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Review Article

Metabolic perturbations after pediatric TBI: It's not just about glucose

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ABSTRACT

Improved patient survival following pediatric traumatic brain injury (TBI) has uncovered a currently limited understanding of both the adaptive and maladaptive metabolic perturbations that occur during the acute and long-term phases of recovery. While much is known about the redundancy of metabolic pathways that provide adequate energy and substrates for normal brain growth and development, the field is only beginning to characterize perturbations in these metabolic pathways after pediatric TBI. To date, the majority of studies have focused on dysregulated oxidative glucose metabolism after injury; however, the immature brain is well-equipped to use alternative substrates to fuel energy production, growth, and development. A comprehensive understanding of metabolic changes associated with pediatric TBI cannot be limited to investigations of glucose metabolism alone. All energy substrates used by the brain should be considered in developing nutritional and pharmacological interventions for pediatric head trauma. This review summarizes post-injury changes in brain metabolism of glucose, lipids, ketone bodies, and amino acids with discussion of the therapeutic potential of altering substrate utilization to improve pediatric TBI outcomes.

1. Introduction

The brain is a metabolically “expensive” organ which requires a continuous supply of oxygen and glucose—loss of blood flow to the brain can result in permanent damage, coma, or death in a matter of minutes. The large majority of the brain's total energy budget (75%) is spent on highly specialized signaling events (i.e. propagating action potentials, restoring and maintaining resting membrane potentials, recycling glutamate, mobilizing and modifying postsynaptic receptors) and only 25% is devoted to basic cellular activities shared by all cells (i.e. phospholipid turnover, mitochondrial proton leak, etc.) (Clarke and Sokoloff, 1999). In children, these metabolic expenses rapidly increase from birth and throughout childhood towards adolescence. Specifically, cerebral oxygen consumption is low at birth but increases rapidly in early childhood such that by age 5–6 years, a child's brain oxygen consumption exceeds that of an adult by 50% (Prins, 2017). This increased demand for oxidative metabolism is attributed to the extra requirement for brain growth and development during early childhood. The developing brain is especially susceptible to disruptions in meeting that energy demand. Hence, pediatric traumatic brain injury (TBI) not only results in structural perturbations of the developing brain structures, but TBI also impairs the highly orchestrated and metabolically expensive processes that are essential for healthy brain development. Here we summarize the metabolic changes associated with TBI of the developing brain by examining several important energy substrates: glucose, lipids, ketone bodies, and amino acids.

2. Glucose metabolism

Glucose is the primary substrate for brain energy metabolism in both adults and children. Specifically, the adult human brain accounts for ~20% of the body's resting metabolic rate and has a respiratory quotient (CO_2 produced/O_2 consumed) of 0.97 which indicates that glucose dominates as an oxidative fuel for the brain (Clarke and Sokoloff, 1999). Hence, glucose has to be delivered continuously in large quantities and must pass through the blood-brain barrier (BBB). In contrast to muscle and liver, which are well-equipped to meet their metabolic demands by being “metabolic omnivores”, brain fuel delivery is tightly regulated by expressing specific transporters and is protected by the presence of tight junctions in the brain capillary endothelium. Glucose transporter 1 (GLUT1) is abundantly present on the endothelium of the BBB, facilitating glucose transport from the circulation into the extracellular fluid (Simpson et al., 2007). In addition, GLUT1 is expressed on astrocytes. The other subtypes of GLUTs are more specific, i.e. GLUT2 is present only in astrocytes (Arluison et al., 2004; Fuente-Martin et al., 2016; Marty et al., 2005; Young and McKenzie, 2004),

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while GLUT1 and GLUT3 are predominantly neuronal. The expression of GLUT1 and GLUT3 increases with synaptogenesis and brain maturation (Vannucci and Simpson, 2003). All these transporters (GLUT1–3) are not insulin dependent, thus ensuring sufficient brain glucose uptake independent of insulin status. Recently, the presence of insulin-dependent GLUT4 and GLUT8 in the cerebral cortex, hypothalamus, and cerebellum has been reported, but the role and regulation of these glucose transporters is not yet elucidated (Gomez et al., 2010; Leloup et al., 1996; Reno et al., 2017; Sankar et al., 2002).

There are many systemic physiological adaptations in place to maintain blood glucose homeostasis so that the brain has access to an adequate and consistent supply of glucose. Many of these regulatory processes are determined by patterns of feeding and fasting, and many tissues and cell types participate in establishing and maintaining this glucose economy. Despite this, following severe TBI many patients develop "metabolic crisis", which is well-characterized in adults and defined as low brain glucose concentration (< 0.8 mmmol/L) with high lactate/pyruvate ratio (> 40) as determined by intracerebral microdialysis (Vespa et al., 2005). These crises are precipitated by low systemic blood glucose levels and fever, and excessive metabolic demand combined with mitochondrial dysfunction is also thought to contribute to metabolic crisis (Carre et al., 2013). While this phenomenon is well-described in adult TBI patients, the incidence, duration and extent of "metabolic crisis" in pediatric patients is unknown. Current guidelines do not recommend glycemic control due to lack of evidence of its effectiveness (Hardcastle et al., 2014; Kochanek et al., 2012; Kochanek et al., 2019). Thus, the "specific approach to glycemic control in the management of infants and children" is left to the decision of the treating physician (Kochanek et al., 2012; Kochanek et al., 2019). One should underscore that hyperglycemia–especially early and persistent hyperglycemia in pediatric TBI patients– is often reported and associated with poor outcomes (Fu et al., 2017; Melo et al., 2010; Seyed Saadat et al., 2012; Smith et al., 2012).

2.1. Intracellular glucose metabolism and the metabolism of glucose-6-phosphate

Following entry into the cell, glucose is phosphorylated into glucose-6-phosphate via the irreversible activity of hexokinase I, thus facilitating continuous entry of glucose into the cell (Fig. 1). Genda and colleagues demonstrated that, in astrocytes, hexokinase-1 is co-compartmentalized with mitochondria and the astrocytic glutamate transporter (GLT-1; responsible for glutamate uptake) (Genda et al., 2011). The close proximity of these metabolic regulators is particularly important in small-diameter astrocytic processes and likely promotes energetic capacity to match the demands imposed by transport (Genda et al., 2011). Glucose-6-phosphate can: (1) enter the pentose phosphate pathway (PPP) which results in synthesis of NADPH essential for lipid synthesis and for regeneration of glutathione and protection from reactive oxygen species, as well as synthesis of nucleic acid precursors; (2) serve as a precursor for glycogen synthesis in astrocytes; (3) be further metabolized via glycolysis to generate ATP, NADH, and pyruvate, the end-product of glycolysis (Fig. 1).

