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Review

Hippocampal injury-induced cognitive and mood dysfunction, altered neurogenesis, and epilepsy: Can early neural stem cell grafting intervention provide protection?

Ashok K. Shetty *

Institute for Regenerative Medicine, Texas A&M Health Science Center College of Medicine at Scott & White, Temple, TX, USA
Department of Molecular and Cellular Medicine, Texas A&M Health Science Center College of Medicine, College Station, TX, USA
Research Service, Olin E. Teague Veterans Affairs Medical Center, Central Texas Veterans Health Care System, Temple, TX, USA

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ABSTRACT

Damage to the hippocampus can occur through many causes including head trauma, ischemia, stroke, status epilepticus, and Alzheimer's disease. Certain changes such as increased levels of neurogenesis and elevated concentrations of multiple neurotrophic factors that ensue in the acute phase after injury seem beneficial for restraining hippocampal dysfunction. However, many alterations that arise in the intermediate to chronic phase after injury such as abnormal migration of newly born neurons, aberrant synaptic reorganization, progressive loss of inhibitory gamma-amino butyric acid positive interneurons including those expressing reelin, greatly declined neurogenesis, and sustained inflammation are detrimental. Consequently, the net effect of postinjury plasticity in the hippocampus remains inadequate for promoting significant functional recovery. Hence, ideal therapeutic interventions ought to be efficient for restraining these detrimental changes in order to block the propensity of most hippocampal injuries to evolve into learning deficits, memory dysfunction, depression, and temporal lobe epilepsy. Neural stem cell (NSC) grafting into the hippocampus early after injury appears alluring from this perspective because several recent studies have demonstrated the therapeutic value of this intervention, especially for preventing/easing memory dysfunction, depression, and temporal lobe epilepsy development in the chronic phase after injury. These beneficial effects of NSC grafting appeared to be mediated through considerable modulation of aberrant hippocampal postinjury plasticity with additions of new inhibitory gamma-amino butyric acid positive interneurons and astrocytes secreting a variety of neurotrophic factors and anticonvulsant proteins. This review presents advancements made in NSC grafting therapy for treating hippocampal injury in animal models of excitotoxic injury, traumatic brain injury, Alzheimer's disease, and status epilepticus; potential mechanisms of functional recovery mediated by NSC grafts placed early after hippocampal injury; and issues that need to be resolved prior to considering clinical application of NSC grafting for hippocampal injury.

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1. Introduction

The hippocampus is an area of the brain vital for functions such as learning, memory, and mood [1,2]. It is also one of the brain regions that react to injury or neurodegeneration with robust plasticity [3–7]. Hippocampal injury can manifest from numerous causes, which comprise head trauma, ischemia, hemorrhagic stroke, acute seizures, status epilepticus (SE), encephalitis, brain tumors, drug withdrawal, exposure to chronic unpredictable stress, and Alzheimer's disease (AD) [8–12]. Typically, the acute phase after hippocampal injury is exemplified by increased neurogenesis from neural stem cells (NSCs) located in the subgranular zone (SGZ) of the dentate gyrus (DG) and enhanced levels of multiple neurotrophic factors [13–16]. Increased neurogenesis is also associated with the aberrant migration of newly-born neurons into the dentate hilus (DH) and the molecular layer, and the projection of axons from newly-born neurons into the dentate molecular layer, which eventually lead to significant synaptic reorganization in the hippocampus [17–19].

Although the abovementioned postinjury changes in the hippocampus are likely innate compensatory mechanisms to restrain overall dysfunction, some of them are not considered beneficial for recovery. For instance, alterations in the migration and connectivity of newly born neurons have been shown to contribute considerably towards DG hyperexcitability and development of chronic epilepsy after injury [17–19]. Furthermore, early postinjury compensatory alterations are inadequate for promoting recovery of function as most injuries to the

* Institute for Regenerative Medicine, Texas A&M Health Science Center College of Medicine at Scott & White, 5701 Airport Road, Module C, Temple, TX 76501, USA.
E-mail address: Shetty@medicine.tamhsc.edu.

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hippocampus have a predilection for evolving into learning deficits, memory and mood dysfunction, and/or chronic temporal lobe epilepsy (TLE) typified by spontaneous recurrent seizures (SRS) [20–22]. These impairments in the chronic phase after injury are typically linked with greatly waned neurogenesis from NSCs [14], reduced neuronal differentiation of newly-born cells [23], altered integration of newly-born neurons through their abnormal migration and/or occurrence of synaptogenesis on basal dendrites projecting from newly-born neurons into the DH [24], and prominently reduced concentration of neurotrophic factors that are important for NSC proliferation and differentiation as well as maintenance of normal cognitive and mood function. These include the brain-derived neurotrophic factor (BDNF), the fibroblast growth factor-2 (FGF-2), and the glial cell-line derived neurotrophic factor (GDNF) [14,15,25]. From this perspective, intervention strategies that are efficient for preventing or restraining the progression of the original precipitating injury into memory and mood dysfunction and chronic epilepsy development have immense value [26]. Ideal therapeutic interventions are those capable of promoting normal levels of neurogenesis with apt incorporation of newly-generated neurons into the injured hippocampal circuitry. These requirements are important because the ongoing hippocampal neurogenesis is widely believed to play vital roles in the formation of hippocampal-dependent memories and the maintenance of mood function [1,27,28] as well as the likelihood that the abnormal neurogenesis that ensues after injury contributes to an aberrant synaptic reorganization in the hippocampus, memory and mood dysfunction, and chronic TLE development [29,30].

