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Endogenous neurogenic cell response in the mature mammalian brain following traumatic injury

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Abstract

In the mature mammalian brain, new neurons are generated throughout life in the neurogenic regions of the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus. Over the past two decades, extensive studies have examined the extent of adult neurogenesis in the SVZ and DG, the role of the adult generated new neurons in normal brain function and the underlying mechanisms regulating the process of adult neurogenesis. The extent and the function of adult neurogenesis under neuropathological conditions have also been explored in varying types of disease models in animals. Increasing evidence has indicated that these endogenous neural stem/progenitor cells may play regenerative and reparative roles in response to CNS injuries or diseases. This review will discuss the potential functions of adult neurogenesis in the injured brain and will describe the recent development of strategies aimed at harnessing this neurogenic capacity in order to repopulate and repair the injured brain following trauma.

Keywords

Traumatic brain injury; endogenous neurogenesis; subventricular zone; hippocampus; cognitive function

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability worldwide, with no cure available for the enduring deficits induced by TBI. It has long been thought that the mature brain cannot be repaired following injury. Recent findings have revealed that multipotent neural stem/progenitor cells (NS/NPCs) persist in selected regions of the brain throughout the lifespan of an animal, rendering the mature brain capable of generating new neurons and glia (Lois and varez-Buylla, 1993; Gage et al., 1998). Over the past 25 years, extensive studies have demonstrated that the adult generated neurons in the dentate gyrus (DG) of the hippocampus in the mature brain play important roles in hippocampal dependent

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learning and memory functions (Deng et al., 2009; Clelland et al., 2009; Aimone et al., 2014), whereas the subventricular zone (SVZ) derived new olfactory interneurons are required for the normal functioning of the olfactory bulb network and some selected olfactory behaviors (Moreno et al., 2009; Breton-Provencher et al., 2009; Sakamoto et al., 2014b). Following TBI, increasing evidence has suggested that these endogenous NS/NPCs may play regenerative and reparative roles in response to CNS injury as an enhanced neurogenic response has been identified in varying types of brain injury models in animal studies and also in human. Furthermore, TBI-induced hippocampal neurogenesis has been linked to the innate cognitive functional recovery following TBI. These studies indicate that the mature brain has the inherent potential to restore populations of damaged or destroyed neurons. This raises the possibility of developing therapeutic strategies aimed at harnessing this endogenous neurogenic capacity in order to regenerate and repair the injured brain.

Adult neurogenesis in the normal mammalian brain

In the mature mammalian brain, the endogenous neurogenic regions are primarily confined to the SVZ surrounding the lateral ventricle and the DG of the hippocampus (Altman and Das, 1965; Lois and Alvarez-Buylla, 1993). Neural stem/progenitor cells (NS/NPCs) reside in the SVZ give rise to neuronal and oligodendroglial progenies (Ortega et al., 2013). The majorities of new neurons derived from the SVZ migrate along the rostral migratory stream and are destined to the olfactory bulb becoming olfactory interneurons (Gritti et al., 2002). A small number of SVZ-derived new neurons migrate into cortical regions for reasons yet to be identified, but probably related to repair or cell renewal mechanisms (Parent et al., 2002). Likewise, the newly generated cells of the DG migrate laterally into the dentate granule cell layer and exhibit properties of fully integrated mature dentate granule neurons (Kempermann and Gage, 2000; van Praag et al., 2002). Most importantly, the newly generated DG granule neurons form synapses and extend axons into their correct target area, the CA3 region (Hastings and Gould, 1999).

