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EDITORIAL

Current advances in neurotrauma research: diagnosis, neuroprotection, and neurorepair

Traumatic brain injury (TBI) and spinal cord injury (SCI) causes significant cell death (Raghupathi et al., 1995; DeKosky et al., 1998; Hall et al., 2005; Farkas and Povlishock, 2007) and tissue lesion in the neocortex (Lighthall et al., 1989; Lyeth et al., 1990), leaving many patients with substantial motor disability and cognitive impairment (Hamm et al., 1992; Scheff et al., 1997). Unfortunately, at present, there are no clinically demonstrated FDA approved drug therapies for treatment of TBI and SCI patients that reduce the neurological injuries. Thus, TBI and SCI are serious health problems. The development of therapeutic approaches to prevent neuronal death and enhance neuroregeneration for promoting post-traumatic functional recovery would be of enormous clinical, social, and economic benefits. The reviews in this specific issue focus largely on the current progress on diagnosis, neuroprotection, and potential neurorepair with stem cells.

Introduction

TBI, a form of acquired brain injury, occurs when a sudden trauma causes damage to the brain. TBI can result when the head suddenly and violently hits an object, or when an object pierces the skull and enters brain tissue. It is estimated that approximately 2.4 million patients were hospitalized with TBI in the United states alone in 2009 (Coronado et al., 2012). TBI is a major cause of death and disability in the United States, contributing to about 30% of all injury deaths and the growing 1.8% of the population that live with long-term physical disabilities (Zaloshnja et al., 2008). Effects of TBI can also lead to cognitive impairment, including memory problems and decreased concentration skills, and psychological symptoms, including irritability, depression, and anxiety. SCI is also one of the major causes of irreversible nerve injury, resulting in both motor and sensory dysfunctions. An estimated 12,000 new cases of spinal cord injury occur every year in the United States.

Over the past 15–20 years, we have gained a great deal of knowledge about the healthy brain and its response to trauma (Buki and Povlishock, 2006; Hall et al., 2008; Greer et al., 2013; Johnson et al., 2013). Based on the results from animal models, controlling brain swelling and intracranial pressure (ICP) have been widely used and have significantly reduced death following TBI (Lundberg et al., 1965). Although during 2001–2010 rates of TBI-related emergency department (ED) visits increased by 70%, death rates decreased by 7% (Coronado et al., 2012).

However, there are still so many questions unanswered, and still so many challenges to diagnose, treat, and repair the damaged brain. To address these challenges, it is very important to advance the knowledge on mechanisms of injury and recovery, and to develop better diagnostic tools and more effective treatments. Thus in this special issue, four laboratories come together to summarize the current progress on neuroimaging, neuroprotection, and potential neurorepair with stem cells following TBI.

Neuroimaging

Different imaging strategies are widely used in the clinic to assess TBI (McAllister et al., 2001; Belanger et al., 2007; Le and Gean, 2009; Kirov et al., 2013). In general, the structural imaging techniques play a role in acute diagnosis and management, while the functional imaging techniques show promise for clarification of pathophysiology, symptom genesis, and mechanisms of recovery (McAllister et al., 2001). Dr. Kuo and Dr. Iraji summarize the most recent evidence of brain plasticity after TBI in human patients from the perspective of advanced magnetic resonance imaging.

Evidence also demonstrates that, even if patients have damaged certain functional structures or networks, *e.g.*, motor control and somatosensory networks, many of them still could pick up these functionalities during their recovery, indicating the existence of an internal neuroplasticity. Dr. Kuo and his colleagues review the most recent imaging evidence of brain plasticity in TBI patients, from synaptic, microstructural levels, to functional network levels of the brain, particularly focusing on advanced MRI.

Neuroprotection

TBI not only results in immediate brain tissue disruption (primary injury), but also causes secondary damage among the surviving cells *via* complex mechanisms triggered by the primary event occurring in the hours, days, and weeks after initial physical impact. Secondary injury includes ischemia/reperfusion injury, inflammation, oxidative stress, and glutamate excitotoxicity, all of which contribute to the eventual tissue degeneration and functional loss.

A prevalent hypothesis is that TBI increases extracellular levels of the excitatory neurotransmitters such as glutamate (Choi, 1985, 1987, 1988; Braughler and Hall, 1989; Miller et al., 1990; Choi, 1992; Juurlink and Paterson, 1998; Hall and Springer, 2004; Yi and Hazell, 2006). Glutamate, in turn, causes excessive stimulation of N-methyl-D-aspartic acid receptors (NMDA), thus mediating calcium over influx and triggering rapid excitotoxic necrosis that results in traumatic damage to the central nervous system (CNS). For patients who have experienced TBI, no specific pharmacological therapy is available that would improve their outcomes. Therefore, recent research on TBI has been focused on developing a therapeutic approach to inhibit glutamate-mediated excitotoxicity with pharmacological glutamate antagonists or calcium blocking agents. However, glutamate is the major excitatory transmitter in the mammalian CNS. Its stimulation of NMDA receptors plays an essential role in excitatory synaptic transmission. Completely blocking NMDA receptors will cause significant side effects. For this reason, clinical trials have had limited success.