One way to measure glucose uptake is to use a non-metabolizable, labeled form of glucose. Autoradiography with [^{14}C]2-deoxy-D-glucose was used to determine regional cerebral glucose metabolic rates in a pre-clinical fluid percussion model of TBI in postnatal day 17 rats (Thomas et al., 2000). In this model, elevated glycolysis and impaired glucose oxidation were observed in cortex, hippocampus, and thalamus, despite little morphological damage. Impaired glucose metabolism was observed within 30 min of injury (the earliest timepoint tested), and by one day after injury all regions exhibited impaired glucose metabolism

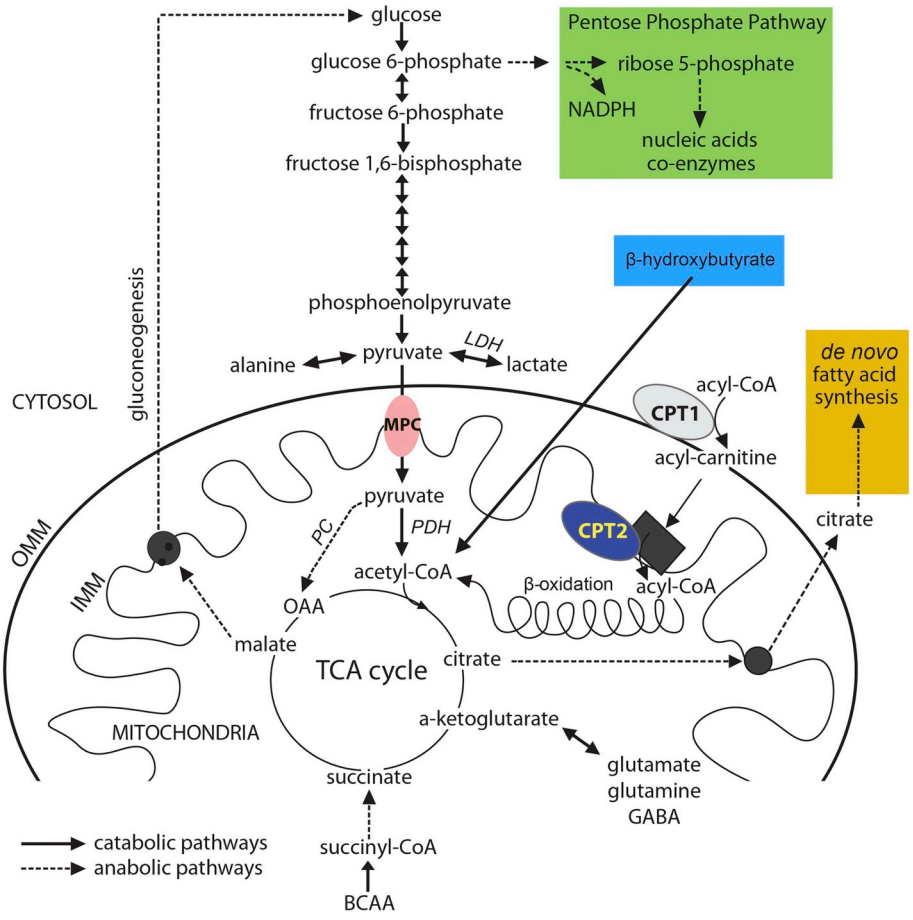

Fig. 1. Summary of brain macronutrient metabolism: Glycolysis, the pentose phosphate pathway, and mitochondrial oxidative metabolism of pyruvate, fatty acids, ketone bodies, and amino acids. Cytosolic glucose can be catabolized by glycolysis or the pentose phosphate pathway. Pyruvate, the end-product of glycolysis can enter the mitochondrial matrix where it is oxidatively decarboxylated to acetyl-CoA by PDH in order to enter the TCA cycle. Long-chain fatty acids are converted to acyl-CoAs which traverse the mitochondrial membranes via the subsequent enzymatic activities of CPT1 and CPT2 in the carnitine shuttle. Ketone bodies such as β-hydroxybutyrate enter the TCA cycle as acetyl-CoA. Certain amino acids can enter the TCA cycle as acetyl-CoA, α-ketoglutarate, or succinyl-CoA. TCA cycle intermediates and NADPH and intermediates from the pentose phosphate pathway promote anabolic reactions in the cell.
OMM = outer mitochondrial membrane; IMM = inner mitochondrial membrane; LDH = lactate dehydrogenase; CPT = carnitine palmitoyltransferase; MPC = mitochondrial pyruvate carrier; PDH = pyruvate dehydrogenase; PC = pyruvate carboxylase; OAA = oxaloacetate; TCA = tricarboxylic acid; CoA = coenzyme A; GABA = gamma-aminobutyric acid; BCAA = branched-chain amino acids.

(Thomas et al., 2000). Interestingly, the post-injury metabolic depression was resolved after 3 days in rat pups, whereas the metabolic depression in adult rats persisted for 10 days (Yoshino et al., 1991). The accelerated recovery of metabolic rate in young pups may spare prolonged neurological damage; however, the implications of having a higher baseline cerebral metabolic rate at the time of injury are not fully understood.

2.1.1. Pentose phosphate pathway

Glucose serves not only as a fuel for brain energy production, but glucose also enters the pentose phosphate pathway (PPP) for nucleotide and NADPH synthesis (Jalloh et al., 2015a). Glucose-6-phosphate can enter the pentose phosphate pathway (PPP) and generate ribose-5-phosphate for nucleotide biosynthesis – the building blocks of DNA, RNA and nucleic acids (Fig. 1). Using an adult rat model of TBI (fluid percussion), Bartnik and colleagues (Bartnik et al., 2005) demonstrated that the PPP is upregulated after TBI in rat, while Jalloh et al. (Jalloh et al., 2015a) also showed that it is upregulated in a subset of adult patients after TBI. In adult humans, PPP flux was highest in patients tested within 48 h of injury suggesting that this metabolic shift could be specific to the acute post-injury period (Dusick et al., 2007). Changes in glucose utilization via the PPP have yet to be studied in pediatric models of TBI. Nevertheless, at baseline, the healthy neonatal brain has higher glucose flux into the PPP than the adult brain, consistent with the large biosynthetic demand during early brain development (Morken et al., 2014). Moreover, in a neonatal rat model of hypoxic-ischemic brain injury, PPP flux was reduced upon injury and may contribute to the higher susceptibility of neonatal brain to oxidative stress upon ischemic injury (Brekke et al., 2014). Characterizing changes in PPP flux is an important first step in determining the metabolic fate of glucose upon injury; however, further experiments will be needed to determine whether alterations in PPP flux are adaptive or maladaptive and whether these changes are secondary to impairments in mitochondrial oxidative metabolism of glucose.

