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Strategies targeting endogenous neurogenic cell response to improve recovery following traumatic brain injury

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Abstract

Traumatic brain injury (TBI) affects over 1.7 million people in the United States alone and poses many clinical challenges due to the variability of the injuries and complexity of biochemical mechanisms involved. Thus far, there is still no effective therapy for TBI. Failure of preventative therapeutic strategies has led studies focusing on regenerative approaches. Recent studies have shown evidence that mature brains harbors multipotent neural stem cells capable of becoming mature neurons in the neurogenic regions. Following brain insults including TBI, the injured brain has increased level of neurogenic response in the subventricular zone and dentate gyrus of the hippocampus and this endogenous response is associated with cognitive function following injury. In this review, we highlight recent development and strategies aimed at targeting this endogenous cell response to enhance post-TBI functional recovery.

Keywords

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

Introduction

Millions of people suffer from traumatic brain injury (TBI) every year. According to the Centers for disease control and prevention, in the United States alone, about 1.7 million people sustain a TBI annually (Faul et al., 2010). Following TBI, the primary injury induces irreversible brain damage which is untreatable. The subsequent secondary injury plays a profound role in the evolution of the injury and clinical prognosis. Thus, preventing/treating the additional tissue damage caused by secondary brain insults is the major focus of therapies for TBI. Drug therapies aimed at controlling the spread of secondary injury have shown great success in experimental TBI models, however, more than 30 phase III clinical trials have failed to show successful results in clinical setting (Maas et al., 2010; Schouten,

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2007). These failures may be due to the overwhelming complexity of variables involved in TBI and complications of translating animal research to human clinical trials. To date, there is no effective treatment for TBI, proving the urgent need to explore new strategies. Recent findings of the existence of neural stem cells in the adult brain and their ability to proliferate and generate functional neurons following injury have raised the hope of developing therapies targeting these endogenous cells to achieve repair and regeneration in the injured brain following TBI.

Neurogenesis was once thought to be discontinued after development in the mammalian brain. Recent studies show that certain areas of the brain, specifically the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ), retain the ability to generate neurons and glia (Lois and Alvarez-Buylla, 1993; Gage et al., 1998). Neural stem cells (NSC) in these areas continue the developmental mechanisms to replace and replenish old and damaged cells. The primary physiological role of the NSC of the SVZ surrounding the lateral ventricles is to give rise to olfactory interneurons (Gritti et al., 2002). Whereas in the DG, newly proliferated cells become dentate granule neurons forming axon connections to their target CA3 region (Kempermann and Gage, 2000; van Praag et al., 2002; Hastings and Gould, 1999). In both regions, this neurogenic process continuously produces significant number of new neurons enough to affect network functions (Cameron and McKay, 2001; Imayoshi et al., 2008). Studies have shown that in the hippocampus, newly generated neurons integrate into the existing neuronal circuitry involving learning and memory functions, and enhancing or inhibiting this hippocampal neurogenesis can affect cognitive ability (van et al., 1999; Sun et al., 2009; Jessberger et al., 2009; Sun et al., 2015). Similarly, olfactory interneurons generated in the SVZ of the adult brain are involved in some olfactory functions such as olfactory discrimination, acquisition of new odor related behaviors, and short term olfactory memory functions (Breton-Provencher et al., 2009; Gheusi et al., 2000; Moreno et al., 2009).

