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METABOLIC RESPONSE OF PEDIATRIC TRAUMATIC BRAIN INJURY

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Brain Development and Metabolism

Cerebral development includes a series of progressive and regressive programmed events that interact with environmental input to shape the structure and function of the brain. In addition to developmental milestones including neurogenesis, myelination and synaptogenesis, there are significant changes in brain metabolism. Between in utero and post-weanling stages of development, the brain shifts between different types of metabolic substrates to meet its energy needs.[1] The pre-weanling brain is well designed for ketone metabolism; there is a rapid elevation in blood ketone concentration, increased expression of the monocarboxylate transporter which transports ketones across the blood brain barrier and an increase in ketone metabolizing enzyme activities.[2,3] During the period of peak ketone metabolism (postnatal day 15–23 in rats), the immature brain's capacity to take up and process ketones is 6 times greater than in the adult brain.[4,5] These sharp changes in ketone metabolism are in contrast to the brain's gradual up-regulation towards glucose metabolism. Plasma concentrations of glucose reach peak levels by postnatal day 10 in the developing rat, which precedes the increases in blood brain barrier expression of glucose transporters and glycolytic enzyme activities. [2,3, 6, 7] Upon weaning, circulating concentrations of ketones drop rapidly followed by decreases in monocarboxylate transporters and ketone metabolizing enzyme activities, as the brain shifts towards glucose as its primary fuel source. Extensive evidence has now demonstrated that the post-weanling and adult brains are not static in their fuel source. It has been well documented that under conditions of energy stress such as starvation, hyperketonemia, hypoxia/ischemia, and diabetes, the brain can shift its metabolism to alternative substrates such as ketones. [4, 8, 9, 10, 11] Ketones remain the only *endogenously* circulating alternative substrate that is known to significantly support cerebral metabolism.[4,8,11] After weaning, both the young developing and adult brain retain the ability to revert back to utilizing ketones, but in an age dependent manner. Following energy challenges, the younger animal achieves ketosis faster with greater cerebral ketone uptake and metabolism. [4, 8, 12, 13, 14] Collectively, these studies show that the younger brain’s potential to revert to ketone metabolism is greater than adults and is a developmental characteristic that can be therapeutically utilized under states of energy challenge.

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Pathophysiology of Moderate and Severe Traumatic Brain Injury and Age

Neurochemical

Traumatic brain injury induces dynamic neurochemical and metabolic changes. Immediately upon impact, the neuronal ionic equilibrium is disrupted with a 4–6 fold increase in extracellular potassium concentrations within the first five minutes following adult rat fluid percussion injury.[15] Intravenous injections of isotope labeled ^{45} calcium at different times after fluid percussion injury showed calcium accumulation between 6 hours and 7 days after injury in adult rats.[16,17] The pattern of early calcium accumulation showed age differences with younger animals showing earlier normalization after injury, but 28 day old (analogous to an early adolescent age group) and adult rats showed subsequent subcortical secondary calcium accumulations associated with cell loss.[18] These acute ionic perturbations require energy for re-establishment of ionic equilibrium and have direct consequences on cerebral glucose metabolism.

Glucose Changes

Consequent to these immediate neurochemical disruptions, there is a rapid increase in cerebral glucose uptake that has been shown to last 30 minutes in adult fluid percussion injury[19] and has been observed within the first 8 days after human traumatic brain injury.[20] This initial transient increase in glucose uptake is followed by a prolonged period of decreased glucose metabolism in the brain as observed in both experimental and clinical head injury.[19,21–29] This metabolic depression has been established as a hallmark metabolic response after traumatic brain injury. While the magnitude and duration of this glucose metabolic depression increases with injury severity in experimental models [30,31,32], the decrease in overall cerebral glucose metabolic is not closely associated with level of consciousness in human head injuries.[28] However, in human traumatic brain injuries glucose metabolic rates specifically in the thalamus, brain stem and cerebellum do significantly correlate with level of consciousness as measured by the Glasgow Coma Scale. [33]