Thus far, multiple studies have quantified the degree of cytogenesis occurring in these regions and have clearly shown that large numbers of new cells are constantly produced (Lois and Alvarez-Buylla, 1993; Cameron and McKay, 2001). Specifically, the rat dentate gyrus produces ~9000 new cells per day which equates to ~270,000 cells per month (Cameron and McKay, 2001). Considering that the total granule cell population in the rat is 1–2 million cells, this degree of new cell addition is certainly large enough to affect network function. A more recent study found that in the olfactory bulb almost the entire granule cell population in the deep layer and half of the super layer were replaced by newly adult generated neurons over a 12-month period (Imayoshi et al., 2008). The same study also reported that in the hippocampus, the adult generated neurons comprised about 10% of the total number of dentate granule cells and they were equally present along the anterior-posterior axis of the DG (Imayoshi et al., 2008). However, studies have also found that in normal adult rodent brains under normal housing condition, approximately half of the newly generated neurons in the DG and olfactory bound SVZ cells have a transient existence of two weeks or less (Gould et al., 2001; Mouret et al., 2008; Sultan et al., 2011b; Dayer et al., 2003). While this interval is long enough for supportive glial roles; neuron formation and integration into an existing network takes approximately 10–14 days (Alvarez-Buylla and

Nottebohm, 1988; Kirn et al., 1999). It must be noted, however, that most of the surviving neurons become mature neurons and are sustained for months to years (Gould et al., 2001; Dayer et al., 2003; Sultan et al., 2011a), strongly supporting the theory of network integration. Furthermore, this dramatic loss of newly generated cells might be a recapitulation of network pruning seen in early mammalian development. Whether the limited life-span represents network pruning or merely distinct cell specific roles is yet to be understood.

Following the discovery of persistent adult neurogenesis throughout life in the mature mammalian brain, the physiological roles and the importance of this adult neurogenesis particularly hippocampal neurogenesis in relationship with learning and memory functions has been extensively studied. Studies have shown that conditions which enhance hippocampal neurogenesis such as exposure to enriched environments, physical exercise, or growth factor treatment, can improve cognitive abilities (van et al., 1999; Kempermann et al., 1997; Brown et al., 2003; Sun et al., 2009). Additionally, studies that aim to inhibit adult neurogenesis using varying types of approaches have further confirmed the causal relationship between neurogenesis and hippocampal function. For example, in studies that use either brain irradiation, systemic or focal administration of anti-mitotic agents, or genetic ablation of dividing progenitor cells to eliminate adult neurogenesis, it has been shown that adult-generated dentate granule neurons have important roles on many types of hippocampal-dependent learning and memory tasks in rodents. These include trace eyeblink and fear conditioning (Shors et al., 2001; Shors et al., 2002), formation of contextual fear memory (Saxe et al., 2006; Imayoshi et al., 2008; Hernandez-Rabaza et al., 2009), long-term retention of spatial memory in the water maze task (Snyder et al., 2005; Jessberger et al., 2009), object recognition task (Jessberger et al., 2009; Suarez-Pereira et al., 2014) and active place avoidance task (Burghardt et al., 2012). Moreover, targeted deletion of adult generated dentate granule neurons at the maturation stage induced retrograde memory deficits in contextual fear, water maze and visual discrimination memories (Arruda-Carvalho et al., 2011). Although some variable and partially contradictory results have been reported from these studies due to the methods used to knockdown neurogenesis or the nature of behavioral tasks, this growing body of data provides compelling evidence that adult hippocampal neurogenesis is directly involved in many aspects of hippocampal-dependent learning and memory functions.

Compared to hippocampal neurogenesis, the role of SVZ neurogenesis in normal brain is less defined. The majority of newly generated neurons derived from the SVZ reaches the olfactory bulb and differentiates into granule cells; approximately 5% become periglomerular cells in the olfactory bulb (Moreno et al., 2009; Lemasson et al., 2005). The newly generated olfactory inhibitory interneurons integrate into the olfactory circuity and are involved in some, but not all, olfactory functions. Studies that inhibit olfactory neurogenesis using similar approaches as hippocampal neurogenesis inhibition have found that adult generated neurons in the olfactory bulb are involved in olfactory discrimination (Gheusi et al., 2000; Moreno et al., 2009; Kageyama et al., 2012), olfactory perceptual learning functions and the acquisition of new odor-related behaviors (Moreno et al., 2009; Moreno et al., 2012), innate olfactory responses (Sakamoto et al., 2011), short-term

olfactory memory function (Breton-Provencher et al., 2009), flexible olfactory associative learning and memory function (Sakamoto et al., 2014a).