Neurogenic response includes three different phases: proliferation or generation of new cells, migration of new cells to target areas, and differentiation into proper cell types (Hallbergson et al., 2003). The degree of adult neurogenesis is affected by many factors. Biochemical factors such as growth factors and steroids tightly regulate the proliferation and differentiation of the NSC (Tanapat et al., 1999; Cameron and Gould; 1994 and Kuhn et al., 1997). Other factors such as exercise, enriched environment, or stress can also affect the level of neurogenesis (Gould et al., 1997, Kempermann et al., 1997, van et al., 1999 and Kempermann et al., 2000). Studies have shown that TBI induces an up-regulation of neurogenesis in varying types of TBI models as described in a previous review (Sun 2015). The injury-induced adult born neurons are also capable of functional integration into the hippocampal network (Villasana et al., 2015) and are directly associated with spontaneous cognitive functional recovery observed following injury (Sun et al., 2007; Sun et al., 2015; Blass et al. 2013). Thus far, strategies such as supplementing varying types of growth factors, manipulating transcriptional regulators, or other pharmacological approaches targeting different aspects of the endogenous neurogenic response have shown promising results improving functional recovery following TBI as summarized in a recent review (Sun 2015). These studies clearly demonstrate that manipulation of this endogenous cell response holds potential for therapeutic advances in TBI treatments. This review will provide more

detailed information about factors/strategies that are utilized to influence adult neurogenesis following TBI.

Growth/Neurotrophic Factors

In the developing brain, high levels of many growth factors and neurotrophic factors, such as basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1) etc., are expressed at high levels responsible for the proliferation, differentiation and survival of cells in the central nervous system (CNS) (Caday et al., 1990; Plata-Salaman, 1991; Maisonpierre et al., 1990). Some of these factors and their effects on post-TBI neurogenesis have been briefly mentioned in a previous review (Sun, 2015), and they will be discussed in more detail in this review. The expression levels of these factors and the degree of endogenous cell proliferation decreases with increasing age (Seki and Arai, 1995). Among these factors, bFGF and EGF are essential for maintenance and proliferation of neural stem and progenitor cells (NS/NPC) *in vitro* and *in vivo* during developmental neurogenesis (Vicario-Abejon, 2004; Cameron et al., 1998). In the normal mature brain, administration of bFGF or EGF enhances proliferation of NS/NPCs in the SVZ and the DG (Kuhn et al., 1997; Wagner et al., 1999.). Furthermore, exogenous bFGF can also restore neurogenesis in the hippocampus and SVZ in the aged animals (Jin et al., 2003; Rai et al., 2007). Following TBI, in a controlled cortical impact (CCI) model of bFGF-null mice, the absence of injury-induced proliferative response in the DG can be restored by focal intracerebral injection of exogenous bFGF one hour after injury at 0.1 μl/min for 10 minutes, as demonstrated by a significant increase of bromodeoxyuridine (BrdU) positive cells in the DG at 9 days post-injury (Yoshimura et al., 2003). In a lateral fluid percussive injury (LFPI) model, we have shown that intraventricular infusion of bFGF or EGF significantly increases injury–induced cell proliferation in the DG and SVZ, leading to increased total number of newly generated neurons in the DG and enhanced cognitive functional recovery (Sun et al., 2009; Sun et al., 2010). In our studies, adult male Sprague-Dawley rats were subjected to a moderate LFPI and received a 7-day intraventricular infusion of recombinant bFGF or EGF (400 ng/day) through an osmatic mini-pump immediately after injury, significant increases of BrdU+ cells in the SVZ and DG at 7 days and 4 weeks post-injury and improved cognitive recovery measured by Morris Water Maze (MWM) were observed (Sun et al., 2009; Sun et al., 2010). Compared to bFGF and EGF, which function by promoting cell proliferation, two other notable trophic factors, IGF-1 and BDNF, have been reported playing a more specific role in enhancing survival and maturation of newly generated neurons in the DG following TBI. IGF-1, a mitogenic factor with multiple functions in the developing and adult brain, can enhance cell proliferation in normal adult and aged rats when administrated exogenously (Aberg, 2000; Aderson et al., 2002). In the injured brain following CCI, transgenic mice overexpressing IGF-1 had a significant increase in the number of BrdU+/doublecortin (DCX) double-labeled new neurons in the hippocampus and with better dendritic development whereas the level of cell proliferation was not changed (Carlson et al., 2014). Similarly, BDNF, a member of the neurotrophin family of growth factors which regulates diverse and important functions in the CNS, has also shown to enhance neurogenesis through promoting survival of newly

generated neurons, dendritic arborization, and synaptic formation rather than cell proliferation in the injured brain (Gao and Chen, 2009; Gao et al., 2009).

