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Review Article

Stem Cells Based Therapy for Temporal Lobe Epilepsy

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Abstract

Temporal lobe epilepsy (TLE) is the most common and difficult to treat form of epilepsy. Nearly, 30% of TLE patients are refractory to anti-epileptic drug treatments. Thus, identifying alternative treatment strategies for drug resistant TLE is warranted. Cell therapy is evolving as one of the promising treatment option for drug-resistant TLE. However, the functional efficacy of engrafted cells is still a matter of debate while the possibilities of teratoma formation and immune rejection are the major impediments which preclude the application of cell therapy for treating TLE. Nonetheless, the recent consensus is that host tissue regeneration may be partly attributed to growth factors released by the transplanted cells. In this concise review we describe the neurobiological features of TLE and summaries experimental data which provide proof of principle in support of the possibilities of treating TLE with stem cell based approaches.

Key words: Epilepsy, Hippocampus, Stem cells, Neurodegeneration, Neuroprotection

Introduction

Epilepsy affects 65 million people worldwide and in India alone, more than 5.5 million people are affected with epilepsy. Epilepsy is typically characterized by unpredictable occurrence of seizures owing to imbalance in excitatory and inhibitory activity between the brain structures. One of the well characterized epilepsies is temporal lobe epilepsy (TLE) and almost 40% of patients with epilepsy are categorized as TLE [1,2]. Typically, a sequelae is observed in TLE i.e. an initial precipitating injury (IPI) due to status epilepticus, stroke, head injury, febrile seizure, brain tumor or encephalitis followed by a latent period of no seizure activity and then the development of spontaneous recurrent motor seizure (SRMS) [3,4].

Pathophysiology of Temporal Lobe Epilepsy

Hippocampal Sclerosis

Animal prototypes of TLE have served as a valuable tool in understanding the molecular and cellular changes underling epileptogenesis (i.e. from IPI to SRMS). Such studies revealed that different brain structures and in particular, the hippocampus undergo massive cytoarchitectural changes following IPI. Hippocampal sclerosis is one of the hallmark features of TLE that includes reduction in hippocampal volume[5], neuroinflammation [6,7], neurodegeneration [5,8,9], loss of inhibitory function [10,11], abnormal neurogenesis [12,13] and aberrant mossy fiber sprouting [8].

Role of Astrocytes in Epileptogenesis

Inflammatory responses mediated through reactive astrocytes contribute directly and indirectly to epileptogenesis. The direct contribution of reactive astrocytes to the hyperexcitability in an epileptic brain attributes to retarded spatial buffering of K^+ ions, decreased inward rectifying K^+ channels, augmented glutamate release coupled with dysfunction in glutamate re-uptake mechanisms and altered Ca^+

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Furthermore, the overwhelming proliferation of astrocytes following IPI also contributes indirectly to the pathophysiology of TLE by compromising the integrity of blood brain barrier (BBB) and extravasation of plasma proteins into the CNS [15,16]. Several studies have shown direct correlation between seizure severity and BBB damage in TLE subjects [14,17]. Another important manifestation is the fast degradation of adenosine by reactive astrocytes [14]. Adenosine is an inhibitory (Mehta et al 2008) and an endogenous anti-convulsant that was shown to be neuroprotective in animal models of TLE [18,19]. The extracellular adenosine level is determined by adenosine kinase (ADK) that is mostly expressed by astrocytes. However, following SE there is a surge in ADK activity due to hyper proliferation of reactive astrocytes resulting in faster degradation of extracellular adenosine[20], thus hampering the excitatory-inhibitory balance.