Changes in cerebral metabolic rate of glucose after brain injury have been shown to be age-dependent. Experimental models of traumatic brain injury have shown that the *duration* of glucose metabolic depression increases with age. Glucose metabolic depression lasted 3 days in 17 day old rats given a moderate fluid percussion injury[34] compared to 10 days in similarly injured adult rats. In this diffuse injury model, adult-like patterns in cerebral metabolic rates of glucose depression are achieved in the adolescent rat. [35] In the controlled cortical impact injury model, which delivers a more focal injury pattern, adolescent rats demonstrate recovery of metabolic rates of subcortical structures within 3 days, compared to 7 days in postnatal day 90 (adult) rats, and recovery of cortical metabolic rates by day 7 in both age groups.[32] In general, the younger animals appear to show faster recovery of glucose metabolic depression. Regardless of the age, the prolonged glucose metabolic depression reflects a period of time during which glucose uptake and metabolic processing in the brain is compromised. While two clinical studies have examined glucose uptake after traumatic brain injury in children [36,37] both examined only delayed changes between 18–643 days post injury. Acute age-dependent differences in glucose metabolism have not yet been studied in humans.

The post-injury period of glucose metabolic depression is accompanied by adenosine triphosphate decreases[38], increased flux of glucose through the pentose phosphate pathway [39], free radical production[40], activation of poly adenosine diphosphate ribose polymerase via DNA damage [41,42] and inhibition of glyceraldehyde dehydrogenase (a key glycolytic enzyme) via depletion of the cytosolic nicotinamide adenine dinucleotide pool. Under these post-brain injury conditions of impaired glycolytic metabolism, glucose becomes a less favorable *energy* substrate.

Concussions and Repeat Traumatic Brain Injury in the Pediatric Brain

The growing national attention on concussions in sports and the military has increased the development of experimental models of concussion and repeat concussions. However while the total number of models has increased, the number of studies specifically addressing pediatric concussions remains sparse. The few mild and repeat traumatic brain injury models have shown that subtle cellular behavioral deficits and metabolic changes can be detected in the younger animal in the absence of gross pathology

Cellular Pathology & Behavioral Deficits

Huh and colleagues[43] used a modified controlled cortical impact device to deliver injuries to a postnatal day 11 rat within a stereotaxic frame. A single impact, 2 impacts or 3 impacts (5 minute intervals) were delivered in these studies, with histology conducted between 1–7 days and cognitive testing using the Morris water maze performed at 14 days post injury. While a single injury did not result in gross damage at 7 days, multiple (two or three) impacts caused ventricular enlargement, white matter atrophy, cortical reactive astrocytosis and axonal swellings that increased with repeated injuries. Morris water maze results showed no latency differences between the sham group and any of the injury groups. Thus, although rats receiving repeat concussions did not demonstrate any behavioral or cognitive deficits, increasing number of concussions was associated with the accumulation of significant structural cerebral pathology. Of note, the controlled cortical impact model delivers a force directly to the surface of the cortex through a craniotomy, and therefore the histologic changes demonstrated in this study may overestimate the damage which occurs in the clinical setting, where most concussions are not necessarily associated with a displaced skull fracture. Prins and colleagues[44] utilized the controlled cortical injury device on the closed head of the adolescent rat to better mimic common pathophysiological processes described after concussions, including transient memory impairment, white matter and axonal dysfunction in the absence of overt cell death. Adolescent (35-day old) rats that were given either a sham injury, a single injury, or two injuries 24 hours apart showed increasing β-amyloid precursor protein and glial fibrillary acidic protein immunohistochemical labeling with increasing number of injuries. β-amyloid precursor protein and glial fibrillary acidic protein were seen in the ipsilateral white matter and grey/white matter junction, respectively, in single and repeat traumatic brain injury groups. Glial fibrillary acidic protein was increased bilaterally in adolescent animals receiving repeat traumatic brain injury. Animals received cognitive/memory testing in the form of the novel object recognition task, 24 hours after the last injury. All groups were able to recognize the novel object when the interval between familiar objects and novel object was 1 hour. Increasing the interval to 24 hours