Apart from aforementioned factors, vascular endothelial growth factor (VEGF) and S100β also show effectiveness in enhancing neurogenesis and improving functional recovery of the injured brain following trauma. Adult male mice which were subjected to a closed head injury and exogenously infused with recombinant VEGF into the lateral ventricles for 7 days immediately following injury at a dose of 0.5μl/h, had increased BrdU+ cells in the SVZ, corpous callosum, and perilesion cortex, and reduced lesion size and better motor functional performance (Thau-Zuchman et al., 2010). In another study, adult rats infused with recombinant VEGF 1 day after LFPI at the rate of 0.5 μl/h for 13 days showed increased survival of newly generated neurons in the DG marked by Prox1+/BrdU+ double labeling (Lee and Agoston, 2010). S100β, a neurotropic protein secreted by astrocytes, when given intraventricularly for 7 days immediately following LFPI, increased cell proliferation and generation of new neurons in the hippocampus and improved cognitive function were observed (Kleindienst et al., 2005).

Small Molecules Imitating Growth/Neurotrophic Factors

Growth/neurotrophic factors can enhance neurogenesis and improve functional recovery following TBI, however, their utility is limited to invasive delivery such as intraventricular infusion due to their big molecular size incapable of crossing the blood brain barrier and the limited time length of bioavailability. Strategies targeting growth/neurotrophic factor signaling pathways with small molecules/peptides could retain similar beneficial effects with better translation potential. For example, cerebrolysin, a pharmacologically prepared low molecular weight neuropeptide derived from purified porcine brain proteins, which has pharmacodynamic properties similar to endogenous neurotrophic factors (Plosker and Gauthier, 2009), have shown enhancing cognitive improvements in mild TBI in clinical trials (Chen et al., 2013), In a mild impact acceleration model, intraperitoneal injection of cerebrolysin in rats increases the number of DCX labeled neuroblasts and BrdU/NeuN double-labeled newly generated mature neurons in the DG, and significantly improves long-term learning and memory functions of the injured animals (Zhang et al., 2015).

A synthetic neurotrophin TrkB receptor agonist 7,8-dihydroxyflavone, a small molecule that imitates BDNF, when administered intraperitoneally before or after a moderate CCI injury in mice, it can increase the survival of DCX+ newly generated neurons in the hippocampus, and promote their dendritic arborization similar to BDNF (Chen et al., 2015; Zhao et al., 2015). Neurotrophin p75 receptor (p75NTR) plays a physiological role in regulating hippocampal neurogenesis as p75NTR null mice demonstrated reduced number of new neurons in the hippocampus and subtle cognitive impairment (Catts et al., 2008; Bernabeu and Longo, 2010). Following CCI in male Sprague-Dawley rats, intranasal administration of a small-molecule p75NTR signaling modulator, LM11A-31, starting 10 minutes after injury and then once daily for 14 days with 6 μl of 33.3 μM, enhances proliferation and survival of NPCs in the hippocampus and ameliorates spatial learning impairments in MWM tests (Shi et al., 2013). It is also reported that mice treated with a small molecule peptide 6, which corresponds to an active region of human ciliary neurotrophic factor (CNTF), increases the

number of neurons in the DG and improves memory function following CCI (Chohan et al., 2014)

Other Peptides or Pharmacological Agents

Erythropoietin (EPO), a hormone that regulates production of red blood cells, has shown neuroprotective effects in stroke and TBI studies (Wang et al., 2004; Lu et al., 2005; Xiong et al., 2010). Intraperitoneal administration of carbamylated EPO either as a single dose (50 μg/kg) at 6 hours post CCI injury or once daily at 1, 2, and 3 days post injury in young male rats significantly increases BrdU+ cells and new neurons co-stained with BrdU+/NeuN+ in the DG; animals also show better functional recovery assessed by spatial memory task in MWM tests (Xiong et al., 2010), while inhibition of EPO-enhanced endogenous neurogenesis with mitotic inhibitor Ara-C blocks EPO-enhanced functional recovery (Zhang et al., 2012).

