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Therapeutic strategies to target acute and long-term sequelae of pediatric traumatic brain injury

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Abstract

Pediatric traumatic brain injury (TBI) remains one of the leading causes of morbidity and mortality in children. Experimental and clinical studies demonstrate that the developmental age, the type of injury (diffuse vs. focal) and sex may play important roles in the response of the developing brain to a traumatic injury. Advancements in acute neurosurgical interventions and neurocritical care have improved and led to a decrease in mortality rates over the past decades. However, survivors are left with life-long behavioral deficits underscoring the need to better define the cellular mechanisms underlying these functional changes. A better understanding of these mechanisms some of which begin in the acute post-traumatic period may likely lead to targeted treatment strategies. Key considerations in designing pre-clinical experiments to test therapeutic strategies in pediatric TBI include the use of age-appropriate and pathologically-relevant models, functional outcomes that are tested as animals age into adolescence and beyond, sex as a biological variable and the recognition that doses and dosing strategies that have been demonstrated to be effective in animal models of adult TBI may not be effective in the developing brain.

Introduction

Traumatic brain injury (TBI) in infants and children remains one of the leading causes of long-term disability and mortality worldwide[1–7] and occurs as a result of either accidental or inflicted causes (abusive head trauma)[8,9]. Advancements in pediatric neurosurgical interventions and neurocritical care has reduced mortality in cases of severe pediatric TBI[10]. However, survivors face life-long behavioral problems exacerbated by the paucity of pharmacological interventions that are aimed at reversing or attenuating specific cellular mechanisms in order to limit these behavioral pathologies. Pediatric TBI is a "chronic" disease, as long-term intellectual and psychosocial deficits are observed in adult survivors

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following childhood injury[11,12]. A number of age-appropriate animal models have been developed over the past 2 decades which have validated some of the acute and chronic behavioral deficits and the structural and cellular alterations typically observed in patients[13]. These animal models are important for testing hypotheses for the underlying cellular mechanisms, cellular alterations and behavioral deficits. In this review, we will briefly describe human pathologies and their validation in animal models of pediatric TBI and describes some of the attempts to attenuate these pathologies using standard pharmacological approaches.

Functional deficits following pediatric TBI

The negative consequences of TBI early in life manifests during childhood and extends throughout their life as these individuals have difficulty in developing new cognitive or social skills[14–16]. Age-appropriate behavior and levels of arousal and responsiveness were significantly decreased in infants and young children that sustained moderate to severe TBI[17]. Intelligent quotient measures did not improve between 6 months and 24 months post-injury indicating a lack of improvement and developmental arrest[18]. Children with brain trauma also exhibit deficits in verbal working memory, visuo-spatial memory, and attention that may contribute to difficulties in a school setting[19–21]. Psychosocial problems such as depression, anxiety, and sleep disturbances become more apparent as these children become older[15,16]. Brain injury sustained in early childhood led to decreased social competencies, an increase in irritability and aggression associated with disinhibited verbalizations, and the development of novel depressive and anxiety disorders[22–24]. Children with severe brain injuries had significantly decreased motor scores at the initial testing time which only improved in the first 6 months[25]. Children that sustain severe injuries demonstrate an increased incidence of seizures in the early stages following injury which are typically observed in those under the age of 1 and/or following abusive head trauma[26,27].

Cognitive function in animal models of pediatric TBI have been restricted to simple cognitive tasks such as spatial navigation learning and memory in the Morris water maze or visual recognition memory in the novel object recognition test, although these deficits were evident for weeks to months after the initial injury[28–35]. It is important that more complex cognitive function such as retrograde or anterograde spatial memory, episodic memory and working memory be evaluated as neonate animals age into adolescence and adulthood[36]. Contusive brain trauma in the neonate mouse resulted in prolonged hyperactivity, a decrease in general anxiety-like behavior, and deficits in social behavior weeks to months after the injury[30–37]. Motor function deficits in animal models of pediatric TBI are typically observed in only the first few weeks after injury[34]. Video-electroencephalograph recordings and susceptibility to seizure-inducing agents have been utilized in animal models to demonstrate the incidence of seizure activity in the acute and chronic post-traumatic periods following pediatric TBI[38–40].

