Chapter

Current Status and Potential Challenges of Cell-Based Therapy for Treating Status Epilepticus and Chronic Epilepsy

Huifang Zhao and Zhiyuan Li

Abstract

Epilepsy is the fourth most common neurological condition characterized by recurrent unprovoked seizures. Chronic and recurrent seizures may give rise to cell necrosis, astrocyte activation, neuron death, reactive oxygen species (ROS) production, and mitochondria dysfunction. Recent studies have shown that cell-based therapy is a promising treatment option for epilepsy. Various stem cell types were used for treatment of epilepsy in basic and experimental researches. It is especially vital to gauge the efficacy of distinct donor cell types, such as the embryonic stem cells and induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), hippocampal precursor cells, γ-aminobutyric acid-ergic progenitors, neural stem cells. The goal of this chapter is to evaluate the progress made hitherto in this area and to discuss the prospect for cell-based therapy for epilepsy.

Keywords: epilepsy, seizures, mesenchymal stem cells, neural stem cell transplantation

1. Introduction

Epilepsy is a neurological disorder, characterized by recurrent (two or more) epileptic seizures resulting from excessive and abnormal cortical neural activity. There are tens of millions people experiencing epilepsy [1]. Causes of epilepsy are complex, such as a toxic ingestion, serious head injury, stroke, tumor, complications of other brain diseases and genetic mutation. Epilepsy may occur after some brain infections such as meningitis, herpes simplex encephalitis, pork tapeworm (cysticercosis), cerebral malaria, toxoplasmosis, and toxocariasis. Genetics is believed to be involved in the majority of cases, either directly or indirectly. Around 0.095% of all deaths are on account of status epilepticus or seizure [2]. Approximately 30% of epileptic patients have temporal lobe epilepsy(TLE) which causes neuronal cell death, aberrant mossy fiber sprouting (MFS) [3], hippocampal damage [4] and cognitive deteriorations [5]. The past 30 years have seen the introduction of over fifteen kinds of third-generation antiepileptic drugs (AEDs) that provide more options for different types of seizures [6]. However, approximately 30% of patients continue to have process of epilepsies [7, 8]. For drug-resistant epilepsy, AEDs are unable to prevent or reverse the process of disease. The treatment was not effective [9]. Furthermore,

the patients that respond to AEDs typically experience adverse systemic side effects, underscoring the urgent need to develop new therapies that target epileptic foci rather than more systemic interventions.

Based on the high incidence of this disease and the limited treatment options available, it makes sense to explore and analyze the new treatment strategies to inhibit or prevent epileptic-related neuronal changes. Due to the potential for providing neuroprotection, diminishing inflammation and curbing epileptogenesis of Mesenchymal stem cells, the development of chronic epilepsy typified by spontaneous seizures and learning and memory impairments may be restrained. In this chapter, the efficacy of MSCs to restrain neurodegeneration, inflammation, and epileptogenesis were discussed [10]. Neural stem cells and neural progenitors (NSC/NPCs) have broad application prospect in neuro-restorative therapy due to their survival of intracerebral grafting, remarkable capacity for self-renewal, release a multitude of neurotrophic factors, plasticity, and ability to integrate into host brain circuitry [11]. This paper reviewed different cell sources and strategies of using MSC and progenitor cells to treat epilepsy by establishing new neurons that incorporate into host brain circuits.

2. Mesenchymal stem cells and epilepsy

2.1 Properties of mesenchymal stem cells

MSCs were discovered in bone marrow in 1966 for the first time [12]. The therapeutic potential of bone marrow mesenchymal stem cell (BMSC) transplantation has recently been investigated in various pathological conditions of the central nervous system (CNS) [13–16]. Subsequently, MSCs were widely and gradually isolated from various tissues, including adipose, tooth root, umbilical cord, muscle [17–19]. For more scientific comparison and contrast of research results, the minimal criteria for MSCs was defined by the International Society for Cellular Therapy (ISCT) including plastic adherent growth, express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79 or CD19 and HLA-DR surface molecules [20]. MSC were able to differentiate into adipocytes, cardiomyocytes, chondrocytes, osteocytes, and myoblasts, both in vitro and in vivo. Early studies showed that MSC can differentiate into CNS glia and neurons and express neural cell markers in vivo. In addition, these cells are readily available as donor cells because MSCs can be obtained freshly from human umbilical cord, bone marrow and cord blood. MSCs or MSC-like cells can also be amplified from fresh and frozen samples of several other tissues.

2.2 MSC-based therapy for epilepsy

Some evidence shows that MSC secretes a large number of cytokines and growth factors through a paracrine mechanism to stimulate endogenous protection and recovery responses [21, 22]. In addition, mesenchymal stem cells express gene-encoded proteins, which are involved in a variety of biological activities, including immunity, angiogenesis, and neuronal functions [23]. After an experimental stroke in rats, intravenous injection of human mesenchymal stem cells can enhance the production of neurotrophins and reduce the death of ischemic tissue [24]. Direct implantation of human mesenchymal stem cells into the hippocampus of mice can induce the proliferation, migration, differentiation and neurogenesis of endogenous neural stem cells [25]. Mesenchymal stem cells have neuroprotective properties by enhancing the antioxidant effect of cells in nerve cells in vitro. At the

same time, they also show immunomodulatory effects in vitro, including inhibiting the maturation of dendritic cells and the proliferation of T cells and B cells [26]. Mesenchymal stem cells have the ability to transdifferentiate into nerve cells and have the properties of immune regulation and neuroprotection. Thus, mesenchymal stem cells are involved in many physiological and pathological processes, including cell homeostasis, aging, tissue damage, and inflammatory diseases.

A number of approaches have been tested using cell therapy in epilepsy models (**Table 1**). The pilocarpine model of rat epilepsy is the most common model in the study, because it is similar to the characteristics of human epilepsy. After the injection of pilocarpine, the animal has cholinergic effects, seizures and subsequent chronic epilepsy symptom. 3×10^6 rat autologous BMSCs in 500 μl PBS were injected intravenously to adult male Sprague–Dawley rats 24 and 36 hours after the first seizure. The results of the behavioral test revealed that the number of seizures in the treatment group was significantly reduced. The histopathology of untreated rat tissue showed cell death and neurophagy. The digital density of neurons in each area was significantly higher in the treated group than in the untreated group [27].

Gianina Teribele Venturin et al. found that bone marrow mononuclear cells (BMMCs) transplantation to chronic epileptic rats via tail vein injection decreased the frequency of spontaneous recurrent seizures (SRS), prevented the learning and memory deterioration [28]. In that work, 1×10^7 cells were administered 22 days after Status epilepticus (SE). Here, they showed for the first time that BMMCs reduced the frequency but not the duration of SRS. To evaluate whether BMMCs can reverse the cognitive deficits, the Morris water maze was used to test spatial memory. A 60-s probe test confirmed that lithium–pilocarpine impairs the acquisition of spatial memory and that BMMCs reverse this effect. In other words, Transplantation of BMMCs improved the learning and long-term spatial memory impairments after cell transplantation. This is a pioneering study providing behavioral evidence supporting cell-based therapy for chronic epilepsy. Further research is needed to clarify the mechanism by which transplanted cells exert their effects.