Thymosin β4 (Tβ4), a small peptide G-actin sequestering molecule, has pro-survival properties to promote tissue regeneration (Goldstein et al., 2005; Smart et al., 2007), and is involved in many cellular properties including proliferation and neuronal survival (Sun and Kim, 2007; Morris et al., 2010; Yang et al., 2008). Intraperitoneal injection of Tβ4 starting at 6 hr post CCI in rats for three doses shows increased number of BrdU+ newly proliferated cells and BrdU/NeuN double-labeled new neurons in the DG, with improved cognitive functional recovery (Xiong et al., 2012).

P7C3 class of aminopropyl carbazole agents, are small drug-like molecules with neurogenic effects identified through a target-agonist screen study. P3C3 and its derivative P7C3-A20 have shown to induce hippocampal neurogenesis by enhancing survival of newly generated neurons (Pieper et al., 2010). Following TBI in a rat LFPI model, P7C3-A20 given at 30min post-injury for 7 days can increase cell proliferation and survival of newly generated neurons in the subgranular zone and improve cognitive recovery in the MWM tests (Blaya et al., 2014).

Physical/Electrical Stimulations

Increased hippocampal neurogenesis is observed in response to several physiological stimulants such as physical exercise and environmental enrichment (EE). Studies have shown experimental treatments with EE result in increased survival rate of NSC and newly generated mature neurons (Nilsson et al., 1999). EE consists of animals being placed in large housing conditions equipped with objects such as climbing ladders, plastic tubing, racks of different dimensions, etc., allowing the animal to explore and receive exercise (Gaulke et al., 2005). EE has also shown to increase number of new neurons, dendritic branching, induces neuroplasticity, and improves performance in spatial learning (Kempermann et al., 1997; Greenough and Volkmar, 1973; Nakamura et al., 1999; Nilsson et al., 1999). Over the past two decades, many studies have demonstrated the beneficial effects of EE for TBI (Bondi et al., 2014). In an experimental study of TBI, rats that were exposed to EE for 20 days after LFPI showed significant increase in NS/NPCs in the DG due to increased survival of these cells (Gaulke et al., 2005). Physical exercise, another easy to implement stimulant, has

shown enhancing neurogenesis in normal brains (Brown et al., 2003). Studies have shown that running wheel exercise implemented in rats 14–20 days after LFPI can improve cognitive functional recovery due to exercise-induced production of BDNF (Griesbach et al., 2009). A more recent study compared early post-TBI running wheel exercise (starting 1 week post-TBI) to delayed exercise (starting at 5 weeks post-injury) in a CCI mice model, and found that delayed exercise significantly increased generation of new neurons, reduced lesion volume and inflammation together with reduced cognitive deficits in injured animals whereas early exercise had no such effects (Piao et al., 2013).

Recently, some radical approaches have been explored to stimulate the endogenous neurogenic response after TBI. Transcranial low light laser therapy (LLLT) is a new approach for TBI treatment. LLLT penetrates through the scalp and skull reaching the brain and has shown neuroprotective and neurogenic effects after brain injury (Xuan et al., 2015). In a CCI mice model, LLLT delivered either as a single treatment at 4 hours post TBI or daily treatment starting 4 hours post-injury for 3 days with 810 nm laser 1 cm in diameter positioned centrally showed increased cell proliferation, reduced lesion size, and significant improvement in sensorimotor functions, however, daily treatment for 14 days had no beneficial effect (Xuan et al., 2013). Single or 3 daily LLLT treatment starting at 4 hours post-CCI with 810-nm laser can also increase the number of newly generated neurons, decrease apoptosis and improve cognitive function in MWM performance tests (Xuan et al., 2014). The beneficial effect of LLLT is likely due to the increased expression of BDNF in the DG and SVZ following LLLT (Xuan et al., 2015).