The proliferation and maturational fate of cells within the SVZ and DG is modulated by a number of physical and chemical cues. For example, biochemical factors such as serotonin, glucocorticoids, ovarian steroids, and growth factors tightly regulate the proliferative response, suggesting that cell proliferation within these regions have a physiologic importance (Banasr et al., 2001; Tanapat et al., 1999; Cameron and Gould, 1994; Kuhn et al., 1997). In addition, physical stimuli such as exercise, enriched environment, or stress produce alterations in cell production suggesting a role in network adaptation (Gould et al., 1997; Kempermann et al., 1997; van et al., 1999; Kempermann et al., 2000). For example, physical exercise or environments that are cognitively and physically enriched increase cell proliferation and neurogenesis in both the SVZ and DG, while stress reduces this type of cellular response (Kempermann et al., 1997; Gould et al., 1999; Gould and Tanapat, 1999; Kempermann et al., 1998). Nevertheless, a functional role for these new cells is dependent upon a significant number of cells being generated, their survival, differentiation and integration into existing neuronal circuitry.

TBI-induced neurogenesis in experimental studies in TBI animal models

Studies from our lab and others have shown that TBI significantly increases cell proliferation in both the SVZ and DG in adult mice and rats in varying TBI models including fluid percussive injury (FPI) (Chirumamilla et al., 2002; Rice et al., 2003), controlled cortical impact injury (CCI) (Dash et al., 2001; Gao et al., 2009), closed head weight drop injury (Villasana et al., 2014) and acceleration-impact injury (Bye et al., 2011). Common to all reported TBI models, the most prominent endogenous cell response in both the DG and SVZ following TBI is an increase in cell proliferation. This injury-enhanced cell proliferation is relatively transient and is observed during the first week post-injury, with a peak time at 2 days in the DG in both rat FPI and mouse CCI models (Sun et al., 2005; Gao and Chen, 2013). In FPI model, increased cell proliferation in the SVZ also peaks at 2 days post-injury (Sun et al., 2005), and this injury-induced proliferative response persists for up to 1 year (Chen et al., 2003). As for the degree of neuronal differentiation, different results have been reported. In diffuse injury models such as the closed head weight drop model and the fluid percussion model, an increased total number of new neurons in the subgranule zone and granule cell layer of the DG were observed following injury (Sun et al., 2007; Villasana et al., 2014). Whereas in a focal injury model such as CCI, the number of new neurons generated following TBI was not significantly increased as compared to sham control despite enhanced cell proliferation (Gao and Chen, 2013). This discrepancy is likely due to variations of model differences, severity of injury, post-injury time point for tissue assessment, cell markers used and/or quantification methods. The difference of injury model on cell response is particularly significant. For example, in the CCI model, TBI induces significant death of immature neurons in the DG at an early time post-injury before injury-enhanced cell proliferation is observed (Rola et al., 2006; Gao et al., 2008). However, in a closed head diffuse injury model, increased hippocampal neurogenesis in both cell proliferation and generation of new neurons is only observed in the more severely injured animals (Villasana et al., 2014). Despite these differences, it is clear that TBI stimulates

activation of endogenous neural stem cells in the neurogenic regions in the mature rodent brain.

In the normal brain, the extent of neurogenesis in the neurogenic regions decreases with increasing age. Following TBI, our lab has also found that the juvenile brain displays a more robust neurogenic response following injury than the adult and aged brain (Sun et al., 2005). This age-related difference in the degree of injury-induced endogenous cell response has also been recently reported in species with gyrencephalic brains. In this study, Costine and colleagues have found that in a cortical impact injury piglet model, TBI significantly increased cell proliferation in the SVZ in piglets that were injured at post-natal day 7 but not in animals injured at 4 months old (Costine et al., 2015). Furthermore, we and others have found that injury-induced newly generated granular cells integrate into the existing hippocampal circuitry (Emery et al., 2005; Sun et al., 2007), and this endogenous neurogenesis is directly associated with the innate cognitive recovery observed following injury (Blaiss et al., 2011; Sun et al., 2015). Although TBI-enhanced cell proliferation and generation of new neurons are observed in these TBI models, unlike stroke where robust generation and migration of new neurons from the SVZ to the site of ischemic injury is observed (Parent et al., 2002), in TBI models, migration of newly generated neurons to the site of injury is not significant although increased number of migrating neurons are observed along the white matter tract (Costine et al., 2015; Ramaswamy et al., 2005). Nevertheless, these studies have strongly indicated the inherent attempts of the mature brain to repair and regenerate following injury through the endogenous neurogenic response. This notion is supported by the evidence that the level of injury-enhanced hippocampal neurogenesis is correlated to the increased expression of the activity-dependent early gene, c-fos, in the hippocampus following injury (Villasana et al., 2014).