made the task more difficult and resulted in both single and repeat traumatic brain injury groups showing significant impairments that recovered by day 3 in the single injury group and day 5 in the repeat traumatic brain injury group.[44] In addition to these rodent models of developmental concussions and repeat concussions, Raghupathi and Marguilies[45] used a novel rotational piglet injury model to address axonal injury and cognition after repetitive injury. Piglets (3–5 days old) were given either a single or 2 injuries (15 minute interval) and histological processing for axonal injury was conducted 6 hours post injury. While the density of the injured axons did not differ between single and double injured groups, the number of axonal swellings per axon did increase in the repeat traumatic brain injury brains.[46] In their second study, piglets were a given either a single injury, 2 injuries (24 hour interval) or 2 injuries (1 week interval). Animals that received 2 injuries with a 24 hour interval had a greater mortality rate and poorer cognitive composite score than other groups. Those with 2 injuries at the 1-week interval showed greater β-amyloid precursor protein staining, but no behavioral differences were observed the on open field testing, T-maze testing, or glass barrier task.[47] Collectively, experimental models have been able to mimic the acute memory deficits often clinically reported in the absence of gross pathology in both the adult and younger age groups. These studies also indicate cumulative damage with increasing number of concussions.

Cerebral Metabolic Changes

Examination of cerebral metabolic markers after single and repeat concussive injuries has provided some of the first evidence to support the concept of increased cerebral vulnerability following a concussion. The first to examine this idea of a temporal window of vulnerability was Vagnozzi et al., who varied the interval between mild traumatic brain injuries to examine the effects on mitochondrial function and oxidative injury in the adult rat brain.[48, 49] A second weight drop injury (450gram/1meter) was delivered 1, 2, 3, 4 or 5 days after the primary injury and mitochondrial function and oxidative injury were assessed. The injuries with the 3 day interval showed the greatest cumulative effects on adenosine triphosphate depletion, N-acetylaspartate decreases, and increases in both redox and oxidative damage. Another study examining the cognitive effects of multiple injuries (1, 7 or 30 days apart) in adult mice demonstrated that daily injuries produced the greatest impairments at 1 month that persisted to 1 year.[50] Mice that received 2 injuries at 30 day intervals showed no significant cognitive deficits. The cumulative effect of cognitive dysfunction when injuries occur at shorter intervals suggests the duration impact interval reflects duration of cerebral vulnerability. This concept of a window of vulnerability following concussion has also been clinically observed. Adult non-professional athletes that sustained a concussion showed an 18.5% decrease in N-acetylaspartate/Creatine ratios 3 days after injury that recovered by 30 days post injury.[51] Three patients resumed normal activities before full recovery and sustained a second concussion that resulted in prolonged N-acetylaspartate/Creatine alterations, delaying full recovery until 45 days post injury. Thus the recovery of metabolic alterations after concussions appears to denote the duration of adult cerebral vulnerability.

Previous observations regarding the changes in the cerebral metabolic rates of glucose after various injury types and severities within different age groups suggests that changes in

cerebral glucose metabolic rates should be present after concussive injuries as well. There is currently only one study that has examined the window of cerebral metabolic vulnerability after concussive injuries in the younger brain. Utilizing the previously mentioned adolescent closed-head model of concussion/repeat concussion, the effect of injury interval was examined after single and multiple injuries. Postnatal day 35 rats showed significant decreases in brain glucose uptake at 24 hours after a single concussion that recovered in most structures within 3 days. The duration of the glucose metabolic depression increased in both magnitude and duration if a second concussive injury was delivered within the first 24 hours, when the brain was still recovering from the primary injury. This cumulative effect was not observed if the second injury was delivered after the primary injury recovered (5 day interval).[52] These results support the idea of a window of vulnerability following a concussive injury in the adolescent brain and suggest that post-injury metabolic disruptions can be potentially used as a biomarker of concussion. Given that the duration of metabolic depression varies with age, [19, 34,35] it is likely that the metabolic window of vulnerability will also vary with cerebral maturation, further emphasizing the need for age-specific metabolic research.