Cellular pathology following pediatric TBI

Macroscopic structural pathology following TBI include focal contusions which are related to impact forces or diffuse injury which may occur due to rotational forces[41]. The pliancy and relatively thinner skull of the infant results in a decreased ability to absorb energy during

the application of an external force leading to a greater deformations than the area of direct application and a more diffuse pattern of injury in the developing brain[42]. Skull fractures occur in both accidental and abusive head trauma, with subdural hematomas present more frequently in children who sustained abusive TBI and epidural hematomas much more likely in children with accidental TBI[43,44]. Evidence of brain atrophy and ex-vacuo ventriculomegaly (enlarged ventricular space) has been reported following accidental or abusive TBI[43,45,46]. Subarachnoid hemorrhage and subdural hematomas have been observed in animal models in which impact occurred on the skull surface either via a weight-drop method[47,48] or using the controlled cortical impact device[49,50], or as a result of non-impact, rotational-acceleration[51,52]; in some cases ex-vacuo ventriculomegaly was observed[49,50,53].

Microscopic alterations to the traumatically-injured pediatric brain include axonal injury, cell death, gliosis and inflammation. Damage to the white matter tracts resulting in traumatic axonal injury (TAI) has been identified as the predominant cellular pathology in cases of infant TBI. Magnetic resonance imaging has revealed evidence of shearing and impaired myelination in the corpus callosum which is associated with slower interhemispheric transfer times measured using event-related potentials and indicative of impaired function[20,54–57]. Diffuse tensor imaging has demonstrated reduced fractional anisotropy in the corpus callosum, internal capsule, and longitudinal fasciculus, which has been associated with cognitive and psychosocial deficits in patients who sustained a TBI in early childhood[20,54,55,58,59]. Post-mortem evaluation using silver staining or beta-amyloid precursor protein (β-APP) immunohistochemistry[60,61] has detected axonal injury in the corpus callosum, internal capsule, midbrain and brainstem[62–64]. These clinical observations have been validated in multiple animal models of impact and non-impact TBI using either imaging[65] or immunostaining for β-APP and/or neurofilament[35,49–52,66–68]. A decrease in axonal function in the white matter tracts (measured using compound action potential in ex vivo preparations) has also been documented[65,69], along with observations of atrophy in the white matter tracts over time associated with axonal degeneration[70,71]. Evidence of brain atrophy in head-injured children suggests that neuronal cell death may be a component of TBI pathology[45,72,73]. Direct indication of cell death in various pre-clinical pediatric TBI models has been facilitated via the use of markers specifically associated with necrosis, apoptosis, and excitotoxicity[48,49,74,75]. Associated with neuronal loss is evidence of glial reactivity. Severe TBI in children is associated with an increase in pro-and anti-inflammatory cytokines such as the interleukins −1β, −6, and −10[76,77], chemokines interleukin-8 and macrophage inflammatory protein-1α indicating migratory signaling to other immune cells[77], and significantly higher concentrations of quinolinic acid indicative of microglia/macrophage activation[78]. These are by no means an exhaustive list of cytokines and chemokines underscoring a need to extend these observations to other chemokines such as chemokine C-C motif ligand (CCL) and CXCL families that have demonstrated roles in mediating the cellular immune response. Recent evidence indicates that TBI in neonate and juvenile animals is associated with an increase in tissue and serum concentrations of various cytokines and chemokines such as tumor necrosis factor-α, IL-1β, IL-6, CXCL1, CCL5 and CCL3 to name a few[79–81]. Head trauma in the immature animal also resulted in microglial activation along with infiltration of peripheral immune cells in multiple brain regions such as

the cortex, thalamus, hippocampus and subcortical white matter tracts which demonstrate evidence of neurodegeneration and axonal injury[28,70,71,74,79,82].

Treatment strategies in pediatric TBI focused on specific cellular pathology

Axonal injury—Despite the identification of axonal injury as a predominant cellular pathology in pediatric TBI, surprisingly few studies have focused on attenuating axonal degeneration. Proposed secondary mechanisms underlying traumatic axonal injury include ionic dysregulation, impaired axonal transport, calpain-mediated proteolysis, calcineurin-mediated dephosphorylation, microtubule degradation, and neurofilament compaction[83–89]. Calpain activation has been documented within injured axons in the immature rat[75,90] although administration of calpain inhibitor III (MDL28,170) at doses of either 30mg/kg or 60mg/kg over the first 24 hours following TBI in the juvenile rat reduced calpain activation but not axonal function deficits (unpublished observations). Calcineurin-mediated neurofilament dephosphorylation and compaction has been reported following diffuse brain injury in the immature rat[67,69] although the calcineurin inhibitor tacrolimus (FK-506) did not improve axonal function despite reducing neurofilament dephosphorylation[69]. These observations underscore the possibility that mechanisms of TBI-induced axonal damage and degeneration may not occur via similar mechanisms in the immature and adult brains[89,91–93].