Neurogenesis in human brain

Compared to rodent brains, the degree and function of adult neurogenesis in the human brain is less clear. Similar to rodent brains, the SVZ and the hippocampus in human brains are the active neurogenic regions (Eriksson et al., 1998; Sanai et al., 2004). Proliferating NS/NPCs have been found in these areas from autopsy brain samples. Under culture conditions, cells isolated from the adult human brain are capable of generating both neurons and glia (Kukekov et al., 1999; Nunes et al., 2003; Murrell et al., 2013). Using a groundbreaking birth-dating method by measuring the concentration of nuclear bomb- test-derived carbon-14 (14C) that is lastingly incorporated into the DNA of dividing cells, researchers at the Karolinska Institute in Sweden have published a series of studies examining neurogenesis in human brains. They have reported that in human brains, substantial hippocampal neurogenesis is observed with a modest decline during aging and that the rate of adult neurogenesis in the hippocampus is comparable between middle-aged humans and mice (Spalding et al., 2013). However, the degree of neurogenesis in the SVZ and the subsequent migration of newly generated neurons from SVZ to the neocortex and olfactory bulbs are rather limited and are only observed in the early childhood (Bhardwaj et al., 2006; Sanai et al., 2011; Bergmann et al., 2012). Surprisingly, in the striatum of the adult human brain, unlike other species, a robust generation of new neurons is observed in areas adjacent

to the SVZ, and these adult-generated striatal interneurons are depleted in the brains of patients with Huntington's disease (Ernst et al., 2014).

Due to the difficulties of obtaining human brain samples as well as technical challenges to birth-dating NS/NPCs, there are very few studies reporting endogenous neurogenesis following TBI in human subjects. Using doublecortin (DCX), a marker for neural progenitor cells and migrating neuroblasts, Taylor and colleagues have found that the number of DCX+ cells in the SVZ, hippocampus and the periventricular white matter is closely related to the age of the patients with the brains in younger children having more DCX+ cells in these regions than those in older children. Whereas brain trauma had no effect on the number of DCX+ cells in TBI patient samples although abundant DCX+ cells were found in brain regions around a focal infarct lesion in a non-TBI patient (Taylor et al., 2013). Contrary to this, Zheng and colleagues have reported an increased number of DCX+ cells in the injured cerebral cortex from TBI patients (Zheng et al., 2013). The discrepancy of these two studies may be due to the source of tissues, markers used or potential artifacts associated with postmortem intervals. From the limited studies examining post-TBI endogenous neurogenesis in human brain, clear evidence of TBI-induced generation of new neurons in humans is lacking. Nevertheless, this does not completely rule out the possibility of a small scale injury-induced generation of new neurons in human brains, given the evidence of persistent neurogenesis existing in neurogenic regions and the ectopic generation of new striatal neurons in mature human brains (Spalding et al., 2013; Ernst et al., 2014), as well as the observed new neurons in brain regions around lesions of focal infarction (Taylor et al., 2013) and subarachnoid hemorrhage (Sgubin et al., 2007).