Another study in a mouse model examined the effects of intravenous route of EGFP transgenic mice or male Wistar rats BM-derived MSCs [29]. Transplantation of BMCs prevents spontaneous seizures in pilocarpine-treated rats. They also examined the electrophysiological properties of rat brain sections from the different experimental groups. In saline-epileptic animals, the field excitatory postsynaptic potentials (fEPSPs) by stimulation of Schaffer's vein was reduced 10 days after SE compared with the non-epileptic rats in the control group; however, an incremental increase in fEPSPs amplitude was observed in the BMC-epileptic animals. Qualitative analysis of Nissl-stained neurons showed histological lesions in the epileptic rats including neuron shrunken, pycnotic nuclei and severe reduction in the neuronal density. The digital density of neurons in each area was significantly higher in the treated group than in the untreated group. After transplantation, cells were localized in the cortex and/or hippocampus, perirhinal cortex and basomedial amygdale. In addition, no tissue damage or tumor formation was found in animals transplanted with BMSCs, and no systemic complications or increased morbidity occurred in epileptic animals with intravenous BMSCs.

Several studies have also examined the bystander effects of the mesenchymal stem cells that modulate the host environment. Daejong Jeon et al. demonstrate that a cytosolic extract of human ASCs (ASCs-E) mitigated the activity of seizure spikes following diazepam treatment and inhibited SRS in mice [30]. The evidence indicates that ASCs-E can effectively regulate the pathogenesis in epilepsy models and improved behavioral performance. They also suggest a stem cell–based, noninvasive therapy for the treatment of epilepsy. Further investigation of the capability of MSCs for anticonvulsant potential showed matching results.

References	Model	Type of MSC	Number of MSC	Route of administration	Period after SE	Outcome measures examined	Major findings
[29]	SE injecting pilocarpine	BMCs from EGFP transgenic mice	1×10^6 cells	Intravenous route via the tail vein	15-21 days 110-117 days	Electrophysiological immunofluorescence volume estimation neuronal density	Reduced seizures in the chronic phase Protective effects on LTP Decreased neurodegeneration Engrafting of some BM-MNCs into the hippocampus and cortex
[30]	SE injecting pilocarpine	Human ASCs	1×10^6 cells	Intraperitoneally administrated to C57BL/6 mice	7 days	Blood-brain barrier (BBB) leakage EEG Behavioral tasks	Earlier attenuation of seizure spike activities; reduction of BBB leakage, and inhibition of the development of epilepsy. Human ASCs-E treatment (for 7 days) during the chronic epileptic stage suppressed SRS and reduced abnormal epileptic behavioral phenotypes.
[32]	Pentylenetetrazole (PTZ)-induced epileptogenesis	MSCs	1×10^6 cells	Intravenous injection	Two weeks	Determination of GABA level by HPLC; immunohistochemistry; determination of oxidant and antioxidant markers; assessment of cognitive function and motor coordination	Enhanced the motor coordination; increased ambulation frequency; they enhanced the GABA neurotransmitter levels;
[37]	Pilocarpine-induced SE	Human umbilical mesenchymal stem cells	1×10^5cells	Intra-hippocampal transplantation	Two to four weeks	Simultaneous video and electroencephalographic recordings	The number of SRMS was significantly decreased; reduced pyramidal neuron loss

References	Model	Type of MSC	Number of MSC	Route of administration	Period after SE	Outcome measures examined	Major findings
[38]	Pilocarpine-induced SE	BMSCs	1×10^5 cells	Injected either intravenously (IV) or in hippocampus bilaterally (1C)	15 days	Determination of reduced glutathione content, lipid peroxidation, paraoxonase activity, IL-1β and TNF-α; histopathological investigation; immunohistochemical assay	Ameliorated the pilocarpine-induced neurochemical and histological changes, retained amino acid neurotransmitters to the normal level, downregulated the immunoreactivity to insulin growth factor-1 receptor, synaptophysin, and caspase-3 and reduced oxidative insult and inflammatory markers.

Table 1.
Stem cell transplantation studies in epilepsy models.

The results of Filip et al. [31] clearly demonstrated that gabapentin enhances GABA-ergic neurotransmission and reduced the severity of epilepsy caused by PTZ kindling. Their results showed that the injection of mesenchymal stem cells enhanced the level of GABA inhibitory neurotransmitter and had a greater reduction in the severity of epilepsy [32]. In addition, research results showed that MSCs can not only improve the severity of seizures and oxidative stress damage, but also improve pentylenetetrazol (PTZ)-induced motor incoordination and cognitive impairment. These functions may benefit from the ability of mesenchymal stem cells to migrate and return to damaged areas, and self-renewal and differentiation potential for neuronal death during epilepsy [33, 34]. In this study, they also found that the expression of microglia and neuronal markers were increased after injections of MSCs, which can be clearly seen from the immunohistochemical expression of the glial cell marker S100β protein. Previous studies have reported that mesenchymal stem cells can differentiate into glial cell-like cells in phenotype and function, and can be used as a suitable glial cell substitute for nerve repair and regeneration in clinical applications [35]. In addition, transplanted cells can provide a large amount of neurotrophic factors including brain-derived neurotrophic factor, nerve growth factor, and neurotrophic factor-3 [36]. In conclusion, MSCs could be a promising therapeutic option in the management of chronic epilepsy.

Indeed, a follow-up study using a mouse model of status epilepticus demonstrated that transplantation of human umbilical mesenchymal stem cells (HUMSCs) into bilateral hippocampi ameliorated seizure activity [37]. They examined the effects of intra-hippocampal transplantation of HUMSCs on pilocarpine-treated rats. The results of video and electroencephalography (EEG) recordings from two to four week after PBS injection or HUMSC implantation showed that pilocarpine-induced SE in terms of onset, incidence, and duration were attenuated. In addition, other pathological changes after pilocarpine-induced SE such as brain edema, hippocampal cytoarchitecture, and integrity of the hippocampal pyramidal neurons were evaluated. Magnetic resonance imaging [MRI] was performed on each rat at one week before SE and one, eight, 15, 22, and 29 days afterward. The edema in the lateral ventricles, piriform cortex, and hippocampus at eight days was similar to that at one day after HUMSCs transplantation. Then, histo-morphologically on Nissl stained coronal sections was performed to examine possible changes in the cytoarchitecture. The dorsal hippocampus was significantly enlarged in the SE + HUMSC group than those in the SE group, suggesting the neuroprotective potential of transplanted HUMSCs. In general, intra-hippocampal transplantation of HUMSCs can prevent tissue damage and neuronal loss, provide supplemental neuronal protection and stimulate neurogenesis, and suppress the spontaneous recurrent seizures in a pilocarpine TLE model.

Another study examined the effects of implantation of Bone marrow derived mesenchymal stem cells either through intravenously (IV) or in hippocampus bilaterally (IC). BMSCs treatment reduced the hippocampal excitatory amino acid neurotransmitters, downregulated inflammatory cytokines (TNF-α, IL-1β), ameliorated histological changes, and reduced oxidative insult and inflammatory markers [38]. After 22 days of Pilocarpine induction of status epilepticus [SE], intrahippocampal injection of BMSCs was performed. Hippocampal GABA content is lower in SE epileptic animals than the sham control group. BMSCs transplantation through both routes significantly elevated hippocampal GABA content as compared to SE rats. In addition, the frequency of epileptic seizures in video surveillance analysis showed a significant reduction in the number of animals injected with MSC compared with the carrier group.

