



Editorial

Multi-disciplinary perspectives on pediatric traumatic brain injuries: Where we currently stand and future directions



1. Introduction

This special issue, entitled, “Defining the terrains that support recovery after traumatic injury to the developing brain” represents the culmination of research that spans almost a decade. This is the first comprehensive, state-of-the art assessment of the field since the 2010 special issue, “Pediatric traumatic brain injury: From Basic Research to Clinical Practice”, that was published in *Developmental Neuroscience* and edited by M.C. McKenna, L.J. Noble-Haesslein, and C.L. Robertson. We thank all of the contributors to this issue who have devoted their time and energy to produce a thoughtful and thorough review. This issue examines the basic biology of injury and reparative processes in the unique environment of the developing brain, offers insights into mechanisms underlying extent of recovery, and serves as foundation for developing therapeutics that are specifically tailored to the brain-injured child.

2. Metabolic dysregulation

The brain is a metabolically “expensive organ” that is dependent upon continuous supply of oxygen and glucose, both of which can be compromised after a traumatic brain injury. While dysregulated oxidative glucose metabolism after injury has been an area of interest, Scafidi et al. emphasize the ability of the injured immature brain to use alternative substrates, including lipids, ketone bodies and amino acids. However, a key challenge is that metabolic demands change during maturation. Thus, there is a need to better understand these temporal changes in order to develop therapeutics that are appropriately matched to age-specific metabolic demands.

Greco et al. have tackled mild traumatic brain injuries, including concussions, where there is greater risk of a subsequent injury. Concussions are associated with metabolic vulnerability in the injured adult brain. Current evidence reinforces the view that the magnitude of neurological deficits is dependent upon at least several major factors; namely, the number of repeat injuries and the interval between these injuries with proximal injuries producing more pronounced deficits than those with greater temporal distance. From a mechanistic standpoint, vulnerability may be moderated by adverse metabolic events which may vary according to sex.

3. Inflammation: context- and cell dependent impact on the injured brain

There is a strong interest in inflammation in this special issue, a direction which is well founded given clinical findings linking

inflammatory cytokines in the CSF with poor prognosis in brain-injured children. Microglia are largely responsible for perpetuating an injury-induced inflammatory response. Using a strategy to deplete microglia, Hanlon et al. report new findings that speak to the beneficial role of activated microglia in the removal of dying neurons after a closed head injury to the neonatal brain.

Von Leden et al. consider the understudied role of neutrophils in the injured brain, where these leukocytes may not only be initiators of early tissue damage but may be determinants of recovery. This position is based upon their potential for phenotypic diversity, which may be modified in accordance with the local environment. While they are perhaps best known for their ability to generate oxidative stress, neutrophils also release proteases that are capable of degrading the extracellular matrix, releasing angiogenic factors that may facilitate wound healing.

Nassr et al. review the innate and adaptive immune responses, beginning with non-specific danger signals that are released from damaged cells and have broad impact on neutrophil recruitment and early glial activation. These authors highlight understudied areas including the role of the immune system in normal brain development, how immune function changes with age and injury induced, and age-dependent immune dysregulation that may impact plasticity and reparative processes.

4. Behavioral consequences of early age TBI

Sta Maria et al. provide an overview of the developing brain, including developmental processes that confer vulnerability as well as adaptability. Building upon the observation that brain injuries in children pose a high risk of developing impairments in social behaviors, Zamani et al. outline the challenges of defining the underlying biological substrates which define risk versus resilience. These include the dynamic interactions between variables that are unique to the individual child such as age at time of injury, genetics and severity of the injury, and environmental factors associated with the family environment and parental health, and socioeconomic status.

There is a growing body of literature that supports an increased risk of substance abuse disorders in those who have experienced early-life traumatic brain injuries. Cannella et al. address age-dependent vulnerability within regions of the brain associated with the perception of reward. An early age brain injury may disrupt ongoing maturation and result in aberrant development of the reward pathways. The authors present compelling evidence based upon models of early-life traumatic brain injuries that are associated with neuroinflammation in the reward pathways and addiction at adulthood.