Deep brain stimulation (DBS) is another radical approach to target neurogenesis. DBS has been used to treat many neurological disorders such as depression, movement disorders, and psychiatric disorders (Encinas et al., 2011). DBS has shown to induce sustained hippocampal neurogenesis by implanting electrodes in the anterior thalamic nucleus and stimulating at variable frequencies (10, 50, 130 Hz) for one hour (Toda et al., 2008). Thus far there is no report about the beneficial effects of DBS in TBI studies.

Existing FDA Approved Drugs

Recent studies have found several drugs that have already been used in clinic to treat other diseases having a specific effect on neurogenesis. Statins, a class of hydroxymethylglutaryl-coenzyme A reductase inhibitors, are used to treat hyperlipidemia in clinic, and have shown beneficial effects for neurological disorders including TBI (Peng et al., 2014; Béziaud et al., 2011). Oral administration of synthetically derived statins, simvastatin or atorvastatin, to rats at a dose of 1mg/kg starting at day 1 following CCI injury significantly increases BrdU-labeled newly proliferated cells and BrdU/NeuN co-labeled new neurons in the DG, and improves functional recovery of the injured animals, and the effect is particularly significant with simvastatin treatment (Lu et al., 2007; Xie et al., 2014).

Tissue plasminogen activator (tPA) is the only FDA approved drug for stroke. Intranasal administration of tPA 600μg given at days 7 and 14 following a moderate CCI injury in rats, significantly enhances neurogenesis by increasing the number of DCX+ cells and BrdU/

NeuN double-labeled cells in the DG, and improves motor function and cognitive performance (Meng et al., 2014).

Imipramine, a commonly used tricyclic antidepressant, selectively inhibits reuptake of serotonin and norepinephrine. Chronic treatment of imipramine has shown significant neurogenic effect in the DG (Santarelli et al., 2003). When administered intraperitoneally at 20 mg/kg daily for 2 or 4 weeks to mice starting 1 hour following CCI injury, imipramine treated mice showed significant increase in cell proliferation and in the total number of new neurons in the DG which is accompanied with better cognitive performance (Han et al., 2011). Similar effect of chronic imipramine treatment-enhanced post-TBI cell proliferation was observed in rats following a fluid percussive injury (Zhang J et al., 2014). Fluoxetine, another selective serotonin reuptake inhibitor, has similar effects as imipramine in inducing hippocampal neurogenesis in normal animals (Wang et al., 2008). When administered intraperitoneally at 10 mg/kg daily starting 4 days after a severe CCI injury, mice treated with fluoxetine for 4 weeks had significantly higher number of DCX+ cells in the DG, although functional improvement was not observed in the treated animals (Wang et al., 2011).

NeuroAid (MLC601 and MLC901), a traditional Chinese medicine used for stroke treatment, has shown effects of neuroprotection, neuroplasticity, and neurogenesis (Heurteaux et al., 2013; Quintard et al., 2014). In a rat LFPI study, animals which received MLC901 single i.p. injection at 2h post-injury, thereafter through drinking water until sacrificed, had significantly increased BrdU+ cells and BrdU/NeuN double-labeled cells in the DG, and improved cognitive recovery compared to vehicle-treated animals (Quintard et al., 2014).

Angiotensin II receptor type 2 (AT2) agonists have shown to limit brain ischemic insult and to improve functional outcome (Chao et al., 2013; Gendron et al., 2003; Li et al., 2005). Activation of AT2 increases the expression levels of BDNF and its receptors in neurons (Namsolleck et al., 2013). Activating AT2 via pharmacological agent CGP42112A in a closed head injury model in mice via intraventricular infusion for 3 days immediately following injury shows a dose dependent improvement in functional recovery accompanied by enhanced cell proliferation and generation of new neurons in the DG (Umschweif et al., 2014a & 2014b).

