Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Review

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

*Kaushal Patel, Dong Sun**

Department of Neurosurgery, School of Medicine, Virginia Commonwealth University, Richmond, VA, United States

ARTICLE INFO

Article history:
Accepted 29 January 2016
Available online 8 February 2016

Keywords:
Traumatic brain injury
Endogenous neurogenesis
Subventricular zone
Hippocampus
Cognitive function

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.

This article is part of a Special Issue entitled SI:Brain injury and recovery.

Contents

*Correspondence to: Department of Neurosurgery, Medical College of Virginia Campus, Virginia Commonwealth University, P.O.Box 980631, Richmond, VA 23298-0631, United States. Fax: +1 804 8283276
E-mail address: dsun@vcu.edu (D. Sun).

http://dx.doi.org/10.1016/j.brainres.2016.01.055
0006-8993/

1. 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, 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; 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; 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; Blaiss et al., 2011). 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.

2. 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 (Raballo et al., 2000; 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