One study reported that BMSCs transplantation reduced hippocampal excitatory amino acid neurotransmitters and inhibited BDNF-mediated excitatory toxicity

by either I.V. or I.C. pathways, similar to inhibition of synaptophysin immune response. The observed improvements extended to neurotransmitter balance, in which inhibitory tension was increased and excitatory metastases were observed in rats with epilepsy restored to normal balance. Bone marrow mesenchymal stem cell therapy improved the neurochemical and histological changes induced by triclosan, retained amino acid neurotransmitters to normal levels, down-regulated immune responses to insulin growth factor 1 receptors, synaptophysin, and caspase-3, and reduced detection of oxidative damage and inflammatory markers in epileptic models.

The number of GAD67+ GABAergic inhibitory neurons was significantly decreased in the CA1 and DH regions in the vehicle group at 2 months after SE inducing by the lithium-pilocarpine [39]. Furthermore, both Manganese-enhanced magnetic resonance imaging (MEMRI) and Timm (zinc) staining showed that the abnormal mossy fiber sprouting of the hippocampus in the MSC group was lower. Therefore, their results showed that intravenous infusion of bone marrow mesenchymal stem cells reduced the occurrence of epilepsy by inhibiting abnormal MFS in the SE rat model. Moreover, previous research has focused on reducing the loss of inhibitory neurons as a therapeutic mechanism for infused mesenchymal stem cells. Injection of mesenchymal stem cells inhibited the onset of epilepsy after SE and retained cognitive function. Injected GFP+ MSCs accumulated in the hippocampus and were related to the preservation of GAD67+ and NeuN+ hippocampal neurons.

3. Neural stem/progenitor cell and epilepsy

3.1 Potential of NSC/NPC for epilepsy

Epilepsy affects 1%-2% of the population worldwide [40]. Approximately 40% of epilepsy patients have temporal lobe epilepsy (TLE). Up to 35% of patients with TLE continue to have chronic seizures due to resistant to antiepileptic drugs [41, 42]. TLE is characterized by complex partial seizures hippocampal sclerosis, inhibitive gamma aminobutyric acid-ergic (GABAergic) interneuron loss, gliosis in hippocampal [43]. The main pathological changes of human temporal lobe epilepsy are hippocampal sclerosis and mossy fiber sprouting (MFS). Hippocampal sclerosis is mainly manifested in morphology as hippocampal atrophy and induration, and in histology, it is mainly manifested as necrosis of selective CA3 pyramidal neurons and secondary glial fibrosis. Mossy fibers (MF) are the axons of granular cells in the dentate gyrus, which normally project to the dendrites of pyramidal neurons in the CA3 and CA4 regions. MFS means that the postsynaptic site of MF is vacant and the target area of its normal projection disappears, resulting in budding to the inner molecular layer after the death of pyramidal neurons in these areas [44]. At the molecular level, the imbalance of excitatory and inhibitory neurotransmitters may be the main factor of seizures.

Although surgical removal of the hippocampus decreased seizure activity, this choice is bound to cognitive impairment [45], loss of viable tissue during resection [46], hemiplegia, hemianopia, and memory impairment. Bilateral resection is not suitable for patients with bilateral hippocampal sclerosis. Therefore, exploring through neural stem cells transplantation for the repair and reconstruction of hippocampal function has important clinical significance. Hence, the development of alternative therapies that have the potential for both reversing the epileptogenic circuitry and suppressing chronic epileptic seizures is extremely valuable.

Neural stem cells exist in the nervous system. After transplantation into the damaged central nervous system, they may differentiate into nerve neurons,

astrocytes and oligodendrocytes by asymmetric division. Release of chemokines after partial tissue injury attracts neural stem cells to the site of injury. Neural stem cells also secrete a variety of neurotrophic factors to promote the repair of damaged cells.

Neural stem cells contribute to strengthen synaptic connections and create new neural circuits. It is proved that the directional differentiation of neural stem cells makes the repair and replacement of dead nerve cells possible. In order to reduce the sequelae of nerve injury, delay or inhibit the further development of the disease, and achieve better recovery effect, it is very necessary to repair and activate necrotic nerve cells fundamentally.

Neural stem cells have the capacity of self-renewal and express various growth factors. Multipotent NSCs can be obtained from multiple sources such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), fetal, postnatal and adult brain tissues [47, 48]. NSCs can survive well intracerebral grafting, migrate into regions of the brain displaying neuron loss, increase concentration of proinflammatory cytokines, positively influence the survival of host cells and tissues, replace significant numbers of lost interneurons, promote functional recovery and maintain normal network function [49, 50].

3.2 Efficacy of neural stem/progenitor cell grafts in rat model

Astrocytes have the capable of secreting beneficial neurotrophic factors that promote neuroprotection, reduce frequencies of SRMS [51] and enhance neurogenesis. It provides an attractive approach for stimulation neurogenesis endogenous NSCs in the dentate subgranular zone [52, 53]. NSC transplantation can suppress neuroinflammation. Therefore, neural stem cells become potential donor cells for the treatment of brain injury or neurodegenerative diseases. Transplantation of NSCs in hippocampal injury rat is efficacious for thwarting mood and memory dysfunction and abnormal neurogenesis [54]. Studies have shown that in animal models with TLE seizures, the number of hippocampal GABA-ergic interneurons decreased [55, 56]. Status epilepticus [SE] typically progresses into temporal lobe epilepsy [TLE].

Several studies have examined the efficacy of NSCs for controlling seizures when administered in SE model (**Table 2**). A study reported that the transplant intravenously of beta galactosidase-encoded human NSCs could prevent spontaneous recurrent seizure formation in adult rats with pilocarpine-induced status epilepticus [57]. Ruschenschmidt et al. [58] have demonstrated that embryonic stem cell-derived neurons displayed intrinsic and synaptic properties characteristic of neurons when transplanted into the hippocampus of chronic epileptic animals. Transplantation techniques using bilaterally placed grafts of striatal precursors in the acute phase of the disease reduced the frequency of spontaneous recurrent motor seizures (SRMS) on a long-term basis in the chronic epilepsy period [59]. Adult neural stem cells had anti-epileptic effect in rats with status epilepticus (SE) induced by kainic acid. NSC transplantation increased the number of neuropeptide Y (NPY) and glutamic decarboxylase 67 (GAD67) positive interneurons, and inhibited the moss fiber germination to the inner molecular layer [60, 61].