The duration that the brain remains vulnerable to subsequent injury is the time that athletes should remain "out of play." While there are currently, numerous "return to play" guidelines for professional and pediatric sports activities, there are no biological markers that define this window of vulnerability. Establishing a biological marker would allow physicians to assess the recovery of a concussion independent of the patient's self-reporting. Understanding the cerebral metabolic responses to traumatic brain injuries has not only provided potential biomarkers for concussion diagnosis and management, but brings to attention to the potential utility of alternative cerebral metabolic substrates.

Pituitary Damage and Growth

Traumatic brain injury-induced pituitary damage has been described in both adult and pediatric patients. The pituitary gland is particularly vulnerable to injury because it is suspended by the infundibular stalk and located within a rigid bony depression. Hypopituitarism has been described in 16–61 percent of children following traumatic brain injury, however the long-term consequences of traumatic brain injury-induced hypopituitarism in children have not been studied in either the clinical or research setting.[53] The first research study to address the issue of repeat concussions on pituitary function in the adolescent brain was recently published documenting evidence of concussive pituitary injury, decreases in body weight, body length, pituitary weight and decreases in both circulating growth hormones and insulin-like growth hormone.[54] This data demonstrates early and sustained hormonal changes after repeat concussions during a time of critical hormone-dependent maturation. More research in this area is needed to address the multitude of consequences that hypopituitarism can influence, including: cerebral glucose metabolism, brain/body growth, reproductive/sexual maturation, cognitive, and behavioral maturation.

Metabolic Interventions

In light of the impairment of cerebral glucose metabolism following traumatic brain injury, manipulation of nutritional support represents a logical avenue for neuroprotective intervention. Nutrition is already of particular interest in the acute clinical setting because post-injury hyperglycemia has been associated with poorer global outcome.[55–57] Although fasting would simultaneously prevent hyperglycemia and promote the use of alternative metabolic substrates to glucose, these aims must be balanced with the body's increased energy needs to ensure proper repair in the aftermath of injury. Prolonged fasting of adult patients who have sustained severe traumatic brain injury resulted in nitrogen losses equivalent to a 15% weight loss per week.[58] Thus, while animal models suggest that a short period of fasting may be beneficial following injury[59], the majority of clinical studies indicate that early nutritional support is associated with reduced mortality, better outcome, and reduced incidence of infectious complications.[60–63] Thus clinical practice guidelines for the treatment of adults with severe traumatic brain injury recommend full caloric feeds within 7 days of injury[58,64], though further studies are required in pediatric populations.

Given the post-injury impairment of cerebral glucose metabolism, the neuroprotective properties of several alternative metabolic substrates have been studied in animal models of traumatic brain injury. One potential strategy employs the ketogenic diet, a high fat, low carbohydrate diet which is already an established treatment for pediatric epilepsy.[65] While other monocarboxylates (lactate and pyruvate) have been shown to be metabolized in cell cultures and adult animal models, these fuels have not been addressed in the pediatric models. Ketone bodies such as beta-hydroxybutyrate and acetoacetate, produced as a result of fatty acid metabolism, are alternative substrates that can significantly contribute to brain energy metabolism.[4] Using a controlled cortical impact model, adolescent rats who were fed a ketogenic diet following traumatic brain injury demonstrated significantly reduced contusion volume and improved cognitive outcome on Morris water maze testing in comparison to those fed a standard diet.[66,67,68] Administration of a ketogenic diet to juvenile animals with traumatic brain injury has also been associated with higher cerebral adenosine triphosphate and N-acetylaspartate, and decreased cerebral edema, lactate and markers of apoptosis.[68,69] Direct intraperitoneal administration of beta-hydroxybutyrate alleviated the injury-induced decrease in adenosine triphosphate levels typically seen in ipsilateral cortex.[70] However, the ketogenic diet may not be a universally applicable solution due to age-dependent differences in ketone body transport. Monocarboxylate transporter 2, which enables ketone bodies to cross the blood-brain barrier, is much more readily up-regulated in adolescent animals than adult.[70,71] Correspondingly, unlike adolescent rats in whom ketogenic diet administration decreased the size of the cortical contusion roughly to half, adult rats who similarly received the ketogenic diet following severe traumatic brain injury did not demonstrate a reduction in contusion volume compared to those fed a standard diet.[32,66,]