2.1.2. Glycogen synthesis

In astrocytes, glucose is predominantly catabolized, but glucose-6-phosphate can also be used for the synthesis of glycogen (Fig. 2), which serves as a small energy store that can be mobilized in moments of intense metabolic need. While the molar amount of glycogen stored in the brain is small enough to be completely exhausted within minutes, recently, there is evidence for rapid degradation and recycling of glycogen during normal neural activation (Dienel et al., 2007; Hertz and Chen, 2018; Hertz et al., 2007). Pharmacological inhibition of glycogen

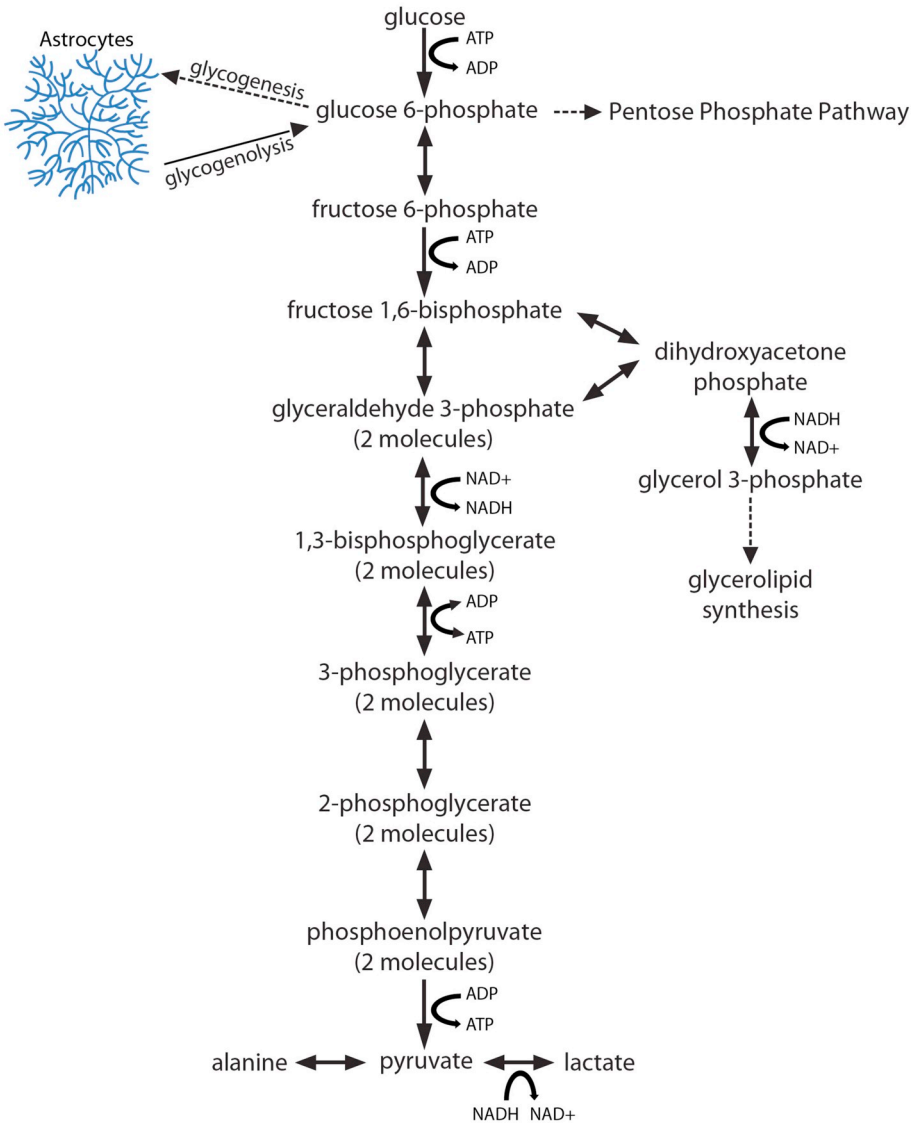

Fig. 2. Glycolysis, glycogen metabolism, and the pentose phosphate pathway.
Glucose 6-phosphate, an intermediate in glycolysis, can be used for glycogen synthesis in astrocytes or can contribute to the pentose phosphate pathway.

phosphorylase increases brain glycogen content which may help sustain brain electrical activity during hypoglycemia (Suh et al., 2007). Although the role and regulation of glycogen storage in the developing brain is incompletely understood, the capacity to mobilize astrocytic glycogen stores increases after birth and may promote cell proliferation as part of normal brain maturation (Gotoh et al., 2017). Astrocytic glycogen content was also observed to increase in a rodent model of early postnatal undernutrition (Lizarraga-Mollinedo et al., 2010). While brain glycogen has not been studied in pediatric TBI, injury in an adult rat fluid percussion (FP) model of TBI increased glycogen content in cortex and hippocampus 24 h after injury (Otori et al., 2004). When rats were subjected to an ischemic injury 24 h after the TBI, remarkably, there was less neuronal death in FP-injured brains than sham controls, suggesting that enhanced glycogen accumulation may be protective upon further metabolic stress (Otori et al., 2004). In this way, astrocytic glycogen may help protect both developing and mature brain from metabolic stresses associated with injury and nutritional deficiencies. Further mechanistic studies will be necessary to determine if glycogen accumulation and mobilization is protective or if these alterations are secondary to other changes in brain glucose metabolism.