Hong Shen et al. [62] demonstrated that Hippocampal stem cells (HSCs) derived from the postnatal hippocampus have the potential of promoting repairs in the epileptic brain. In this study, Hippocampal stem cells were transplanted into the right hippocampus in rats with kainite acid [KA]-induced epilepsy. At 1, 4, 8, and 24 weeks posttransplantation, Timm's stain, Nissl staining, electroencephalogram were performed. The results showed that sharp waves were reduced, Aberrant MFS induced by KA-lesion was suppressed by HSC grafts, and the loss of CA3 pyramidal

References	Model	Type of NSC	Number of NSC	Route of administration	Period after SE	Outcome measures examined	Major findings
[51]	Kainic acid-induced status epilepticus (SE)	NSCs embryonic medial ganglionic eminence (MGE)	8×10^4	Graft into hippocampi of adult rats	Two months	Measurement of postgrafting SRMS; Analyses of learning and memory function	Reduced frequencies of SRMS, duration of individual SRMS and the total time spent in seizures
[57]	Status epilepticus induced by pilocarpine	H7 hESC differentiated into MGE cells	5×10^4	Hippocampus	2 weeks	Behavioral analysis; immunohistochemistry; transmission electron; microscopy (TEM); electrophysiology; neurolucida tracing	Grafted neurons were capable of suppressing seizures and ameliorating behavioral abnormalities such as cognitive deficits, aggressiveness and hyperactivity.
[59]	Kainite acid (KA)-induced epilepsy	Striatal precursors	1×10^5	Hippocampus	9–12 months	Calbindin; immunostaining; neuropeptide Y; immunostaining; Nissl staining analyses of spontaneous recurrent motor seizures	Grafting considerably preserved hippocampal Calbindin but had no effects on aberrant mossy fiber sprouting, reduced the frequency of SRMS on a long-term basis
[62]	Kainite acid (KA)-induced epilepsy	Hippocampal stem cells (HSC)	5×10^5	Transplant HSCs into the right hippocampus	24 weeks	EEG recording; Timm's staining; Nissl staining	Reduced frequency restore the loss of CA3 pyramidal neurons; aberrant MFS was notably suppressed
[63]	Maximum electroconvulsive shock (MES)	GABAergic precursor	5×10^4	Neocortex bilaterally	Sixty days	Immunohistochemistry; MES test	Altered the course of MES acute seizures, increasing seizure threshold, and/or blocked the generalized convulsive activity

References	Model	Type of NSC	Number of NSC	Route of administration	Period after SE	Outcome measures examined	Major findings
[64]	Status epilepticus induced by pilocarpine	Human neural stem/progenitor cells	4×10^5	CA3 region of the right hippocampus	2 weeks	Evaluation of NSPC grafts on kindled seizures and SRMS; Morris water maze; Timm staining	Reduced behavioral seizure duration, after discharge duration on electroencephalograms, and seizure stage in the kindling model, as well as the frequency and the duration of spontaneous recurrent motor seizures
[65]	Status epilepticus induced by Li-pilocarpine	NPCs derived from the medial ganglionic eminence and ventral mesencephalon	STN (8×10^4 or 1.5×10^5 NPCs) or SNr (8×10^4 or 5×10^4 NPCs)	Graft into subthalamic nucleus (STN) or substantia nigra pars reticulata (SNr)	4 months	Immunohistological; effect of intrasubthalamic; cell grafting on seizure thresholds.	Average clonic seizure threshold increased above pre-grafting

Table 2.
Stem cell transplantation studies in epilepsy models.

neurons was partially restored. Given these results, HSC grafts have the therapeutic potentials for the treatment of epilepsy. Further investigation of the capability of NSCs for providing neuroprotection using a maximum electroconvulsive shock (MES) mode showed matching results [63]. Transplantation of medial ganglionic eminence (MGE) cells altered the course of MES acute onset, increased the onset threshold, and increased GABA interneuron selectivity compensates for excitatory activity, thereby reducing susceptibility to epileptic seizures.

Over the past decades, embryonic stem cells, neural stem cells, or neural precursors have been tested in rat models of epilepsy: Li-pilocarpine-induced status epilepticus, kainic acid-induced status epilepticus or kindling-based TLE models. Haejin Lee et al. investigated whether transplantation of human fetal brain-derived NSPC grafts into the hippocampus in both kindling and pilocarpine induced TLE models could improve the epileptic phenotypes [64]. In the study, huNSPCs for transplantation were derived from a cadaver at 13 weeks of gestation. In vitro, huNSPCs can differentiate into three types of nerve cells in vitro: neurons, oligodendrocytes, and astrocytes. Differentiation of human NSPCs was analyzed at 8 weeks posttransplantation in epileptic rats. Confocal microscopic images revealed that grafted cells differentiated into oligodendrocytes, astrocytes and TUJ1+ neurons in kindled rats. In the pilocarpine model, TUJ1+ neurons, GFAP+ astrocytes, and OLIG2+ oligodendrocyte progenitors were observed in confocal microscopy images. In the kindled rats, EEG examination, behavioral seizure duration, and seizure stage were substantial decreased. Nevertheless, the anticonvulsant effect is not persistent and gradually disappeared after 7 weeks. The frequency and severity of spontaneous recurrent motor seizures (SRMS) were significantly reduced at 2 and 3 months after grafting in epileptic rats. Furthermore, the average total time spent in SRMS was significant decreased at 2 and 3 months after grafting. Timm staining show that aberrant sprouting of mossy fibers was not significantly different between the two groups. Water maze testing and probe test were performed at 9 weeks after grafting. The ability of spatial learning and memory function in kindled rats showed no significant difference. Another study examined the effects of transplantation of NPCs from three different donor species [65]. Clonic seizure thresholds were analyzed by statistical evaluation. Average clonic seizure threshold increased above pre-grafting control were observed during this time-point investigation after grafting.

3.3 GABA-ergic progenitors/neuron and epilepsy

Interneurons are a type of nerve cells that can release neurotransmitters such as GABA. They mainly exist in brain areas such as the cerebral cortex and hippocampus [66]. Interneurons account for about 25% to 30% of the total number of brain neurons [67] and play an important role in the regulation of brain functions. Gamma-amino butyric acid (GABA) intermediate neurons refer to nerve cells with GABA as the main transmitter, accounting for about 20% of total neurons in cerebral cortex [68]. GABA intermediate neurons form extensive synaptic connections with pyramidal cells and play an important role in regulating the activity of pyramidal cells and maintaining the excitatory/inhibitory balance of cerebral cortical circuits [69, 70]. In the cerebral cortex, different types of neurons form complex circuits and work together to process and store information in a timely manner. They also interact with glutamate pyramidal cell input in specific ways and support the temporal dynamics of synapses, network oscillations, selection of cell combinations, and realization of brain states. This cellular diversity gives the ability to perform complex biological processes. The relatively uniform pyramidal cells are supported by a rich variety of GABAergic interneurons, which provide

general inhibition and also regulate pyramidal cell activity over time. The type of GABAergic interneuron is not unique to the CA1 region. Similar neurons are also present in the hippocampus and most other areas of the foreign cortex [71]. In addition, these GABAergic inter-neurons can also be found in the cortex of mice, rats, cats, monkeys and humans. Examination of epileptic tissue removed from TLE patients revealed a loss of interneurons that release inhibitory neurotransmitter GABA [72, 73]. GABA-mediated inhibition has been repeatedly demonstrated to be weakened in TLE animal models [74] (**Table 3**).

Several studies have tested the effects of neurons. Neural transplantation of GABA-producing cells into subthalamic nucleus (STN) aims to correct imbalance between excitatory and inhibitory neurotransmission. Grafting of GABA-producing cells into the STN suppressed seizure activity. The STN can be considered a target region [75]. hPSC-derived maturing GABAergic interneurons suppressed seizures and ameliorated behavioral abnormalities such as cognitive deficits, aggressiveness, and hyperactivity. In addition, substantial numbers of the GABA-ergic interneurons and GDNF-secreting cells mediate seizure suppression. Neural cell grafting has shown considerable efficiency for inducing the reactivation of the host hippocampal GABA-ergic interneurons and diminishing the aberrant mossy fiber sprouting in the dentate gyrus. Furthermore, the synaptic integration of graft-derived GABA-ergic interneurons effects host brain activity at both cellular and network levels.