Another hallmark of secondary injury is oxidative stress (Hall et al., 1999; Bains and Hall, 2012), which plays an important role in mediating functional loss after both TBI and SCI. Although there is strong evidence that oxidative stress plays a critical role in the pathogenesis after SCI, clinical trials of free radical scavenging have not produced any effective treatments to promote functional recovery after traumatic SCI. Dr. Shi and his colleagues found that Acrolein is the most reactive electrophile produced by lipid peroxidation, suggesting that Acrolein is a novel therapeutic target to reduce oxidative stress (Shi et al., 2011a, 2011b; Park et al., 2014). Dr Shi and his colleagues summarize the recent devel-

opments in the understanding of the mechanisms of Acrolein in motor and sensory dysfunction in animal models of SCI.

Neurorepair

Recent research has identified neural stem/progenitor cells (NSCs) in the adult mammalian hippocampus that can support neurogenesis throughout life, as demonstrated in rodents and primates, including humans (Kuhn et al., 1996; Eriksson et al., 1998b; Eriksson et al., 1998a; Kornack and Rakic, 1999; Cameron and McKay, 2001; Leuner et al., 2007). Currently the consensus among researchers in the field is that throughout adulthood, NSCs in the subgranular zone (SGZ) of the hippocampal dentate gyrus (HDG) continuously generate new neurons (Kempermann and Gage, 2000; Ming and Song, 2005) and develop into mature granular neurons (Ming and Song, 2005; Shapiro and Ribak, 2005; Zhao et al., 2006). The pool of NSCs is a potential resource for repairing the damaged hippocampus following TBI.

Current studies further show that TBI promotes NSC proliferation in the adult hippocampus (Dash et al., 2001; Kernie et al., 2001; Braun et al., 2002; Chirumamilla et al., 2002; Rice et al., 2003; Yoshimura et al., 2003; Ramaswamy et al., 2005; Sun et al., 2005; Rola et al., 2006; Sun et al., 2007). This finding suggests that innate repair and/or plasticity mechanisms exist in the adult brain. There are distinct classes of NSCs in the adult HDG, including quiescent neural progenitors (QNPs), which carry stem cell properties, and their progeny, amplifying neural progenitors (ANPs) (Seri and Garcia-Verdugo, 2001; Seaberg and van der Kooy, 2002; Filippov et al., 2003; Mignone et al., 2004; Bull and Bartlett, 2005; Encinas et al., 2006; Encinas and Enikolopov, 2008; Encinas et al., 2008). Dr. Chen and his colleagues found that moderate TBI promotes proliferation of QNPs in the adult hippocampus (Gao et al., 2009).

Although TBI promotes NSC proliferation, the effect of TBI on neurogenesis is still controversial. There are conflicting reports about neurogenesis in the HDG. According to some studies neurogenesis decreases after TBI (Braun et al., 2002; Rola et al., 2006), whereas others have reported that it remains unchanged (Chirumamilla et al., 2002; Rice et al., 2003), or that it increases (Sun et al., 2005; Sun et al., 2007). Here, Dr. Sun summarizes the potential of endogenous neurogenesis for brain repair and regeneration in the hippocampus following traumatic brain injury.

TBI causes significant cell death (Raghupathi et al., 1995; DeKosky et al., 1998; Hall et al., 2005; Farkas and Povlishock, 2007) and tissue lesion in the neocortex (Lighthall et al., 1989; Lyeth et al., 1990). However, it is generally agreed that no endogenous NSCs exist or neurogenesis proceeds in the adult neocortex of the mammalian brain, *i.e.,* the neocortex is a non-neurogenic region (Rakic, 2006). Thus, Dr. Chen and his colleagues briefly review the current progress of stem cells, which may potentially be used to generate new neurons in the cortex for brain repair following TBI.

Summary and future research

Little can be done to reverse the initial brain damage and spinal cord injury caused by trauma. Thus, it is important to study the pathological basis of neurological disorders, understand neurodegeneration and plasticity of the CNS, and develop novel neuroprotection and repair strategies to improve anatomical reorganization and functional recovery following TBI and SCI.

Jinhui Chen[1], Riyi Shi[2, 3]

1 Department of Neurological Surgery, Stark Neuroscience Research Institute, Department of Anatomy, Indiana University School of Medicine, Indianapolis, IN, USA

2 Department of Basic Medical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN, USA

3 Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN, USA

Corresponding author: *Jinhui Chen, M.D., Ph.D., Department of Neurological Surgery, Stark Neuroscience Research Institute, Department of Anatomy, Indiana University School of Medicine, Indianapolis, IN 46202, USA, chen204@iupui.edu. Riyi Shi, M.D., Ph.D., Department of Basic Medical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN 47907, USA, riyi@purdue.edu.*

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