Regulation of TBI-induced neurogenesis

The underlying mechanisms regulating adult neurogenesis are not fully understood. Many transcriptional, genetic regulation and signaling pathways that are important for neurogenesis during development are also implicated in regulating neurogenesis in the mature brain (Mu et al., 2010; Ma et al., 2010; Kempermann, 2011; Hsieh, 2012; Faigle and Song, 2013; Aimone et al., 2014). Apart from these physiological regulatory mechanisms, TBI triggers additional pathways that regulate/affect a neurogenic response in the injured brain. For example, in the injured brain, studies have found that elevated expression of vascular endothelial growth factor (VEGF) and VEGF signaling pathway is involved in mediating survival of de novo newly generated granule neurons rather than proliferation of neuroblasts following LFPI (Lee and Agoston, 2010). Using transgenic animals, studies have found that neurotrophin p75 receptor (p75 (NTR)) can influence endogenous neurogenesis at all stages and its expression is induced in the injured brain where it regulates cell survival (Catts et al., 2008), and intranasal administration of LM11A-3, a small molecule p75 (NTR) ligand can enhanced long-term hippocampal neurogenesis and reversed spatial memory impairments (Shi et al., 2013). Transgenic animals studies have also demonstrated that Ephrins and Eph receptors B3 (EphrinB3-EphB3) signaling is involved in regulating cell proliferation and survival of cells in the SVZ in adult brain by negatively regulating cell cycle progression and apoptosis (Ricard et al., 2006). Following TBI, the EphB3 expression in the SVZ is transiently reduced and the EphB3 signaling is down regulated, whereas expansion and survival of endogenous adult stem cells in the SVZ is

observed (Theus et al., 2010). Other growth factors such as bFGF, EGF, IGF-1, BDNF were reported to be involved in regulating post-TBI neurogenesis by enhancing generation of new neurons, and/or promoting survival of new neurons in the injured brain (Carlson et al., 2014; Gao and Chen, 2009; Sun et al., 2009; Sun et al., 2010).

Enhancement of endogenous neurogenesis as potential therapeutic strategies for TBI

The regenerative capacity of the adult brain through endogenous neurogenesis is of particular interest with regards to TBI. As adult generated neurons from both the SVZ and DG have functional roles, harnessing this endogenous population of cells to repopulate the damaged brain is an attractive strategy to repair and regenerate the injured brain. As the spontaneous innate recovery capacity of the brain is rather limited, it is imperative to augment this endogenous process via exogenous means. Thus far, many factors have been identified to be able to enhance neurogenesis, particularly hippocampal neurogenesis together with cognitive functional improvement. Among these factors, many types of growth factors have shown effectiveness in enhancing neurogenesis and improving functional recovery of the injured brain following trauma. Studies from our lab have shown that intraventricular infusion of growth factors bFGF, or EGF can significantly enhance TBI-induced cell proliferation in the hippocampus and the SVZ, and drastically improve cognitive functional recovery of the injured adult animals (Sun et al., 2009; Sun et al., 2010). Intraventricular infusion of S100β can enhance cell proliferation and generation of new neurons in the hippocampus and improve the functional recovery of animals following TBI (Kleindienst et al., 2005). Studies have also reported that post-TBI infusion of recombinant VEGF improves functional recovery of injured animals concomitant with increased cell proliferation in the SVZ (Thau-Zuchman et al., 2010), and enhanced survival of newly generated neurons in the DG (Lee and Agoston, 2010).

Apart from these aforementioned growth factors, several drugs that are currently in clinic trials for treating TBI or other neurological conditions have shown effects in enhancing neurogenesis and cognitive function in TBI animals including statins (Lu et al., 2007), erythropoietin (Lu et al., 2005; Xiong et al., 2010), and anti-depressant imipramine (Han et al., 2011) etc. In a rat CCI model, post-injury treatment with Statins (simvastatin and atorvastatin) at 1 day after and daily for 14 days significantly enhances the total number of BrdU+ cells and BrdU+/NeuN+ cells in the DG and improves spatial learning function (Lu et al., 2007). Similar results were reported in animals receiving erythropoietin treatment at day 1 or days 1–3 following CCI (Lu et al., 2005; Xiong et al., 2010). In a mouse CCI model, imipramine, a commonly used tricyclic antidepressant, was administrated for either 2 or 4 weeks after injury and animals in both treatment regimens have shown significantly improved cognitive function and increased cell proliferation and total number of newly generated neurons in the DG (Han et al., 2011). Other reagents or strategies which have beneficial effect for TBI such as hypothermia, environment enrichment, transcranial low-level laser treatment, CNTF-like peptide 6, a P7C3-class of aminopropyl carbazole agents are also shown to influence the endogenous neural stem cell response in the injured animals (Bregy et al., 2012; Kovesdi et al., 2011; Xuan et al., 2014; Blaya et al., 2014; Chohan et al.,