<https://doi.org/10.1016/j.expneurol.2019.113002>

Alcohol use disorders have been studied in the context of intoxication at the time of injury. Weil et al. consider an alternative perspective that links early age traumatic brain injuries with increased incidence of alcohol use disorders later in life. These authors approach this viewpoint by evaluating both existing clinical literature and biological plausibility, using preclinical models of drinking behavior. The authors present findings in support of biological plausibility between TBI and alcohol use disorders and consider several putative mechanisms that may be involved in the development of these disorders.

5. From membrane transporters to targeted therapeutics

Hagos et al. review the roles of membrane transporters, which are essential for movement of therapeutic drugs as well as mediators of injury between various cells types. In the context of traumatic brain injuries, these transporters are likely integral to clearance of mediators of injury and the transition of an acutely injured brain to the chronic neurodegenerative state. Transporters control movement into the brain and efflux of many drugs, and as such may confer pharmacoresistance and/or pharmacosensitivity.

Several of the reviews address therapeutics for the injured developing brain. There are currently no treatments in the clinical arena to restore function after a pediatric traumatic brain injury. Jantzie et al. examine erythropoietin (EPO), an endogenous pluripotent cytokine that is important in brain development, as a candidate therapeutic for the injured developing brain. These authors address pathophysiologic mechanisms that are unique to the very young developing brain and the cognitive benefits of extended high dose EPO when given after traumatic brain injury at early stages of postnatal brain development.

Schober et al. report new findings regarding docosahexaenoic acid (DHA), which has been shown to function as an immunomodulator in peripheral (nonCNS) organs. Rats, subjected to a brain injury at a very young age and treated thereafter with DHA, showed reductions in oxidative stress and inflammation as well as improvements in memory.

This collective effort argues for the need of developing therapeutics that are uniquely tailored to the brain-injured infant/child, the biological challenges that must be overcome in order to deliver therapeutics, and early promising findings in support of anti-inflammatory interventions.

6. Bridging the gap

Despite the growth in the field of pediatric traumatic brain injury, there remains a sizable gap between preclinical studies and clinical findings. Hajiaghamemar et al. review potential tools, including biomarkers that could serve to bridge this gap and that would have the capabilities of capturing the heterogeneity of clinical traumatic brain injuries and variables including age-dependency and species-specific temporal profiles of biomarkers. These authors argue for large-scale

research and data sharing across multiple centers to achieve these objectives.

While preclinical rodent models of traumatic brain injuries are the most common, it is important to acknowledge the value of larger (porcine) models where there has been opportunity to study parameters, including anatomy, physiology and biomechanics in a gyrencephalic brain that more closely approximates the human brain. Armstrong et al. address impaired cerebral autoregulation in a piglet model, and how age at time of injury and sex are determinants of autoregulation and responsiveness to vasoactive agents.

Sex as a biological variable has been underrepresented in studies of the injured brain and there is a growing responsiveness to address this issue. Arambula et al. build upon preclinical and clinical evidence of sex differences at all ages of brain development, spanning neonates to adolescents. These differences include how the brain responds to injury, extent of recovery, and responsiveness to therapeutics. The challenge now will be to understand the biologic origins of these differences and how they may manifest during different stages of development.

Preclinical studies have traditionally served as the jumping-off point for subsequent clinical studies. Anthonymuthu et al. offer a reverse approach in studies of cardiolipin, a phospholipid that is specific to mitochondria and plays key roles in bioenergetic and metabolism. These investigators found unique brain-type cardiolipins in plasma of patients after cardiac arrest. They now report new findings in a rodent model of traumatic brain injury; there is a time-dependent increase in plasma brain-type cardiolipin species with lower levels in the injured brain. Such findings build upon the hypothesis that these cardiolipins are released into circulation after brain injury and, as such, may serve as pharmacodynamic response biomarkers that can be used in developing therapeutics.

7. Concluding remarks

This special issue highlights both the accomplishments and challenges in understanding the fragility and resilience of the young brain after a traumatic injury. While we celebrate the discoveries, we are also cognizant that the pathway to long-term recovery is predicated on pursuit of yet unanswered questions, cross-disciplinary collaborations that blur the lines between benchtop and clinical research, and an open exchange of ideas. This special issue reflects these attributes and sets a high standard for others to follow.

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