4. Challenges and potential

Currently, MSC-based therapy and Neural stem cell and neurons grafting for epilepsy has become an increasing focus of research. Stem cells can be targeted to focal areas of epileptogenesis and tailored to affect only the dysfunctional constituents of the epileptic circuit. Stem cells could theoretically be used in areas of eloquent cortex and could be more widely inserted into a region of epileptogenesis based on clinical response. Neural stem cells can engraft into the injured brain areas, positively influence the survival of host cells and tissues, and promote functional recovery. Afterward, function of these cells for suppressing seizures and improving cognitive function in chronic epilepsy were determined.

Stem cell therapy for epilepsy mainly involves the replacement of damaged neurons with stem cell differentiation, secretion of protective factors and anti-inflammatory factors to prevent clinical deterioration. Mesenchymal stem cells have great potential in cell therapy because they are easy to obtain, easy to amplify, and can be autologous transplanted with little immune rejection. There is ample evidence that mesenchymal stem cells can differentiate into neuronal destinies and secrete a range of anti-inflammatory, protective cytokines. In addition, bone marrow mesenchymal stem cells have been shown to point to damaged areas, meaning they could be used as vehicles for therapeutic drugs. In fact, various beneficial effects have been reported after transplantation of human bone marrow mesenchymal stem cells into rodent models of epilepsy, such as neurotrophic factor-mediated protection, enhanced neurogenesis, inflammation regulation, and removal of abnormal protein aggregates.

At present, the application of NSCs to repair central nervous system damage mainly takes two ways, namely exogenous transplantation replacement therapy and endogenous activation complementary therapy. Therefore, the function of NSCs to treat neurological diseases is of great significance, and certain progress has been examined in experimental research on the treatment of temporal lobe epilepsy. NSCs have the capacity of self-renewing, highly migratory, low immunogenic, and differentiate into different types of nerve cells. In theory, it overcomes many of the above shortcomings of embryonic tissue and is attractive for the treatment of nervous system diseases.

References	Model	Type of NSC/ Neuron	Number of Neuron	Route of administration	Period after SE (days)	Outcome measures examined	Major findings
[74]	Intravenous pentylenetetrazol e (PTZ) rat	GABAergic cell line hGAD-overexpressing cell line	8×10^4	Grafting into substantia nigra pars reticulata and subthalamic nucleus	10/11 days, 3-5 weeks	Histological analysis thionine (Nissl) and bisbenzimide staining	Anticonvulsant effects can be induced by bilateral transplantation of GABAergic M213-20 cells and hGAD-overexpressing cells into the STN; anticonvulsant effect; more long-lasting than transplantation of the same cell line into the SNr of amygdala-kindled rats
[75]	Pilocarpine intraperitoneally, status epilepticus (SE)	Human MGE Cells	5×10^4	Hippocampus	7 days, 2 weeks	EEG recording; Y maze novel object recognition test; locomotion test handling test; immunohistochemistry	PSC-derived human mGINs migrate extensively within the epileptic hippocampus, integrate into host circuitry and reduce seizure activity and other behavioral abnormalities
[76]	Pilocarpine-induced status epilepticus in mice	Mouse ES cell-derived neural progenitors (ESNPs)	1×10^5	Hilus of the dentate gyrus	2–3 months	Graft differentiation, mossy fiber sprouting, cellular morphology, and electrophysiological	New cells functionally integrate into epileptic hippocampal circuitry; ESNP-derived neurons formed dense axonal arborizations in the inner molecular layer and throughout the hilus

Table 3.
Stem cell transplantation studies in epilepsy models.

A number of experimental studies have shown that cell transplantation can reduce the attack frequency of TLE, inhibit the pathological process of epilepsy, and repair the damaged nerve structure. However, several key problems still need to be solved before cell transplantation therapy for epilepsy can move from preclinical research to clinical research. This means that grafted cells should meet the following requirements.

(1) The activity of transplanted cells should be guaranteed normal physiological activities. They can establish functional synaptic connections with the host and carry out functional integration to meet the requirements of repairing damaged neural pathways; (2) the transplanted cells have a strong ability to migrate from the transplanted area to the appropriate cell layer; and (3) the transplanted cells should have normal differentiation and proliferation ability.

In view of the therapeutic effect of different cell types, application of combined strategies may be considered. This may include transplanting MSC and nerve cells (hippocampus or MGE progenitors or NSCs) into the hippocampus: (1) systemic administration of hippocampal neurogenesis enhancers such as small molecules, antidepressants, antioxidants, or neurotrophic factors; (2) MSC and Neural stem cells engineered to release neurogenic enhancers and adenosine. Enhancing the overall rate of transplantation-derived GABA-ergic intermediate neuron and GDNF derived cells has enormous potential to significantly reduce the neurogenic regional recovery of the hippocampus in the pre-clinical models of chronic frame [77, 78].

5. Conclusions

To sum up, it is of great significance to explore the way of cell transplantation, find a treatment method that can replace the lost neurons, repair the damaged nervous system, increase the secretion of inhibitory neurotransmitter, and effectively control the occurrence and development of epilepsy. At the same time, the method can overcome the shortcomings of drug treatment and surgical treatment, fundamentally cure epilepsy. MSC and Progenitors/Stem cell derived from multiple sources can reduce epileptogenesis and improved cognitive function with grafting performed to epileptic brain regions. This has been demonstrated in animal prototypes of chronic TLE, kindling, SE and absence seizures, and in mutant mice displaying SRS. These abundant studies have laid a solid foundation for the early application of cell transplantation therapy in clinical practice.

Acknowledgements

We would like to thank Lang He for suggestion.

Conflict of interest

The authors declare that they have no competing interests.

Nomenclature

ROS	reactive oxygen species
BBB	damage of blood–brain barrier
iPSCs	induced pluripotent stem cells

MSCs	mesenchymal stem cells
TLE	temporal lobe epilepsy
MFS	mossy fiber sprouting
AEDs	antiepileptic drugs
NSC	neural stem cells
NPC	neural progenitors
BMSC	bone marrow mesenchymal stem cell
CNS	central nervous system
ISCT	International Society for Cellular Therapy
BMMCs	bone marrow mononuclear cells
SRS	spontaneous recurrent seizures
SE	status epilepticus
fEPSPs	excitatory postsynaptic potentials
ASCs-E	extract of human ASCs
PTZ	pentylenetetrazol
HUMSCs	human umbilical mesenchymal stem cells
EEG	electroencephalography
MRI	magnetic resonance imaging
IV	intravenously
IC	hippocampus bilaterally
MEMRI	manganese-enhanced magnetic resonance imaging
MF	mossy fibers
ESCs	embryonic stem cells
SRMS	spontaneous recurrent motor seizures
NPY	neuropeptide Y
GAD67	glutamic decarboxylase 67
KA	kainite acid
HSCs	hippocampal stem cells
MES	maximum electroconvulsive shock
MGE	medial ganglionic eminence
huNSPCs	human neural stem/progenitor cells
TUJ1	β-tubulin III
STN	subthalamic nucleus

Author details

Huifang Zhao and Zhiyuan Li*
CAS Key Laboratory of Regenerative Biology, Guangdong Provincial Key Laboratory of Stem Cell and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

*Address all correspondence to: li_zhiyuan@gibh.ac.cn

References

[1] Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 386 (9995):743-800. DOI: 10.1016/S0140-6736(15)60692-4