2.1.3. Glycolysis

The subsequent glycolytic reactions after glucose-6-phosphate produce fructose-6-phosphate then fructose-1,6-bis-phosphate, which is cleaved by aldolase into dihydroxyacetone phosphate and glyceraldehyde-3-phosphate (Fig. 2). These trioses are interconvertible and dihydroxyacetone phosphate participates in the glycerol-3-phosphate shuttle to transfer reducing equivalents from the cytosol to the mitochondrial matrix. As a part of this shuttle, dihydroxyacetone phosphate in the cytosol is reduced to glycerol-3-phosphate, cytosolic NAD + is regenerated, and mitochondrial $FADH_2$ is made upon the oxidation of glycerol-3-phosphate back to dihydroxyacetone phosphate by the mitochondrial glycerol-3-phosphate dehydrogenase. The cell-type-specific activity of the glycerol-3-phosphate shuttle is not well understood, although oligodendrocytes and astrocytes may use this method of reducing equivalent transfer while neurons predominantly use the malate-aspartate shuttle (McKenna et al., 2006). There is evidence for impairment of the malate-aspartate shuttle in injured immature rat brain (Scafidi et al., 2009), and, in other contexts such as cardiac ischemia-reperfusion injury, pre-ischemic inhibition of the malate-aspartate shuttle has been shown to be protective (Stottrup et al., 2010). It remains to be determined if the observed changes in the malate-aspartate shuttle upon brain injury are protective or maladaptive and whether this response is conserved in developing and adult brains. Furthermore, glycerol-3-phosphate from this offshoot of glycolysis links glucose and lipid metabolism by providing the glycerol backbone for phospholipid synthesis. The role of post-injury lipid synthesis will be further addressed in Section 3.

2.2. Oxidative metabolism of glucose: Pyruvate and lactate

In the cytosol, pyruvate generated from glycolysis can be converted to lactate by lactate dehydrogenase to regenerate NAD+, or pyruvate may be interconverted with the amino acid alanine. Importantly, lactate conversion to pyruvate in neurons is an important part of the proposed intercellular metabolic shuttle between astrocytes and neurons (Pellerin et al., 2007), and while the model remains controversial, lactate is readily taken up and utilized by cultured neurons and astrocytes (Sanchez-Abarca et al., 2001). Importantly, neonatal brain uses lactate as an oxidative substrate before glucose oxidation increases with development (Cremer, 1982), and adult brain can also use lactate when blood levels are high, such as during strenuous exercise (Quistorff et al., 2008). Using a model of diffuse brain injury (Marmarou model) in adult male rats, Prieto et al. demonstrated that at 6 h after TBI administration of sodium lactate did not improve decreased levels of ATP, NAA (neuronal mitochondrial marker) or levels of anti-oxidants (i.e. ascorbic acid and glutathione) (Prieto et al., 2011). Glenn and colleagues conducted a clinical study in which adult TBI patients were infused intravenously with [6,6-$^2H_2$]glucose and [3-^{13}C]lactate and cerebral arterial and venous blood samples were collected simultaneously. The study demonstrated that lactate was metabolized by brain in TBI patients and that lactate may be used to compensate for the reduced cerebral metabolic rate from glucose upon injury (Glenn et al., 2015a). This study also demonstrated increased labeling of glucose from lactate in TBI patients, which suggests a role for gluconeogenesis from lactate in supporting the metabolic demands of the brain post-injury, and the rate of appearance of lactate was also increased in TBI patients (Glenn et al., 2015b). Given that high lactate/pyruvate ratio is part of the clinically defined metabolic crisis of TBI, the timing, extent and effect of lactate administration as an alternative substrate following TBI remains the subject of debate (Brooks and Martin, 2014; Dienel, 2014). Additionally, much is unknown about the cell-type-specific utilization of lactate after injury. No studies to date have assessed the extent of lactate utilization by injured developing brain; although healthy developing brain is known to use lactate as an oxidative substrate (Cremer, 1982).

Subcellular substrate partitioning is a fundamental way to regulate metabolic pathways, and the transport of pyruvate into mitochondria allows for several distinct mitochondrial uses depending on the cell type and metabolic state. The mitochondrial pyruvate carrier (MPC) facilitates pyruvate transport into mitochondria and has been characterized biochemically since the 1970s (Halestrap and Denton, 1974; Papa et al., 1971); however, the molecular identities of the *MPC1* and *MPC2* genes which encode the essential components of the MPC were only recently determined (Bricker et al., 2012; Herzig et al., 2012). Interestingly, prior to its identification as an essential component of the MPC, *MPC1* was found to be upregulated in spinal cord injury and regeneration in lizards (Jiang et al., 2009). Mechanistically, inhibition of the MPC in cultured cortical neurons resulted in rewiring of metabolism and increased glutamate oxidation, providing protection from neurotoxicity (Divakaruni et al., 2017). Mitochondrial pyruvate can (1) be interconverted with mitochondrial alanine; (2) be converted to oxaloacetate by pyruvate carboxylase which is important for amino acid neurotransmitter synthesis; or (3) be oxidatively decarboxylated to acetyl-CoA by the pyruvate dehydrogenase complex (PDH) (Fig. 1). Genetic deficiencies in the enzymes that accomplish these three metabolic fates of mitochondrial pyruvate (or associated cofactors or regulatory proteins) can be associated with severe neurodevelopmental disorders that often present early in life (Celis et al., 2015; Ouyang et al., 2016; Pithukpakorn, 2005; Sofou et al., 2017; Sperl et al., 2015). It is interesting to note that PDH is inherited in both autosomal recessive and X-linked dominant manners while all other enzymes involved in glycolysis and oxidative phosphorylation are inherited in an autosomal recessive manner. The most common cause of PDH deficiency is due to pathogenic variants in the *PDHA1* gene, which is located on the X chromosome, so females may be less affected than males. While sex differences in this Mendelian inherited metabolic disorder of pyruvate metabolism are clear, the effects of sex on brain glucose metabolism and mitochondrial oxidative metabolism may be more subtle. It has been demonstrated that adult females have slightly higher rates of cerebral blood flow and cerebral glucose metabolism than males (Baxter Jr. et al., 1987; Prins, 2017), and the effects of sex on injury outcomes is being characterized in pre-clinical models (Arambula et al., 2019).

Overall, glucose is an essential substrate for the synthesis of carbohydrates, nucleotides, amino acids, lipids, and neurotransmitters (i.e. glutamate and GABA). Insights into perturbations of glucose metabolism are gained via studies using labeled isotopes (see comprehensive review by (Jalloh et al., 2015b)) and are currently being employed in adult TBI pre-clinical and clinical research. Pre-clinical studies in pediatric models of TBI employed ^{1}H and ^{13}C-nuclear magnetic resonance spectroscopy (NMR) and determined that oxidative glucose metabolism

Table 1
Summary of studies of brain metabolism in pre-clinical pediatric TBI models.

