since the approach presented is examined within the framework of stem cell technology, it also provides an important resource for today's regenerative medicine approach, because the point that today's stem cell science has reached is quite remarkable. Early clinical trials show that stem cell treatments can be safe and potentially beneficial, especially for individuals with epilepsy who do not respond to medications. The potential of these treatments to repair and rejuvenate damaged brain tissue represents an optimistic transition towards sustainable seizure management and improved quality of life, but there are still obstacles to overcome. Therefore, it is essential to focus on the long-term safety and effectiveness of stem cell treatments, considering potential risks such as immune rejection, tumor development, and unwanted differentiation. Addressing ethical and regula-

tory issues, as well as dealing with the high costs and technical intricacies of stem cell therapy, also requires attention.

Future studies should prioritize the refinement of treatment protocols, gaining insight into the lasting implications of integrating stem cells and devising economically viable approaches that can be widely implemented in clinical settings. As we delve deeper into refining these treatments, utilizing stem cell therapy has the chance to revolutionize epilepsy care and provide fresh optimism for individuals grappling with this persistent condition. By persisting in research and investigation, stem cell therapy may drastically change how epilepsy is treated, presenting new prospects and hope for millions of people.

Conflict of interest

The authors declare no conflict of interest.

Data availability statement

Data sharing is not applicable to this review article as no datasets were generated or analyzed during the current study.

Ethics committee approval

Ethics committee approval is not required for this study.

Authors' contribution statement

The authors acknowledge their contributions to this paper as follows: **Contributed to the conception and design of the study, conducted the literature review, and wrote the initial draft of the manuscript:** H.B.; **assisted in the literature review, contributed to the analysis and interpretation of data, and provided critical revisions to the manuscript for important intellectual content:** S.O.; **provided expertise and guidance on the subject matter, participated in the design of the study, and contributed to the final editing and approval of the manuscript:** S.I.; All authors reviewed the results and approved the final version of the manuscript.

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