[2] Maria Thom, Maura Boldrini, Elizabeth Bundock, Mary N. Sheppard, Orrin Devinsky. The past, present and future challenges in epilepsy related and sudden deaths and biobanking. Neuropathol Appl Neurobiol. 2018; 44(1): 32-55. DOI: 10.1111/nan.12453

[3] F.E. Dudek, T.P. Sutula. Epileptogenesis in the dentate gyrus: a critical perspective Prog. Brain Res. 2007; 163:755-773. DOI /10.1016/ S0079-6123(07)63041-6

[4] A. Finegersh, C. Avedissian, S. Shamim, I. Dustin, P.M. Thompson, W.H. Theodore. Bilateral hippocampal atrophy in temporal lobe epilepsy: effect of depressive symptoms and febrile seizures. Epilepsia. 2011 Apr; 52(4): 689-697. DOI: 10.1111/j.1528-1167.2010.02928.x

[5] J. Detour, H. Schroeder, D. Desor, A. Nehlig. A 5-month period of epilepsy impairs spatial memory, decreases anxiety, but spares object recognition in the lithium-pilocarpine model in adult rats. Epilepsia. 2005;46: 499-508. DOI/10.1111/j.0013-9580.2005.38704.x

[6] Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov. 2013; 12:757-776. DOI: 10.1038/nrd4126

[7] Temkin, N. R. Preventing and treating posttraumatic seizures: the human experience. Epilepsia. 2009; 50 (Suppl. 2), 10-13. 8. DOI: 10.1038/ nrd4126

[8] Schmidt, D. Is antiepileptogenesis a realistic goal in clinical trials? Concerns and new horizons. Epilept Disord. 2012; 14, 105-113. DOI:10.1684/epd.2012.0512

[9] Löscher, W, Schmidt, D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia. 2011; 52, 657-678. DOI: /10.1111/j.1528-1167.2011.03024.x

[10] Satish Agadi, Ashok K Shetty. Concise Review: Prospects of Bone Marrow Mononuclear Cells and Mesenchymal Stem Cells for Treating Status Epilepticus and Chronic Epilepsy. STEM CELLS. 2015;33:2093-2103. doi: 10.1002/stem.2029. Epub 2015 May 13.

[11] Steven N. Roper, Dennis A. Steindler. Stem cells as a potential therapy for epilepsy. Exp Neurol. 2013; 244: 59-66. DOI:10.1016/j. expneurol.2012.01.004

[12] Friedenstein AJ, Piatetzky S II, Petrakova K V Petrakova. Osteogenesis in transplants of bone marrow cells. J Embryol Exp Morphol. 1966;16:381-90. DOI: 10.1002/jcp.1040740209

[13] Azizi SA, Stokes D, Augelli BJ et al. Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats similarities to astrocyte grafts. Proc Natl Acad Sci U S A 1998;95:3908-3913. DOI: 10.1073/ pnas.95.7.3908

[14] Jiang Y, Jahagirdar BN, Reinhardt RL et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature. 2002;418:41-49. DOI: 10.1038/ nature00870

[15] Sanchez-Ramos J, Song S, Cardozo-Pelaez F et al. Adult bone marrow stromal cells differentiate into neural cells in vitro. Exp Neurol. 2000; 164:247-256. DOI:10.1006/exnr.2000.7389.

[16] A Voulgari-Kokota 1, R Fairless, M Karamita, V Kyrargyri, V Tseveleki. Mesenchymal stem cells protect CNS neurons against glutamate excitotoxicity by inhibiting glutamate receptor expression and function. Exp Neurol.2012;236:161-70. DOI: 10.1016/j.expneurol.2012.04.011

[17] Ferrari G, Cusella-De Angelis G, Coletta M, Paolucci E, Stornaiuolo A et al. Muscle regeneration by bone marrow-derived myogenic progenitors. Science. 1998;279: 1528-1530. DOI: 10.1126/science.279.5356.1528

[18] De Ugarte DA, Morizono K, Elbarbary A, Alfonso Z, Zuk PA, Zhu M et al. Comparison of multi-lineage cells from human adipose tissue and bone marrow. Cells Tissues Organs. 2003; 174: 101-109. doi: 10.1159/000071150

[19] Rogers I, Casper RF. Umbilical cord blood stem cells. Best Pract Res Clin Obstet Gynaecol. 2004;18:893-908. DOI: 10.1016/j.bpobgyn.2004.06.004

[20] Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;12:315-7. DOI: 10.1080/14653240600855905

[21] Phinney, D.G., Prockop, D.J. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair—current views. Stem Cells. 2007; 25, 2896-2902. DOI: 10.1634/stemcells.2007-0637

[22] Uccelli, A., Moretta, L., Pistoia, V., Mesenchymal stem cells in health and disease. Nat Rev Immunol. 2008;8, 726-736. DOI: 10.1038/nri2395.

[23] Phinney, D.G., Hill, K., Michelson, C., DuTreil, M., Hughes, C., Humphries, S., Wilkinson, R., Baddoo, M., Bayly, E. Biological activities encoded by the murine mesenchymal stem cell transcriptome provide a basis for their developmental potential and broad therapeutic efficacy. Stem Cells. 2006; 24, 186-198. DOI: 10.1634/stemcells.2004-0236

[24] Li, Y., Chen, J., Chen, X.G., Wang, L., Gautam, S.C., Xu, Y.X., Katakowski, M., Zhang, L.J., Lu, M., Janakiraman, N., Chopp, M. Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery. Neurology. 2002; 59, 514-523. doi:10.1212/wnl.59.4.514.

[25] Munoz, J.R., Stoutenger, B.R., Robinson, A.P., Spees, J.L., Prockop, D.J. Human stem/progenitor cells from bone marrow promote neurogenesis of endogenous neural stem cells in the hippocampus of mice. Proc Natl Acad Sci U S A. 2005; 102, 18171-18176.DOI: 10.1073/pnas.0508945102

[26] Lanza, C., Morando, S., Voci, A., Canesi, L., Principato, M.C., Serpero, L.D., Mancardi, G., Uccelli, A., Vergani, L. Neuroprotective mesenchymal stem cells are endowed with a potent antioxidant effect in vivo. J. Neurochem. 2009; 110, 1674-1684. DOI: 10.1111/j.1471-4159.2009.06268.x

[27] Alireza Abdanipour, Taki Tiraihi, Javad Mirnajafi-Zadeh. Improvement of the pilocarpine epilepsy model in rat using bone marrow stromal cell therapy. Neurological Research. 2011;33(6):625-32.DOI: 10.1179/1743132810Y.0000000018

[28] Gianina Teribele Venturin, Samuel Greggio, Daniel Rodrigo Marinowic, et al. Bone marrow mononuclear cells reduce seizure frequency and improve cognitive outcome in chronic epileptic rats. Life Sciences. Life Sci. 2011;15;89(7-8):229-34. DOI: 10.1016/j.lfs.2011.06.006

[29] Costa-Ferro ZS, Vitola AS, Pedroso MF et al. Prevention of seizures

and reorganization of hippocampal functions by transplantation of bone marrow cells in the acute phase of experimental epilepsy. Seizure. 2010; 19:84-92. DOI: 10.1016/j.seizure.2009.12.003

[30] Daejong Jeon, Kon Chu, Soon-Tae Lee, Keun-Hwa Jung et al. A cell-free extract from human adipose stem cells protects mice against epilepsy. Epilepsia. 2011;52(9):1617-26.DOI: 10.1111/j.1528-1167.2011.03182.x.