Cell death—High concentrations of glutamate have been reported in the cerebrospinal fluid of children that sustained a severe TBI[94], suggesting that excitotoxicity leading to either apoptotic or necrotic cell death may occur in the pediatric brain[95,96] and may be identified using activation of caspases and calpains, respectively[97]. Traumatic injury to the 9-day-old, 11-day-old or 17-day-old rat demonstrated activation of calpains and caspases in multiple brain regions[75,98,99]. Similarly, decreased expression of the anti-apoptotic protein Bcl-2 along with activation of the pro-apoptotic protease caspase-3 suggests that apoptotic cascades are activated following trauma to the developing brain and discovered that these apoptotic markers were most severe in the youngest animals[48]. As observed in models of adult TBI[100,101], glutamate receptor antagonists administered acutely following neonate TBI appears to provide neuroprotection[102]. However, this strategy must be considered with caution as NMDA receptor antagonists were observed to increase apoptosis in the developing brain following TBI[103]. Moreover, excitatory neurotransmission is critically important for proper development of the immature brain[104]; in this regard, the co-agonist of the N-methyl-D-aspartate receptor (NMDAR), D-cycloserine has been observed to limit post-traumatic decreases in NMDAR expression, novel object recognition deficits and improve the response of the brain to experience-dependent plasticity[105].

Inflammation—Targeting the activation of astrocytes, microglia and infiltrating leukocytes and monocytes for therapeutic purposes in models of pediatric TBI has only been a recent development[106,107], albeit with limited success. Decreasing the expression of the astrocytic protein aquaporin-4 via RNA silencing reduced edema and blood-brain barrier disruption in the acute post-traumatic period and spatial learning deficits in the months after injury but did increase microglial activation[107]. The protease elastase is released from activated neutrophils that enter the brain after trauma but inhibition of this protease in the acute post-traumatic

period only served to reduce cell death and had no effect on long-term behavioral outcomes[108]. Similarly, manipulation of infiltrating mast cells after trauma to the neonate mouse using a degranulation inhibitor or with genetic approaches had little to no effect on cell death, axonal injury or microglial activation[109]. Short-term minocycline administration in the first week following trauma to the neonate rodent reduced microglial proliferation and activation but was accompanied by increased neurodegeneration and no attenuation of spatial learning and memory deficits[70,71,79]. These observations are suggestive of a differential age-at-injury inflammatory response because similar strategies in the adult TBI models have demonstrated marked efficacy in increasing neuroprotection, reducing microglial activation and attenuating locomotor and spatial learning and memory deficits[110–116]. Because microglia in the developing brain are important for sculpting of neuronal circuits, synapse and axonal remodeling, and pruning of unwanted or excess cells and clearance of unwanted cellular debris[117–120], a better approach may be targeting the pro-inflammatory cytokines that may mediate secondary damage after trauma. In this regard, the interleukin-1 receptor antagonist (anakinra) has been reported to reduce post-traumatic seizure susceptibility in a mouse model of pediatric TBI[38].

Treatment strategies in pediatric TBI focused on multiple cellularpathologies

Pediatric TBI, as in the case of adult TBI, exhibits complex pathologic alterations indicative of multiple mechanisms[13]. Whereas strategies targeting a single mechanism may yet be viable, a second approach is using either a combination of pharmacologic agents, or a single pleiotropic agent/intervention that targets multiple mechanisms. The former strategy has had limited success in models of pediatric TBI and is reviewed by Margulies et al[121]. Here we describe a few examples of the latter approach based on their successes in models of adult TBI.

Progesterone—The steroid hormone progesterone (PROG) has multiple mechanisms of neuroprotection from reducing edema, inflammation, oxidative damage to apoptosis and excitotoxic cell death[122]. It has been extensively used in models of adult TBI but failed in phase III clinical trials in moderate-severe adult TBI[123–126]. Despite this setback, PROG has been tested in a few different models of pediatric TBI albeit with limited success. In male but not female immature rats, PROG reversed mitochondrial dysfunction and improved anti-oxidant reserves[127]. Similarly, PROG treatment following contusive trauma in 4-week old mice improved motor function in male mice while worsening performance in female mice and did not reduce neurodegeneration in either sex[128]. When 4-week-old male and female rats were subjected to bilateral frontal lobe contusive trauma, PROG attenuated spatial learning and locomotor deficits in both sexes, along with a reduction in lesion volume[129,130]. It must be noted that few, if any, of these studies have evaluated the mechanistic basis of the actions of PROG but do highlight the importance of the differential efficacy of interventions on the basis of sex.