2014). For example, post-TBI hypothermia treatment increases survival of newly generated neurons (Bregy et al., 2012). Intraventricular infusion of angiotensin receptor type 2 agonist (CGP42112A) for 3 days following a closed head injury induces cell proliferation in both the SVZ and DG, and increases the total number of new neurons in a dose-dependent manner (Umschweif et al., 2014). Post-TBI treatment with the P7C3 class of aminopropyl carbazole agents (P7C3-A20) 30min post LFPI for 7 days increases cell proliferation and survival of newly generated neurons in the SGZ (Blaya et al., 2014). In a CCI model, transcranial laser treatment post-TBI has also shown increasing cell proliferation and generation of new neurons in the SVZ and DG (Xuan et al., 2014). Collectively, these strategies all significantly improved cognitive functional recovery of injured animals with increased mobilization of endogenous stem cell pools. Although many of these aforementioned treatment strategies also exert neuroprotective and/or neural plasticity effects which would contribute to improved functional recovery, for example, EGF, statin or erythropoietin treatment reduces TBI-induced mature neuronal cell loss (Sun et al., 2010; Lu et al., 2007; Lu et al., 2005), whereas VEGF, LM11A-3, P7C3-A20 or transcranial laser treatment decreases contusion lesion volume and number of degenerating neurons (Thau-Zuchman et al., 2010; Xuan et al., 2014; Shi et al., 2013; Blaya et al., 2014); nevertheless, the association of enhanced endogenous neurogenesis and improved cognitive functional recovery from these studies strongly suggest that augmenting the endogenous repair response could be an attractive strategy for treating TBI.

While ample studies have shown the beneficial effect of enhancing injury-induced endogenous neurogenesis for post-TBI functional recovery, it is not clear whether there is any long term adverse consequence of this cell response. It is known that epilepsy or seizure activity is accompanied with enhanced aberrant hippocampal neurogenesis (Parent et al., 1997; Parent, 2008), whereas ablating this seizure –induced aberrant hippocampal neurogenesis can reduce chronic seizure frequency and normalize epilepsy-induced cognitive deficits (Cho et al., 2015). It has been speculated that TBI-induced neurogenesis may contribute to the onset of post-TBI epilepsy (Pitkanen et al., 2014). If so, further augmenting TBI-induced hippocampal neurogenesis may exacerbate this symptom. Another long term concern is the limitation of NSC pool in the mature brain. In the neurogenic niches, NSCs that proliferate in normal condition generally undergo asymmetric divisions to self-renew and generate committed progenitor cells (Kempermann et al., 2004; Alvarez-Buylla et al., 2001). When the balance of self-renewal and generation of daughter cells is not properly maintained by exogenous stimuli, the NSC pool could be exhausted leading to deletion of neurogenesis in long term which would be detrimental. Although there is no direct evidence linking neurogenesis to post-TBI epilepsy or post-TBI treatment induced depletion of neurogenic pools, caution needs to be taken when implementing therapies targeting endogenous neurogenesis.

Conclusion

Endogenous neurogenesis persists throughout life in the adult mammalian brain. The adult generated cells become functional neurons that participate in neural network function. The level of adult neurogenesis increases following TBI and has a direct role in the spontaneous cognitive functional recovery observed following brain insults. Augmenting or manipulating

this endogenous cell response could be a promising avenue for researchers seeking to develop new therapies for brain repair and regeneration following brain injury. Thus far, published studies were mostly limited to enhancing cell proliferation, survival of new neurons in the neurogenic niche. As neural stem cells and their progenies are regionally specific, they generate and migrate to specific regions. For brain repair, it is imperative that these injury-enhanced neural stem cells can migrate to the site of injury, survive and become functional neurons replacing cells lost to injury. Future studies should focus on strategies which can attract or guide endogenous neural stem cell migration to the site of injury.

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