Ketones aside, lipid supplementation specifically with omega-3 fatty acids has also demonstrated neuroprotective benefits. The most prominent omega-3 fatty acid in the mammalian brain is docosahexanoic acid, which due to its flexible structure contributes to the fluidity and function of neural and synaptic membranes.[73–76] Docosahexanoic acid and

eicosapentanoic acid have roles in pathways involved in neuronal differentiation, regulating gene expression, learning, memory, and neuronal plasticity.[77–81] Supplementation with omega-3 fatty acids normalized the levels of factors involved in synaptic transmission, plasticity and learning which are depleted by traumatic brain injury in animal models, and furthermore improved performance on functional measures of learning and cognition.[82,83]

Other substances related to ketogenic diet pathways have also been shown to benefit outcome following traumatic brain injury. Levo-carnitine is a necessary cofactor for the transport of long-chain fatty acids into the mitochondrial matrix and has demonstrated antioxidant properties in several ischemia-reperfusion models.[84–87] Intraperitoneal administration of acetyl-L-carnitine, which is metabolized to acetyl coenzyme A and levo-carnitine, to juvenile rats in a controlled cortical impact model resulted in improved behavioral outcomes and decreased contusion volume. [88]

However, relatively few metabolic interventions have been explored in clinical trials. Ritter and colleagues randomized 20 adult patients with severe traumatic brain injury to receive either standard enteral feeds or a ketogenic-like diet which was carbohydrate-free with moderately high fat content.[89] Those receiving the carbohydrate-free diet demonstrated lower blood lactate concentration, higher ketone body levels and better urinary nitrogen balance. Global outcome measures were not compared between groups, and long-term follow-up was not reported. Interestingly, although several episodes of hyperglycemia were documented in the group receiving standard enteral formula, those randomized to the carbohydrate-free diet maintained normal blood glucose levels without hyperglycemia.

Conclusion

In the aftermath of moderate/severe traumatic brain injury, concussions and repeat concussions, a number of significant metabolic and hormonal changes occur which cumulatively impair the brain’s ability to efficiently and effectively metabolize glucose. Understanding these changes opens a number of possibilities to improve the diagnostic evaluation and treatment of traumatic brain injury. However, in the light of the age-dependent cerebral metabolic response to injury, and the age-dependent changes in the body’s physiologic ability to upregulate ketone transport and metabolism, any investigation must be performed in an age-specific manner. As demonstrated in the animal models, what is effective in the child or adolescent may not be as helpful in the adult.

Better neuroprotective strategies are needed to improve outcome after traumatic brain injury. The exploration of alternative metabolic substrates represents an attractive opportunity to address a known pathophysiologic process which impairs the brain’s ability to produce energy from its preferred metabolic substrate, glucose, in the wake of traumatic brain injury. Further studies are now needed to translate these findings into the clinical setting, and determine in an age-specific fashion whether the ketogenic diet, omega-3 fatty acids, or other alternative fuel sources can improve functional, cognitive and behavioral outcomes following various severities of traumatic brain injury.

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