	Model	Age	Species	Findings	References
Glucose	Focal (CCI)	17 d	Rat	24 h after injury, 2D gel analysis found increase in astrocyte specific glucose transporters (Glut3) and changes in glycolytic proteins.	Jenkins et al., 2002
	Focal (CCI)	21 d	Rat	6 h after TBI, ipsilateral and contralateral cortex and hippocampus initiation of mitochondrial oxidative metabolism has delayed onset but increased overall.	Scafidi et al., 2009
	Focal (CCI)	17 d	Rat	Pyruvate dehydrogenase activity and cytochrome c content is decreased at 4 hrs after TBI	Robertson et al., 2007
	Focal (CCI)	17 d	Rat	Using ^{13}C-glucose NMR, oxidative glucose metabolism recovers 24 hrs after TBI	Robertson et al., 2013
	Focal (CCI)	17 d	Rat	2D gel analysis demonstrates decreased expression of the PDHE1 complex at 2 weeks after TBI. The glutamate-glutamine cycling proteins were increased.	Kochanek et al., 2006
Lipids/Ketones	Diffuse (percussion)	7 d	Rat	Alpha-Lipoic acid supplementation increased glutathione peroxidase and superoxide dismutase activities	Ozbal et al., 2015
	Focal (CCI)	17 d 35 d 45 d 65 d	Rat	Ketogenic diet decreased cortical contusion lesion in PND35 and 45 rats, as well as less Fluoro-Jade positive cells and earlier clearance of plasma lactate	Prins et al., 2005
	Focal (CCI)	35 d	Rat	Ketogenic diet improved ATP, creatine and phosphocreatine at 24hr after TBI	Deng-Bryant et al., 2011
	Focal (CCI)	17 d	Rat	Cardiolipin peroxidation preceded apoptosis and oxidative stress. There is decreased glutathione 24 h after injury.	Bayir et al., 2007
	Focal (CCI)	17 d	Rat	TBI results in increased oxygenation of mitochondrial specific phospholipid cardiolipin leading to neuronal death. Inhibition of cardiolipin oxidation decreased neuronal death and behavioral deficits.	Ji et al., 2012
	Focal (CCI)	21 d	Rat	Treatment with acetyl-L-carnitine in the first 24 h after TBI improved neurobehavioral performance at 7 d post injury.	Scafidi et al., 2010
Mitochondrial (non-specific)	Focal (CCI)	4 wk	Piglet	Decreased citrate synthase activity 24 h after CCI. There was also decreased Complex I driven respiration and increased Complex II & IV respiration.	Kilbaugh et al., 2015
	Focal (CCI)	21 d	Mice	No compensatory increase in Glutathione Peroxidase activity at 24 hrs post injury in different brain regions.	Fan et al., 2003
	Focal (CCI)	17 d	Rat	^{1}H-NMR showed decreased mitochondrial synthesis of NAA at 24 h and 7 d post TBI. Lactate peak occurred at 24 h post TBI in both hemispheres.	Casey et al., 2008
	Focal (CCI)	35 d	Rat	Complex II-III activity decreased following TBI, but unaffected in ketogenic diet treatment group at 6 h and 24 h after TBI.	Greco et al., 2016
Amino acids				To date, there have been no studies that have assessed metabolism of amino acids after TBI in immature brain. Adult TBI supplemented with 100 mM branched chain amino acids in the drinking water had improved sleep wake cycle	None

is reduced at 6 h post TBI (Casey et al., 2008; Scafidi et al., 2009) (see Table 1). However, despite this suppression, there is an accumulation of labeled metabolites (glutamate, glutamine and GABA), suggesting impaired metabolite trafficking between astrocytes and neurons as well as decreased glutamate entry into mitochondria because of impairment of the malate-aspartate shuttle. However, this delay and label accumulation is resolved similarly to adult pre-clinical studies by 24 h after TBI (Robertson et al., 2013). While both pediatric and adult studies demonstrate increased labeling of lactate from glucose—evidence of elevated glycolysis—studies in adults also demonstrate upregulation of PPP flux (Bartnik et al., 2007; Bartnik et al., 2005), which has not yet been characterized in pediatric TBI models. Altogether, the oxidative metabolism of glucose is decreased by TBI, and while labeled glucose experiments demonstrate increased glycolysis, enhanced PPP flux, and impaired intercellular metabolic shuttling, the consequences of these metabolic changes on post-injury outcomes are not fully understood, especially in pediatric patients where hyperglycemia is correlated with poor outcomes.

3. Lipid metabolism

The brain is an extremely lipid-rich organ, second only to adipose tissue in terms of lipid content. In contrast to other organs such as adipose, liver, and muscle, where lipid can be stored and mobilized to meet energetic demand during times of nutrient depletion, brain lipids are primarily used for structural and signaling functions. Brain lipids are essential for myelin synthesis, plasma membrane composition, and lipid raft formation which all help support neurotransmission and which can be dysregulated in pathological conditions (Brady et al., 2011).

Lipids can be acquired from the diet, as is the case for the essential polyunsaturated fatty acids that contribute to the unique lipid composition of the brain, or they can be synthesized de novo. Endogenously produced brain lipids can be mobilized from other tissues or they can be synthesized locally, as the brain has high expression of fatty acid synthase (FASN). De novo lipid synthesis begins with carboxylation of two-carbon acetyl-CoA (largely derived from glucose) to become three-carbon malonyl-CoA which is elongated by the addition of acetyl units via fatty acid synthase. The products of fatty acid synthase are long-chain fatty acids that can be activated to acyl-CoAs for subsequent biochemical reactions to make complex lipids (such as sphingolipids, phospholipids, neutral lipids, and signaling lipids) or for covalent modification of proteins (protein palmitoylation, for example) or for energy production by mitochondrial β-oxidation of long-chain acyl-CoAs. Many uses of fatty acids, acyl-CoAs, and complex lipids are cell type-specific in the brain, as will be discussed in further detail. The structural damage associated with TBI results in increased demand for the synthesis of membrane phospholipids, and a nutritional supplement developed to promote complex lipid synthesis was recently shown to improve recovery post-injury in rodents (Thau-Zuchman et al., 2019). While this study offered several different nutrients to promote phospholipid synthesis including essential fatty acids, choline, uridine, and vitamins and cofactors, fatty acids are an important branchpoint for both biosynthetic and energy-producing metabolic pathways.