Erythropoietin—The pleiotropic cytokine, erythropoietin (EPO) is currently in use as a neuroprotective agent in preterm infants at risk for central nervous system injury[131,132]. EPO, like PROG, has multiple mechanisms of action including limiting apoptosis and promoting neural tissue repair[133]. EPO, particularly at high doses administered over an

extended period of time after injury, has been effective in reducing post-traumatic pathology and behavioral deficits in multiple animal models of adult TBI[134]. In either 12- or 17-day-old rat pups, EPO was administered over the first week post-injury and was observed to reverse motor deficits, cortex and white matter damage, attenuate hippocampal apoptosis and improve recognition memory[80,135]. A recent study reported that the improvement in recognition memory was maintained into adulthood[136]. However, neither the specific mechanism of action of EPO in the injured neonate brain nor the dependence of efficacy on sex are currently known.

Future directions for treating pediatric TBI

The importance of evaluating multiple outcome measures (cognitive, motor, psychosocial) during the chronic phase of injury following a therapeutic intervention cannot be overstated, as most pediatric TBI patients survive but are left with profound morbidity in adulthood. Preclinical pediatric TBI studies have successfully modeled acute (days to weeks) cellular pathologies observed in the human condition and have associated these changes with simple behavioral tasks of learning and memory. The investigation of long-term (weeks to months) pathologic and functional outcomes and evaluation of psychosocial behaviors have only recently been implemented and need additional evaluation. Intervention strategies aimed at specific cellular pathologies such as axonal injury, cell death or inflammation that have worked in adult TBI models are not always effective in attenuating functional deficits in the immature animal and therefore must be carefully examined in future studies. These data underscore the need for further studies to have a much better understanding of age-dependent mechanistic responses to trauma. In addition, mechanisms of brain damage sustained after trauma at the different maturational stages in development (infant, toddler, adolescent) need to be evaluated with a view to developing age-specific treatment strategies. For example, the decrease in glucose utilization that occurs over time after pediatric TBI[137] allows ketone bodies to be administered as an alternative substrate although this approach was effective in reducing lesion size and behavioral deficits in a narrow range of ages (post-natal days 35–45)[138,139]. Future research aimed at attenuating deleterious processes using pharmacological means may also be augmented by using strategies to enhance reparative (plasticity) responses, not only during the acute post-traumatic period, but also at the subacute or chronic post-traumatic period. In this regard, environmental enrichment or transcranial magnetic stimulation offer promising leads to improve recovery of the immature brain from a traumatic injury[140,141]. It is becoming increasingly apparent that the gender affects outcome following pediatric TBI[142,143] and the efficacy of the intervention paradigm in the acute post-traumatic period to limit pathology in preclinical studies[127,128,144]. In addition to the preliminary studies with progesterone[127,128], vasopressor studies have demonstrated that phenylephrine (Phe) resulted in a greater reduction in metabolic crisis than with norepinephrine in female brain-injured piglets[145], whereas Phe exacerbated cerebrovascular dysregulation in male brain-injured piglets[144]. Further studies on the role of sex and gender at different stages of maturation and the role of circulating sex hormones especially during the adolescent stages of TBI may dictate effective therapeutic strategies. Finally, as the field continues to develop mechanism-specific pharmacologic strategies, care must be given to exploring the potential for age-dependent differences in pharmacodynamics

(target engagement) and pharmacokinetics (drug metabolism). Despite these challenges, it is encouraging to see the growth in preclinical pediatric TBI research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Pediatric TBI is a leading cause of morbidity in children below the age of 14.

As brain-injured children age into adulthood, they exhibit multiple cognitive and behavioral deficits.

The cellular pathology of brain injury in children includes axonal injury, neurodegeneration and inflammation.

Pleiotropic agents may be better suited to treat pediatric TBI.

Factors such as age, sex and pharmacokinetics need to be considered.

Long-term behavioral measures need to be incorporated into the study design.