Abnormal Hippocampal Neurogenesis and Mossy Fiber Sprouting Status epilepticus mediated hippocampal neuronal loss can be evidenced in dentate hilus (DH), CA3 and CA1 sub-field of hippocampus as early as 24 hours (Rao et al., 2006). It has been demonstrated that due to loss of CA3 cells in epileptic brain, mossy fibers that originate from granule cells of DG, sprout aberrantly and innervate the molecular layer of DG and forms recurrent connections with granule cells themselves [21]. Furthermore, recent studies are emerging to shed light on the role of hippocampal neurogenesis during SE in mossy fiber sprouting and hyper excitation [22,23,24,25]. Adult neurogenesis is a continuous process during which new neurons are produced and integrated into the brain circuitry. Dentate gyrus sub-granular zone (SGZ) is considered to be one of the neurogenic niches in the adult brain. The newly formed neurons in SGZ migrate to granule cell layer and become part of the hippocampal circuitry. However, in the context of epilepsy several studies have demonstrated striking differences in the behavior of newly born neurons under epileptic and non-epileptic conditions in such a way that in the epileptic brain the newly born neurons migrate ectopically to DH, display abnormal apical and basal dendritic arborization [26], possess different electrophysiological properties [27] and form wrong axonal connections into dentate gyrus supragranular layer rather than with CA3 cells [26,28]. Given the aforementioned molecular and cellular alterations following SE, behavioral comorbidities associated with TLE are multitude. It is not uncommon to witness cognitive impairments, depression, anxiety and abnormal social behaviors in patients with TLE [29]. In summary, TLE is a complex neurological condition and any novel therapeutic approaches to curtail seizure intensity should aim to address the issues at the molecular-cellular-behavioral levels.

Need for Alternative Approach for Treating Temporal Lobe Epilepsy . The currently available anti-epileptic drugs (AED) only provide symptomatic relief and do not influence the course of the disease. Moreover, significant percentages (~30%) of patients with TLE do not respond to AED [2]. In patients with retractable epilepsy, surgical resection of the temporal lobe is recommended. Unfortunately, such procedures can also lead to behavioral and psychological disturbances leaving the patient hopeless. Thus, there is a pressing need to develop alternate therapeutic strategies to prevent the hippocampal abnormalities following IPI and to restrain the development of SRMS and co-morbidities associated with it.

Stem Cell Based Therapy

Cell therapy is emerging as a plausible therapeutic option for drug resistant epilepsy. Preclinical studies demonstrated that cell therapy can be effective in treating TLE [30-34]. Intra-hippocampal transplantation of neural progenitor cells into epileptic rodents restrains seizure frequency and improves cognitive functions [9,11,35 - 37]. Likewise, neuronal graft enriched with interneurons have shown to reduce the frequency and intensity of SRMS [30,32,38,39]. However, the major obstacles which prohibit the use of cell therapy for treating CNS disorders are the ethical concerns associated with obtaining neural cells, survival of transplanted cells, immune rejection, functional efficacy of grafted cells and possible teratoma formation. In spite of all these challenges, a consensus is emerging that the host regeneration may be partly attributed to growth factors and cytokines released by the transplanted cells [40 - 45]. In this context, condition medium (CM) derived from stem cell cultures are excellent sources of growth factors and cytokines that might possess protective properties against various disease conditions [42,46]. In support of this notion, recent studies using an in vitro model of neurodegeneration demonstrated that introducing conditioned medium derived from non-neuronal cells like adipose stromal cells (ASC-CM) and bone marrow mesenchymal stem cells can protect neurons against excitotoxicity [41,46-50]. Likewise, a recent study revealed that a single intravenous injection of ASC-CM protected hippocampal and cortical neurons against ischemic injury [51]. While the majority of the studies investigated the effects of cell transplantation in animal models of TLE, there is no information available on the effects of CM per se on preventing the hippocampal damage following SE and restraining the development of SRMS.

As a proof of principle, we conducted preliminary experiments in which CM derived from HEK cell line completely protected hippocampal cells against kainic acid induced neurodegeneration in in vitro condition. Further analysis revealed that exposure of HEK-CM to hippocampal culture up-regulates endogenous neuroprotective factors like erythropoietin and BCL-2 supporting the conception that the paracrine factors per se can be sufficient to recapitulate the therapeutic efficacy of cell transplantation in treating neurodegenerative diseases.

Conclusion and future perspective

Stem cell based therapies for TLE, though still in their initial stages of investigation, have shown significant promise in the laboratory but their success in clinical trials will determine how quickly they make the bench-bedside transition. To increase their efficacy in clinical trials a thorough understanding of their biology including factors regulating their migration, proliferation, differentiation in what types of neurons, immunomodulation, and their long-term survival, a complete profiling of growth factors they release in the transplantation site and their effects on host tissues need to be studied in detail in the petri dish as well as in relevant animal models. As of now only time will tell whether stem cell therapy will be able to provide cure to this incurable neurological disorders.

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