[31] Filip M, Frankowska M, Gołda A, Zaniewska M, Vetulani J, Przegaliński E: Various GABAmimetic drugs differently affect cocaine evoked hyperlocomotion and sensitization. Eur J Pharmacol. 2006; 541:163-170. DOI: 10.1016/j.ejphar.2006.05.011

[32] Amira S Mohammed, Mohammed M Ewais, Mona K Tawfik, Soha S Essawy. Effects of Intravenous Human Umbilical Cord Blood Mesenchymal Stem Cell Therapy versus Gabapentin in Pentylenetetrazole-Induced Chronic Epilepsy in Rats. Pharmacology. 2014;94(1-2):41-50. DOI: 10.1159/000365219

[33] Leal MM, Costa-Ferro ZS, Souza BS et al. Earl transplantation of bone marrow mononuclear cells promotes neuroprotection and modulation of inflammation after status epilepticus in mice by paracrine mechanisms. Neurochem Res. 2014;39:259-268. DOI: 10.1007/s11064-013-1217-7

[34] Yasuhara T, Hara K, Maki M, Xu L, Yu G, Ali M, Masuda T, Yu S, Bae E, Hayashi T, MatsukawaN,KanekoY,Kuzmin-NicholsN, Ellovitch S, Cruz E, Klasko S, Sanberg C, Sanberg P, Borlongan C. Mannitol facilitates neurotrophic factor up-regulation and behavioural recovery in neonatal hypoxic-ischaemic rats with human umbilical cord blood grafts. J Cell Mol Med. 2010;14:914-921. DOI: 10.1111/j.1582-4934.2008.00671.x

[35] Sadan O, Shemesh N, Barzilay R, Bahat Stromza M, Melamed E, Cohen Y. Migration of neurotrophic factors-secreting mesenchymal stem cells toward a quinolinic acid lesion as viewed by magnetic resonance imaging. Stem Cells. 2008;26:2542-2551. DOI: 10.1634/stemcells.2008-0240

[36] Ziegler L, Grigoryan S, Yang I, Thakor N, Goldstein R. Efficient generation of Schwann cells from human embryonic stem cell-derived neurospheres. Stem Cell Rev. 2011;7: 394-403. DOI: 10.1007/s12015-010-9198-2.

[37] Xenograft of human umbilical mesenchymal stem cells from Wharton's jelly as a potential therapy for rat pilocarpine-induced epilepsy. Brain Behav Immun.2016; 54:45-58. DOI: 10.1016/j.bbi.2015.12.021

[38] Neveen A Salem, Marwa El-Shamarka, Yasser Khadrawy, Shaimaa El-Shebiney. New prospects of mesenchymal stem cells for ameliorating temporal lobe epilepsy. Inflammopharmacology. 2018;26(4):963-972. DOI: 10.1007/s10787-018-0456-2

[39] Shinobu Fukumura, Masanori Sasaki, Yuko Kataoka-Sasaki, Shinichi Oka, Masahito Nakazaki. Intravenous infusion of mesenchymal stem cells reduces epileptogenesis in a rat model of status epilepticus. Epilepsy Res. 2018 ;141:56-63. DOI: 10.1016/j.eplepsyres.2018.02.008

[40] Strine TW, Kobau R, Chapman DP, et al. Psychological distress, comorbidities, and health behaviors among U.S. adults with seizures: results from the 2002 National Health Interview Survey. Epilepsia. 2005;46:1133-1139. DOI: 10.1111/j.1528-1167.2005.01605.x

[41] Engel J Jr. Intractable epilepsy: Definition and neurobiology.

Epilepsia. 2001;42 Suppl 6:3. DOI: 10.1046/j.1528-1157.2001.0420s6003.x

[42] Litt, B., Esteller, R., Echauz, J., et al. Epileptic seizures may begin hours in advance of clinical onset: A report of five patients. Neuron. 2001; 30(1), 51-64. DOI: 10.1016/s0896-6273(01)00262-8

[43] Dudek, FE, & Sutula, TP. Epileptogenesis in the dentate gyrus: A critical perspective. Prog Brain Res. 2007;163:755-73. DOI: 10.1016/S0079-6123(07)63041-6

[44] Shibley H, Smith BN. Pilocarpine-induced status epilepticus results in mossy fiber sprouting and spontaneous seizures in C57BL/6 and CD-1 mice. Epilepsy Res. 2002; 49(2):109-20. DOI: 10.1016/s0920-1211(02)00012-8

[45] Helmstaedter C. Temporal lobe resection--does the prospect of seizure freedom outweigh the cognitive risks?. Nat Clin Pract Neurol. 2008;4(2):66-7. DOI: 10.1038/ncpneuro0657

[46] Shamim S, Wiggs E, Heiss J, et al. Temporal lobectomy: resection volume, neuropsychological effects, and seizure outcome. Epilepsy Behav. 2009;16:311-314. DOI: 10.1016/j.yebeh.2009.07.040

[47] Xu T, Zhang M, Laurent T, Xie M, Ding S. Concise review: chemical approaches for modulating lineage-specific stem cells and progenitors. Stem Cells Transl Med. 2013; 2:355-361. DOI: 10.5966/sctm.2012-0172

[48] Shetty AK. Hippocampal injury-induced cognitive and mood dysfunction, altered neurogenesis, and epilepsy: Can early neural stem cell grafting intervention provide protection? Epilepsy & Behav. 2014; 38:117-124. DOI: 10.1016/j.yebeh.2013.12.001

[49] Ryu JK, Cho T, Wang YT, McLarnon JG. Neural progenitor cells attenuate inflammatory reactivity and neuronal loss in an animal model of inflamed AD brain. J Neuroinflammation. 2009; 6:39. DOI: 10.1186/1742-2094-6-39

[50] Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Müller FJ, Loring JF, et al. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci USA. 2009; 106:13594-13599. DOI: 10.1073/pnas.0901402106

[51] Waldau B, Hattiangady B, Kuruba R, et al. Medial ganglionic eminence-derived neural stem cell grafts ease spontaneous seizures and restore GDNF expression in a rat model of chronic temporal lobe epilepsy. Stem Cells. 2010; 28:1153-1164. DOI: 10.1002/stem.446

[52] Teng YD, Benn SC, Kalkanis SN, Shefner JM, Onario RC, Cheng B, et al. Multimodal actions of neural stem cells in a mouse model of ALS: a meta-analysis. Sci Transl Med. 2012; 4:165ra164. DOI: 10.1126/scitranslmed.3004579

[53] de Lanerolle NC, Kim JH, Robbins RJ, et al. Hippocampal interneuron loss and plasticity in human temporal lobe epilepsy. Brain Res. 1989;495:387-395. DOI:10.1016/0006-8993(89)90234-5.