Modulating Signaling Pathways

During development, neurogenesis is controlled by several signaling pathways. Notch signaling is the major mitogenic pathway regulating cell genesis in many organs during development and in adulthood. In the developing CNS, the Notch signaling pathways play critical roles in proliferation and differentiation of NSC (Imayoshi et al., 2010). In recent years, Notch signaling has emerged as a dominant player in cell fate and maintenance of NSC in the adult brain. Notch1 is required for the continued production of mitotically active progenitor cells and neuroblasts in the SVZ and olfactory bulb (Imayoshi et al., 2010; Imayoshi and Kageyama, 2011; Basak et al., 2012), as well as in the hippocampus (Ables et al., 2010; Ehm et al., 2010). In the injured brain following TBI, a study showed that Notch 1

signaling may play an important role in regulating post-injury neurogenesis. Intracerebral delivery of adenovirus serotype 5 expressing Hes1 gene, one of the down-stream Notch effector genes, directly to the hippocampus in mice before receiving a fluid percussive injury, decreased cell proliferation and neuronal differentiation in the DG, whereas downregulation of Hes1 via injection of Hes1-siRNA increased neuronal differentiation and improved MWM performance (Zhang Z et al, 2014).

Wnt/β-catenin signaling is another key regulatory pathway influencing cell proliferation and differentiation in the neurogenic regions (Lie et al., 2005; Jang et al., 2013). Increased expression of β-catenin was found in newly derived glial progenitors and astrocytes in the injured cortex following a mild CCI in β-catenin reporter mice (White et al. 2010). Although there is no report examining the effect of manipulating this pathway for treating TBI, studies have found that the neurogenic effect of simvastatin following TBI is through enhancing Wnt signaling pathway to increase generation of new neurons in the DG, and this effect is mediated by inhibition of isoprenoid biosynthesis, independent of cholesterol (Robin et al., 2014). Survivin, a member of the inhibitor of apoptosis (IAP) gene family, is a downstream target gene of the Wnt/β-catenin signaling pathway. Following FPI in mice, increased Survivin expression was observed correlating with the increased cell proliferation in the DG (Zhang et al., 2013).

These limited studies suggest that manipulation of the Notch or Wnt singling pathways can modulate endogenous neurogenesis following TBI. However, as these pathways regulate cell proliferation/differentiation of various stem and progenitor cells in many organs including tumor cells, their therapeutic potential for treating TBI is uncertain.

Conclusion

TBI is perhaps one of the most complicated neurological disorders due to the high degree of heterogeneity of injury. Thus far there is still no effective treatment for TBI. Modulating endogenous repair mechanisms through enhancing neurogenesis could be an attractive approach for TBI therapy. Many strategies for enhancing neurogenesis that are summarized in this review (table 1) are also reported to have other neuroprotective and regenerative effects, which could contribute to their benefits of enhancing functional recovery following TBI. Nevertheless, convincing evidence has clearly demonstrated the importance of this endogenous neurogenic cell response in relation to learning and memory functions, and harnessing this response is important and necessary for therapeutic development for TBI.

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Table 1

Summary of studies cited in this review with treatment targeting endogenous neurogenic response following TBI.