Brain fatty acids (FA) are essential for neurogenesis, metabolism of neural progenitor cells, synaptogenesis, myelination, gene expression, and synaptic activity (McKenna et al., 2015). During normal conditions, the medium-chain fatty acid octanoate (8-carbons) can furnish 20% of brain energy and metabolism in the adult brain (Ebert et al., 2003), and inhibition of FA oxidation can result in decreased ATP (Knobloch et al., 2017). What the contribution of fatty acids towards brain energy and metabolism is at different ages and regions during brain development remains unknown. Despite this, the use of fatty acids by some cell types in the brain under specific circumstances has been described. For example, fatty acid oxidation has been identified as an important process in neural progenitor cells and astrocytes. In order to gain access to the mitochondrial matrix, long-chain acyl-CoAs, which are membrane-impermeable, are shuttled across the mitochondrial membranes via the carnitine palmitoyl transferases (CPTs) (Fig. 1). This pathway is essential for the survival of neural progenitor cells (Knobloch et al., 2017; Stoll et al., 2015) and astrocytes use the CPTs for long-chain FA oxidative metabolism (Edmond et al., 1998; Edmond et al., 1987; Jernberg et al., 2017). Following long-chain acyl-CoA transport into mitochondria, FA are metabolized into acetyl-CoA by β-oxidation. This acetyl-CoA can then directly contribute to the TCA cycle or be used to generate ketones for export to support neuronal oxidative metabolism (Auestad et al., 1991). We recently reported that the expression of CPTs in the brain is developmentally and regionally regulated, and the highest expression is observed in the hippocampus – a brain region responsible for short-term memory formation and long-term consolidation (Jernberg et al., 2017). Furthermore, expression of the enzymatic machinery for mitochondrial FA oxidation peaks at postnatal day 21 in rat brain and remains elevated to support FA oxidation within astrocytes of the adult brain.

Following traumatic brain injury (TBI), there is an increased free FA concentration in cerebrospinal fluid and this is associated with poor outcomes (Pilitsis et al., 2003). These free FAs are generated from membrane phospholipid degradation and activation of phospholipases (Phillis and O'Regan, 2003). Free FAs released in this manner contribute to the propagation of secondary cell death by promoting apoptosis (through activation of caspase-8 and caspase-3 activity), stimulating inflammation via Toll-like receptor 4, and increasing secretion of pro-inflammatory cytokines (Chen et al., 2017; Trepanier et al., 2016). Circulating lysophosphatidic acid (LPA) is another class of bioactive lipid that is also increased in the circulation of TBI patients and in rodent models of TBI (Crack et al., 2014). Administration of a monoclonal antibody against LPA to adult mice 30 min post-injury significantly reduced lesion volume and reduced inflammatory cytokine levels (Crack et al., 2014). The extracellular receptor for LPA is known to be more highly expressed in developing brain than in adult brain (Frisca et al., 2012), but it is unknown if this sensitizes young brain to the pro-inflammatory response to LPA that is observed in adults.

While these data collectively suggest that free FA and other bioactive lipids are contributing to the secondary injury, increasing mitochondrial fatty acid oxidation could be a way of reducing free fatty acid concentrations to lessen post-injury cell death. Enhancing fatty acid oxidation after TBI may also improve energetics, but it is unclear if the mitochondrial dysfunction associated with TBI would impair the capacity for fatty acid uptake and utilization by mitochondria. Enhancing mitochondrial function after TBI has been suggested as a relevant and effective therapeutic target for neuroprotection after injury (Yokobori et al., 2014). The mitochondria-specific lipid cardiolipin may also play a role in neuroprotection. Cardiolipin is a mitochondria-specific complex phospholipid located in the inner mitochondrial membrane and it regulates enzymes of oxidative phosphorylation. Cardiolipin binds to Complexes I, III, IV and V and stabilizes respiratory supercomplexes and mitochondrial carrier proteins of the inner membrane (Claypool, 2009; Paradies et al., 2014; Vartak et al., 2013). Emerging evidence suggests that following injury cardiolipin is externalized to the surface of mitochondria and acts as an elimination signal for mitophagy (Ji et al., 2012). Ji et al. demonstrated that cardiolipin, which often contains acyl chains with a high degree of unsaturation, can easily undergo oxidative modification in a neuronal stretch injury model. Treatment with a mitochondria-targeted electron-scavenger following TBI in immature (postnatal day 17) rats prevented cardiolipin oxygenation and was neuroprotective as evidenced by reduced behavioral deficits and cortical lesion volume (Ji et al., 2012) (Table 1). Furthermore, genetic and pharmacological approaches provide evidence that mitophagy after TBI is beneficial and reduces apoptotic cell death and that cardiolipin externalization is part of this process (Chao et al., 2019). Recently, cardiolipin-containing mitochondrial microparticles released from apoptotic brain cells—but

detected in peripheral blood—were found to impair blood coagulation after injury, which can extend the period of secondary injury post-TBI (Zhao et al., 2016). In this way, circulating lipids and mitochondrial fragments can impact local and systemic responses to traumatic brain injury by both metabolic and non-metabolic means.

4. Ketone body metabolism

Decades ago, it was established that ketone bodies—breakdown products of fatty acids and certain amino acids that can be exported and used to support mitochondrial oxidative metabolism—can be extensively used by developing brain. In addition, the high-fat, low-carbohydrate ketogenic diet has been used with success in the treatment of complex epilepsy in both pediatric and adult patients (Baranano and Hartman, 2008). Several studies have demonstrated that ketogenic diet feeding immediately after TBI decreased lesion volume and cortical cell death in adolescent (postnatal day 35) rats; improved levels of adenosine triphosphate (ATP), creatine, and phosphocreatine; and improved neurological outcomes such as improved performance in the Morris water maze and beam walking (Appelberg et al., 2009; Deng-Bryant et al., 2011; Prins et al., 2005; Prins and Hovda, 2009) (Table 1). Interestingly, some of the beneficial metabolic effects of the ketogenic diet post-TBI were not observed in adult rats, suggesting that adolescent rats had a delayed energy deficit that was more readily met by ketones than in adult brain (Deng-Bryant et al., 2011; Prins et al., 2005). The exact mechanism of the beneficial effect of ketones and the ketogenic diet after TBI has not been determined, and the mechanism for the observed differences in the effectiveness of the diet at different ages also remains to be determined. Compared to a 24 h fast immediately after injury in an adult rat model of TBI, acute administration of β-hydroxybutyrate resulted in similar improvements in tissue sparing, whereas insulin administration to promote lower glycemia (and so mimic one aspect of fasting) failed to improve outcomes (Davis et al., 2008). The rationale for the efficacy of fasting and the ketogenic diet stems from the ability of ketones to directly provide acetyl-CoA moieties for the TCA cycle, especially since pyruvate dehydrogenase activity was found to be impaired within hours after TBI (Sofou et al., 2017). Interestingly, administration of enteral nutrition enriched in medium-chain triglycerides to human TBI patients only modestly increased blood and brain medium-chain free fatty acids without increasing concentrations of ketone bodies in the circulation or brain (Bernini et al., 2018). This finding suggests that alternative methods such as administering exogenous ketones may be necessary to increase circulating ketones in TBI patients. Recent developments in administering ketones as dietary ketone esters—which are already approved for human consumption—may enhance the ability to increase circulating ketone levels without a change in diet, and a ketone ester diet improved neurocognitive performance in a mouse model of Alzheimer's disease (Cox et al., 2016; Hashim and VanItallie, 2014; Kashiwaya et al., 2013). Supplementing nutrition with ketone esters may help dissect the effects of dietary fats and carbohydrates during ketone therapy (ie. Is the provision of ketones sufficient to reduce carbohydrate utilization? Are exogenous ketones more or less effective than dietary fats in improving post-TBI outcomes?).