2. NSCs are well suited for treating hippocampal injury

Neural stem cells are self-renewing, multipotent cells capable of generating all three central nervous system phenotypes (neurons, astrocytes, and oligodendrocytes). Cell therapy using NSCs as donor cells has received great interest as one of the promising therapeutic interventions for restraining hippocampus injury-induced memory and mood dysfunction and chronic TLE development [8,26,31]. This concept is buoyed by multiple characteristics of these cells. First of all, multipotent NSCs can be harvested/generated easily from multiple sources such as fetal, postnatal, and adult brain tissues; embryonic stem cells (ESCs); and induced pluripotent stem cells (iPSCs) [32–35]. Second, NSCs and their progeny can survive well in hypoxic conditions prevailing in the injured brain regions [36] and migrate and integrate into regions of the brain displaying neuron loss and inflammatory reaction in the form of hypertrophy of astrocytes, activation of microglia, and increased concentration of proinflammatory cytokines [37,38]. Third, NSCs have the potential to replace significant numbers of lost interneurons that secrete the inhibitory neurotransmitter gamma-amino butyric acid (GABA; Fig. 1) to regulate the activity of excitatory neurons and to maintain normal network function in the hippocampus [25,39,40]. Fourth, considerable fractions of the progeny of NSCs readily differentiate into astrocytes capable of secreting beneficial neurotrophic factors that promote neuroprotection, mitigate seizures [25,39,40], and enhance neurogenesis via stimulation of the proliferation of endogenous NSCs in the hippocampus [41,42]. Fifth, NSCs give rise to oligodendrocytes after grafting, which can repair myelin sheaths of axons in demyelinated regions of the brain [43]. Sixth, NSCs exhibit considerable anti-inflammatory properties. For example, a single intravenous injection of NSCs can considerably suppress neuroinflammation following experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis [44], and NSC transplantation in an animal model of AD can attenuate inflammatory activity [37]. Additionally, NSCs can be genetically engineered prior to grafting to deliver neuroprotective proteins to the injured brain [45]. These characteristics make NSCs the most versatile type of donor cells for treating brain injury or neurodegenerative diseases.

3. NSC grafting early after hippocampal injury can prevent impairments in memory, mood, and neurogenesis

Several studies using animal models have shown the promise of NSC grafting intervention for reducing hippocampal dysfunction after injury (Table 1). A recent study revealed that grafting of NSCs expanded from the anterior subventricular zone (SVZ) of the postnatal brain into the hippocampus of young adult rats early after injury is an efficacious approach for thwarting memory impairments and depression typically found in the chronic phase after injury [39]. Specifically, NSC grafting preserved the ability to make spatial and recognition memories and prevented increased depressive-like behavior. Maintenance of normal memory and mood function in animals receiving SVZ-NSC grafts after hippocampal injury was linked with excellent survival and widespread migration of graft-derived cells and differentiation of significant percentages of NSC graft-derived cells into different subtypes of GABA-ergic interneurons secreting the calcium binding proteins calbindin and parvalbumin (PV) and glial cells such as astrocytes, oligodendrocytes, and oligodendrocyte progenitors [39; Fig. 2].

Grafting of NSCs also restrained several pathological features that are believed to have adverse effects on memory and mood function in the chronic phase after injury. It appeared that NSC grafting preserved mood and memory function after hippocampal injury via several mechanisms. First, the acute phase after injury typically enhances hippocampal neurogenesis as well as promotes abnormal neurogenesis typified by aberrant migration of newly-born neurons into the DH and the molecular layer and projection of basal dendrites from newly-born neurons projecting into the DH. On the other hand, the chronic phase after injury is characterized by greatly declined production of newly-

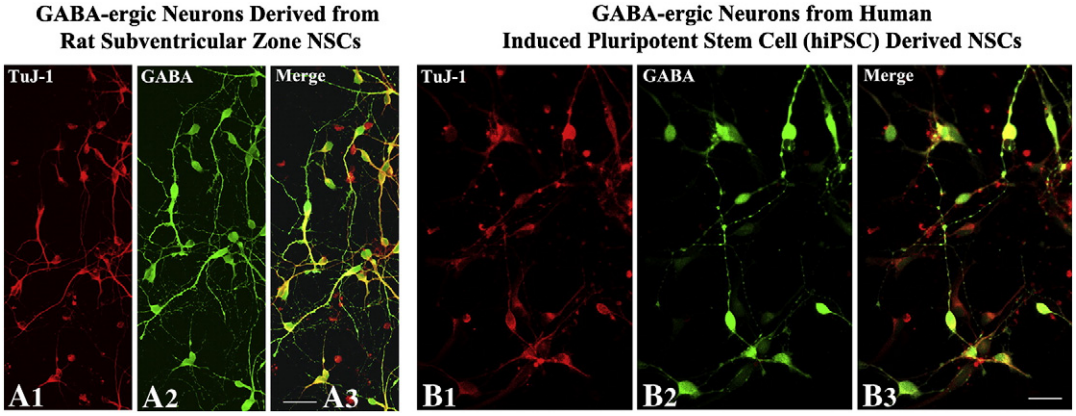

Fig. 1. Gamma-amino butyric acid (GABA) positive neurons derived from postnatal rat subventricular zone neural stem cells (A1–A3) and neural stem cells generated from human-induced pluripotent stem cells (B1–B3). A1 and B1, TuJ-1. A2 and B2, GABA. A3 and B3, merged photographs showing both TuJ-1 and GABA expression. Scale bar, A1–A3 = 50 μm. B1–B3, = 25 μm.