Category	Authors	Study design	Findings
Growth/Neurotrophic Factors	Yoshimura et al., 2003;	CCI, bFGF-null mice, intracerebral injection of bFGF.	Restoration of injury-induced proliferative response in the DG
	Sun et al., 2009	LFPI, rats, intraventricular infusion of bFGF.	Increased proliferation in the DG and SVZ and improved cognitive recovery
	Sun et al., 2010	LFPI, rats, intraventricular infusion of EGF.	Increased proliferation in the DG and SVZ and improved cognitive recovery
	Carlson et al., 2014	CCI, IGF-1 over expression mice.	Increased survival of newly generated neurons in the DG without affecting cell proliferation
	Gao and Chen, 2009 & Gao et al., 2009	CCI, BDNF conditional knockout mice.	Deficits in survival and maturation of newly generated neurons without affecting cell proliferation in the DG
	Thau-Zuchman et al., 2010	Closed head injury, mice, intraventricular infusion of VEGF.	Increased cell proliferation in SVZ, corpous callosum, and perilesion cortex, reduced lesion size, and improved cognitive recovery
	Lee and Agoston, 2010	LFPI, rats, intraventricular infusion of VEGF.	Increased survival of newly generated neurons in the DG
	Kleindienst et al., 2005	LFPI, rats, intraventricular infusion of S100β.	Enhanced cell proliferation and generation of new neurons in the DG and SVZ and improved cognitive recovery.
Small Molecules Imitating Growth/ Neuro trophic Factors	Zhang et al., 2015	Impact acceleration injury, rats, cerebrolysin i.p.	Increased generation of new neurons and improved cognitive functional recovery.
	Chen et al., 2015 and Zhao et al., 2016	CCI, mice, i.p. administration of 7,8-dihydroxyflavone.	Increased survival of newly generated neurons and dendritic development in the DG
	Shi et al., 2013	CCI, rats, intranasal administration of LM11A-31.	Enhanced proliferation and survival of NPC in DG and improved cognitive recovery.
	Chohan et al., 2014	CCI, mice, a small molecule peptide 6, i.p.	Increases the number of neurons in the DG and improves memory function
Other Peptides or Pharmacologic al Agents	Xiong et al., 2010	CCI, rats, carbamylated EPO i.p.	Increased proliferation and generation of new neurons in DG and improved cognitive recovery
	Xiong et al., 2012	CCI, rats, Tβ4 i.p.	Increased proliferation and generation of new neurons in DG and improved cognitive recovery
	Blaya et al., 2014	LFPI, rats, P7C3-A20, i.p.	Increased proliferation and survival of newly generated neurons in DG and improved cognitive recovery
Physical/Electrical Stimulations	Gaulke et al., 2005	LFPI, rats, EE housing	Increased survival of endogenous NSC
	Griesbach et al., 2009	LFPI, rats, running wheel exercise.	Improved cognitive functional recovery
	Piao et al., 2013	CCI, mice, delayed running wheel exercise.	Increased generation of new neurons, reduced lesion volume and inflammation with reduced cognitive deficits
	Xuan et al., 2013, 2014	CCI, mice, LLLT.	1 or 3 treatments increased cell proliferation, reduced lesion size, and improved neurobehavioral function

Category	Authors	Study design	Findings
	Xuan et al., 2015	CCI, mice, LLLT.	Stimulates synaptic plasticity in the SVZ, up-regulates BDNF in the DG and SVZ, and improves cognitive function
Existing FDA Approved Drugs	Xie et al., 2014	CCI, rats, simvastatin or atorvastatin, oral.	Increased proliferation and generation of new neurons in DG and improved cognitive recovery
	Meng et al., 2014	CCI, rats, tPA intranasal administration.	Increased number of new neurons in the DG and improved motor function and cognitive performance
	Han et al., 2011	CCI, mice, imipramine i.p.	Increased proliferation and generation of new neurons in DG and improved cognitive performance
	Wang et al., 2011	CCI, mice, fluoxetine i.p.	Increased generation of new neurons in DG with no observed functional improvements
	Quintard et al., 2014	LFPI, rats, NeuroAid i.p.	Increased proliferation and generation of new neurons in DG and improved cognitive performance
	Umschweif et al., 2014a & 2014b	Closed head injury, mice, AT2 agonist intraventricular infusion.	Increased proliferation and generation of new neurons in DG and improved functional recovery
Modulating Signaling Pathways	Zhang Z et al, 2014	FPI, mice, intracerebral injection of Notch effector genes.	Affecting cell proliferation, neuronal differentiation and cognitive function

Recent studies have shown evidence that mature brains harbors multipotent neural stem cells capable of becoming mature neurons in the neurogenic regions. Following brain insults including TBI, the injured brain has increased levels of neurogenic response in the subventricular zone and dentate gyrus of the hippocampus and this endogenous response is associated with cognitive function following injury. In this review, we highlight recent development and strategies aimed at targeting this endogenous cell response to enhance post-TBI functional recovery.