[54] Shetty AK, Turner DA. Fetal hippocampal grafts containing CA3 cells restore host hippocampal glutamate decarboxylase-positive interneuron numbers in a rat model of temporal lobe epilepsy. J Neurosci. 2000;20:8788-8801. DOI: 10.1523/JNEUROSCI.20-23-08788.2000

[55] Hattiangady B, Shetty AK. Neural stem cell grafting counteracts hippocampal injury-induced impairments in mood, memory and neurogenesis. Stem Cell Transl

Med. 2012; 1:696-708. DOI: 10.5966/sctm.2012-0050

[56] Henderson KW, Gupta J, Tagliatela S, Litvina E, Zheng X, Van Zandt MA, Woods N, Grund E, Lin D, Royston S, Yanagawa Y, Aaron GB, Naegele JR. Long-term seizure suppression and optogenetic analyses of synaptic connectivity in epileptic mice with hippocampal grafts of GABAergic interneurons. J Neurosci. 2014; 34:13492-13504. doi: 10.1523/JNEUROSCI.0005-14.2014.

[57] Cunningham M, Cho JH, Leung A, Savvidis G, Ahn S, Moon M, Lee PK, Han JJ, Azimi N, Kim KS, Bolshakov VY, Chung S. hPSC-derived maturing GABAergic interneurons ameliorate seizures and abnormal behavior in epileptic mice. Cell Stem Cell. 2014; 15:559-573. DOI: 10.1016/j.stem.2014.10.006

[58] Chu K, Kim M, Jung KH, Jeon D, Lee ST, Kim J, et al. Human neural stem cell transplantation reduces spontaneous recurrent seizures following pilocarpine induced status epilepticus in adult rats. Brain Res 2004;1023(2):213-21. DOI: 10.1016/j.brainres.2004.07.045

[59] Hattiangady B, Rao MS, Shetty AK. Grafting of striatal precursor cells into hippocampus shortly after status epilepticus restrains chronic temporal lobe epilepsy. Exp Neurol. 2008;212(2):468-81. DOI: 10.1016/j.expneurol.2008.04.040

[60] Jing M, Shingo T, Yasuhara T, Kondo A, Morimoto T, Wang F, et al. The combined therapy of intrahippocampal transplantation of adult neural stem cells and intraventricular erythropoietin-infusion ameliorates spontaneous recurrent seizures by suppression of abnormal mossy fiber sprouting. Brain Res. 2009;1295:203-17. DOI: 10.1016/j.brainres.2009.07.079

[61] Ruschenschmidt C, Koch PG, Brustle O, Beck H. Functional properties of ES cell-derived neurons engrafted into the hippocampus of adult normal and chronically epileptic rats. Epilepsia. 2005;46(Suppl. 5):174-83. DOI: 10.1111/j.1528-1167.2005.01028.x

[62] Shen H, Liu L, Huo Z, Lin Z. Hippocampal stem cell grafting-mediated recovery of injured hippocampus in the rat model of temporal lobe epilepsy. Int J Neurosci. 2010;120 (10):647-54. DOI: 10.3109/00207454.2010.509526

[63] Maria E Calcagnotto, Lorena P Ruiz, Miriam M Blanco, Jair G Santos-Junior, Maria F Valente, Camila Patti et al. Effect of neuronal precursor cells derived from medial ganglionic eminence in an acute epileptic seizure model. Epilepsia. 2010 ;51 Suppl 3:71-5 DOI: 10.1111/j.1528-1167.2010.02614.x

[64] Haejin Lee, Seokhwan Yun, Il-Sun Kim, Il-Shin Lee, Jeong Eun Shin, Soo Chul Park, Won-Joo Kim, Kook In Park. Human Fetal Brain-Derived Neural Stem/Progenitor Cells Grafted into the Adult Epileptic Brain Restrain Seizures in Rat Models of Temporal Lobe Epilepsy. PLoS One. 2014 Aug 8;9(8):e104092.DOI: 10.1371/journal.pone.0104092.

[65] Bianca Backofen-Wehrhahn, Laura Gey, Sonja Bröer. Anticonvulsant effects after grafting of rat, porcine, and human mesencephalic neural progenitor cells into the rat subthalamic nucleus. Exp Neurol. 2018 ;310:70-83. DOI: 10.1016/j.expneurol.2018.09.004

[66] Lodato S, Arlotta P. Generating neuronal diversity in the mammalian cerebral cortex. Annu Rev Cell Dev Biol. 2015;31,699-720. DOI: 10.1146/annurev-cellbio-100814-125353

[67] Ascoli GA, Alonso-Nanclares L, Anderson SA, Barrionuevo G, Benavides-Piccione R, Burkhalter A,

Buzsaki G, Cauli B, Defelipe J, Fairen A, et al. Petilla terminology: Nomenclature of features of GABAergic interneurons of the cerebral cortex. Nat Rev Neurosci. 2008;9: 557-568. DOI: 10.1038/nrn2402

[68] Freund TF, Buzsa´ki G. 1996. Interneurons of the hippocampus. Hippocampus 6: 347-470. DOI: 10.1002/(SICI)1098-1063(1996)6:4<347::AID-HIPO1>3.0.CO;2-I

[69] Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. 2012; 35, 57-67. DOI: 10.1016/j.tins.2011.10.004

[70] Klausberger T, Somogyi P. Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. Science. 2008; 321:53-57. DOI: 10.1126/science.1149381

[71] Lund JS, Lewis DA. J. Comp. Local circuit neurons of developing and mature macaque prefrontal cortex: Golgi and immunocytochemical characteristics. Neurol. 1993; 328(2):282-312.DOI: 10.1002/cne.903280209

[72] Marco P, Sola RG, Pulido P, Alijarde MT, Sanchez A, Ramon y Cajal S, DeFelipe J. Inhibitory neurons in the human epileptogenic temporal neocortex. An immunocytochemical study. Brain. 1996; 119(Pt 4):1327-1347. DOI: 10.1093/brain/119.4.1327

[73] Spreafico R, Battaglia G, Arcelli P, Andermann F, Dubeau F, Palmini A, Olivier A, Villemure JG, Tampieri D, Avanzini G, et al. Cortical dysplasia: an immunocytochemical study of three patients. Neurology. 1998; 50:27-36. DOI: 10.1212/wnl.50.1.27

[74] Annelie Handreck, Bianca Backofen-Wehrhahn, Sonja Bröer, Wolfgang Löscher, Manuela Gernert Anticonvulsant Effects by Bilateral and Unilateral Transplantation of GABA-Producing Cells Into the Subthalamic Nucleus in an Acute Seizure Model. Cell Transplant. 2014; 23(1):111-32. DOI: 10.3727/096368912X658944

[75] Miles Cunningham, Jun-Hyeong Cho, Amanda Leung, George Savvidis, Sandra Ahn. hPSC-Derived Maturing GABAergic Interneurons Ameliorate Seizures and Abnormal Behavior in Epileptic Mice. Cell Stem Cell. 2014; 15(5):559-73. DOI: 10.1016/j.stem.2014.10.006

[76] Shetty AK, Turner DA. Fetal hippocampal CA3 cell transplants restore host hippocampal GAD-positive interneuron numbers in a rat model of TLE. J Neurosci. 2000;20:8788-8801.DOI: 10.1523/JNEUROSCI.20-23-08788.2000

[77] Hattiangady B, Rao MS, Shetty AK. Chronic temporal lobe epilepsy is associated with severely diminished dentate neurogenesis in the adult hippocampus. Neurobiol Dis. 2004;17:473-490. DOI: 10.1016/j.nbd.2004.08.008

[78] Hattiangady B, Shetty AK. Decreased neuronal differentiation of newly generated cells underlies reduced hippocampal neurogenesis in chronic temporal lobe epilepsy. Hippocampus. 2010;20:97-112. DOI: 10.1002/hipo.20594