In addition to a purely metabolic fate, ketones may also affect signaling or redox balance. A recent study suggests that administration of β-hydroxybutyrate by continuous infusion after TBI in rats improves markers of redox balance but fails to improve the integrity of the blood-brain barrier, which had been hypothesized because one signaling consequence of ketones in cultured endothelial cells was upregulation of gap junction proteins (Orhan et al., 2016). Ketone bodies may affect mitochondrial redox balance in the context of impaired mitochondrial function after TBI by the NAD^+-dependent oxidation of β-hydroxybutyrate to acetoacetate for subsequent metabolism. Ketones are largely generated from hepatic mitochondrial β-oxidation of fatty acids. The liver can generate extensive amounts of ketones, especially in the fasted state, but the liver is unable to use ketones for its own metabolism due to lack of the enzyme 3-oxoacid CoA-transferase 1 (OXCT1). This enzyme, however, is very abundant in the brain, along with the monocarboxylic acid transporters responsible for ketone transport into brain cells. The metabolism of β-hydroxybutyrate results in generation of NADH within the mitochondrial matrix as well as increased production of succinate. Succinate may be further metabolized by succinate dehydrogenase (Complex II) and bypass Complex I, resulting in decreased reactive oxygen species (ROS generation) (see extensive review by Achanta and Rae)(Achanta and Rae, 2017). This is consistent with a recent report by Greco et al. (Greco et al., 2016), who showed that following controlled cortical impact (CCI), mitochondrial respiratory chain Complex II activity was decreased after TBI. Postnatal day 35 rats fed a ketogenic diet after TBI (CCI) were protected from a decrease in Complex II and III activities measured at 24 h after TBI (Greco et al., 2016). It is interesting that ketones can also be generated from certain amino acids (leucine and lysine are exclusively ketogenic while phenylalanine, isoleucine, threonine, tryptophan, and tyrosine are ketogenic and glucogenic), however, whether this process is altered by TBI has not been investigated. Furthermore, the roles of ketone bodies from fats or amino acids in the recovery from pediatric TBI have also not been studied in detail. Altogether, ketone bodies may have both metabolic and non-metabolic mechanisms of action, and there is substantial evidence that, particularly in young brains, ketones can improve TBI outcomes. Furthermore, nutritional support with ketogenic diet or ketone esters is already an important therapeutic strategy for other neurological conditions and could be readily adapted to clinical trials in TBI patients.

5. Amino acid metabolism

Amino acid metabolism is intimately intertwined with glucose and ketone metabolism as certain amino acids can be catabolized to the ketogenic substrate acetyl-CoA while others can be catabolized to the glucogenic substrate succinyl-CoA (or both). There are several amino acids that participate in the de novo synthesis of glucose – i.e. a process known as gluconeogenesis. While gluconeogenesis is well studied and quantified in liver and kidney (and to a lesser extent, intestine), brain gluconeogenesis has not been well studied and is thought to be primarily present in astrocytes.

Gluconeogenesis is not a simple reversal of glycolysis and the enzymes required for gluconeogenesis are expressed in brain. Bhattacharya and Datta (Bhattacharya and Datta, 1993) showed that cerebral cortical slices could produce glucose from the amino acid alanine. Furthermore, this production was increased by glucagon, phenylephrine and phenoxybenzamine. Emerging evidence suggests that brain gluconeogenesis is silenced under normal conditions but is active in pathological conditions such as ischemic stroke and brain tumors (see review by Yip et al. (Yip et al., 2016)).

Several amino acids may be oxidized for energy production and may contribute carbon to the TCA cycle at various entry points. For example, glutamine following uptake into neurons is metabolized to glutamate by glutaminase and subsequently trans-aminated to α-ketoglutarate – an intermediate of the TCA cycle. Using ^{13}C glucose NMR, Scafidi et al. (Scafidi et al., 2009) demonstrated accumulation of labeled glutamate, suggesting that glutamate conversion to α-ketoglutarate is decreased due to decreased activity of α-ketoglutarate dehydrogenase by oxidative stress after TBI.

The essential branched-chain amino acids (BCAA) – leucine, isoleucine and valine – are required for protein synthesis and are facilitators of nitrogen balance in the central nervous system. Furthermore, these BCAA are metabolized to acetyl-CoA (leucine and isoleucine), acetoacetate (leucine), propionyl-CoA and succinyl-CoA (valine and isoleucine) and thus can fuel the TCA cycle (Schousboe et al., 2014; Sperringer et al., 2017). BCAA dietary supplementation following fluid percussion injury in adult mice resulted in improved wake deficits

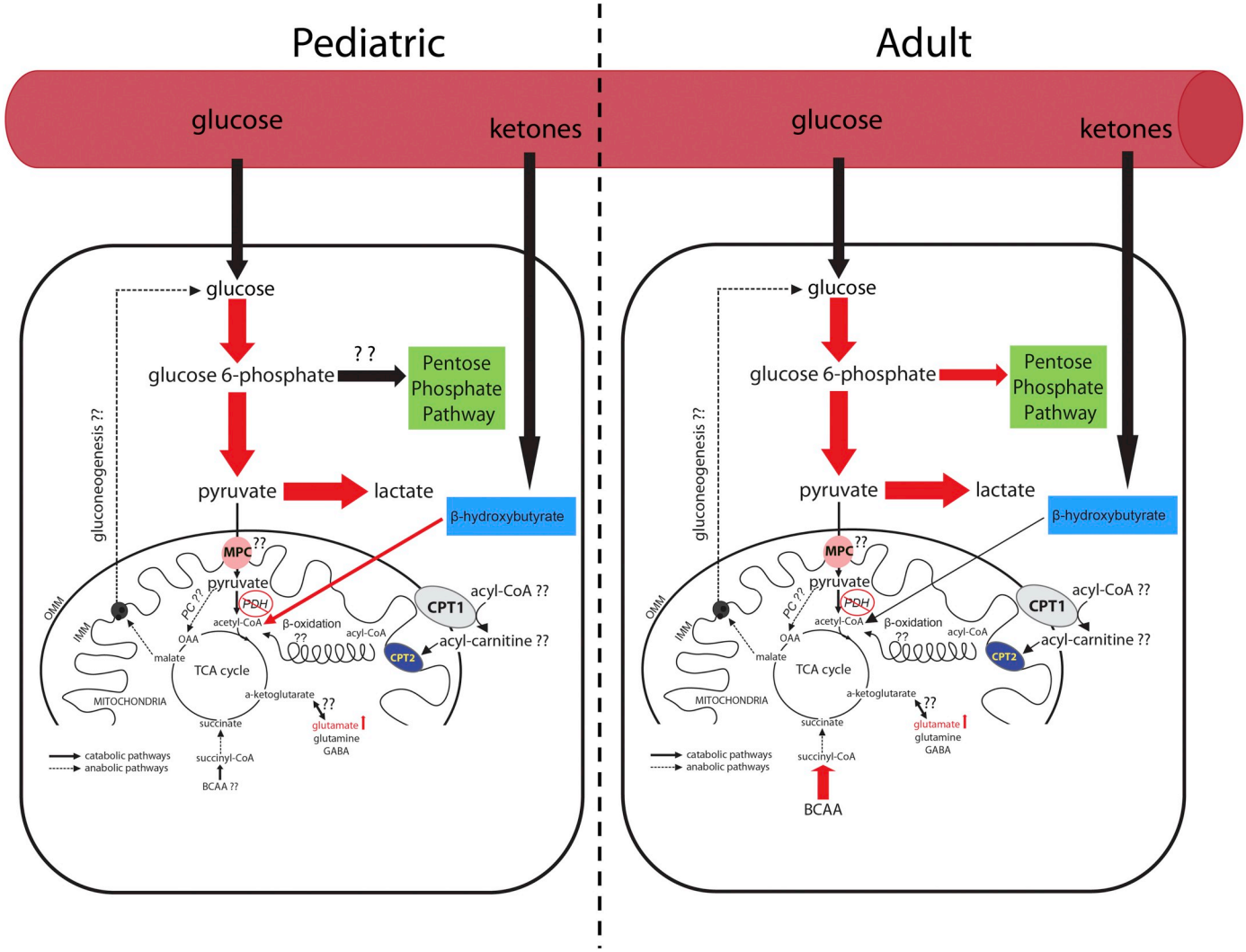

Fig. 3. Comparison of metabolic perturbations in pediatric and adult brain after TBI.
After injury both pediatric and adult brain have impaired mitochondrial oxidative metabolism of glucose as depicted by impaired pyruvate dehydrogenase (PDH). Both exhibit increased glycolysis and lactate production as indicated by the large red arrows. In injured adult brain, an increase in pentose phosphate pathway flux has been observed but this has not been studied in pediatric TBI. Ketone supplementation has been demonstrated to have beneficial metabolic and neurological outcomes in pre-clinical models of pediatric TBI but was not beneficial in adult TBI. BCAA supplementation in adult TBI improved outcomes but has not been studied in pediatric patients or pre-clinical models. The role of mitochondrial fatty acid oxidation during and after injury is not well understood nor is the role of gluconeogenesis nor mitochondrial pyruvate transport. The cell represented here reflects general metabolic perturbations that have been observed largely from studies of whole brain. The cell-type specificity of these metabolic responses to injury remains to be determined. Overall, multiple nutrients contribute to meeting brain energetic and biosynthetic demands, and those that are known to be altered in TBI are summarized here.

which may facilitate cognitive recovery after injury (Lim et al., 2013). In this study, 100 mM BCAA supplementation in the drinking water for 5–10 days was used to improve memory deficits. It is unclear how dietary amino acids may affect cognitive recovery. While adult TBI patients were reported to have decreased levels of these BCAA in jugular venous plasma (Jeter et al., 2013; Vuille-Dit-Bille et al., 2012), it is possible that prolonged supplementation is required since BCAA are only modestly metabolized in isolated murine neurons and astrocytes (Bak et al., 2013). Indeed, 15 days of intravenous BCAA supplementation modestly improved cognitive recovery of patients with severe TBI (Aquilani et al., 2005). A recent study in rats suggested that TBI may impair the enzymatic machinery for BCAA catabolism by a reversible inhibitory phosphorylation of the branched-chain ketoacid dehydrogenase (Xing et al., 2018). Moreover, this study demonstrated an enrichment of this modification in astrocytes, particularly near the lesion site, and these changes could be recapitulated in cultured astrocytes in response to an injury-associated differentiation stimulus (Xing et al., 2018). There is still much to be determined about the cell-type-specific metabolism of amino acids, particularly in the context of injury. To date there are no other studies assessing the effect of dietary BCAA supplementation on brain recovery after TBI in developing brain. Early postnatal brains may have a higher requirement for essential amino acids to promote protein synthesis or support oxidative metabolism, concurrent with the higher oxygen consumption rates of developing brain.

6. Conclusion

Despite significant improvement in promoting survival of children following TBI, our current understanding of alterations in brain energy metabolism after injury remains rudimentary and incomplete. Adult pre-clinical studies demonstrated that the pentose phosphate pathway is upregulated after TBI, as well as treatment with branched-chain amino acids provides neuroprotection. However, these were not tested in models of pediatric TBI (Fig. 3). It is important to point out several challenges that contribute to our current limited knowledge of the

pathophysiology of pediatric TBI. First, incomplete brain maturation and changing metabolic demands during development make it challenging to define a unified description of brain metabolic requirements after pediatric TBI. Second, heterogeneity among the types, locations, and severity of injuries complicate the clinical literature. Third, the contribution of peripheral injuries or peripheral metabolic changes may also affect outcomes. Further clinical and pre-clinical investigations are imperative to delineate metabolic perturbations after pediatric TBI so that targeted therapeutic interventions can be developed. It will be essential to consider developmental changes in brain metabolism in future studies. A comprehensive understanding of metabolic changes associated with pediatric TBI cannot be limited to investigations of glucose metabolism alone, and all energy substrates used by the brain should be considered in developing nutritional and pharmacological interventions for pediatric head trauma.

Conflicts of interest

None of the authors has any conflict of interest to declare.

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