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Cerebral Ketone Metabolism During Development and Injury

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Abstract

Cerebral metabolism of ketones is a normal part of the process of brain development. While the mature brain relies on glucose as a primary fuel source, metabolism of ketone bodies remains an alternative energy source under conditions of starvation. The neuroprotective properties of brain ketone metabolism make this alternative substrate a viable therapeutic option for various pathologies. Since the ability to revert to utilizing ketones as an alternative substrate is greatest in the younger post-weaned brain, this particular therapeutic approach remains an untapped resource particularly for pediatric pathological conditions.

Keywords

Brain; Development; Ketones; Injury; Metabolism; Neuroprotection

1. KETONES AND BRAIN DEVELOPMENT

1.1 The Normal Brain and Substrate Metabolism

The brain's use of metabolic substrates changes with maturation. There is an early transient reliance on lactate shortly after birth, followed by a period of dependence on both ketones and glucose during suckling. After weaning, the brain relies exclusively on glucose metabolism under normal conditions. These changes in cerebral substrate metabolism are accompanied by alterations in systemic substrate availability, substrate transport and enzyme activities for substrate metabolism. These parameters change dramatically for ketone metabolism during brain development. The suckling animal has higher circulating ketone levels, greater number of blood brain barrier transporters and greater enzymatic activities of ketone metabolizing enzymes (Booth et al., 1980; Vannucci et al., 2003). Non-vascular monocarboxylate transporter (MCT)1 and neuronal MCT2 expression remains constant throughout development (Vannucci and Simpson, 2003). In contrast, microvascular MCT1 peaks during suckling and decreases to low levels in the adult brain (Vannucci and Simpson, 2003). During the period of peak ketone utilization, the brain's capacity to take up ß-hydroxybutyrate (ßOHB) is 6 times greater than the adult rat brain (Cremer, et al. 1976; Hawkins et al. 1971). Upon weaning, there is a decrease in arterial ketone concentrations, followed by a drop in cerebral uptake and finally a down regulation of the monocarboxylate transporters (MCT).

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In contrast, changes in glucose metabolism during development are more gradual. At birth, circulating concentrations of glucose are half that of the adult with concentrations gradually increasing to achieve adult levels at postnatal day (PND)10. Changes in substrate availability occur before both the increased expression in cerebral glucose transporters (Glut1 and Glut 3; Vannucci and Simpson, 2003) and the increased activity of glycolytic enzymes (Leong and Clark, 1984). These parameters do not reach maturation until PND30 when adult levels of glucose metabolic rates are achieved (Nehlig et al., 1987).

1.2 The Substrate Metabolism During Starvation

The greatest contribution to the understanding of cerebral metabolic adaptation has come from the early studies of starvation. Prolonged starvation in humans was shown to increase plasma ßOHB levels and decrease brain glucose uptake (Owen et al., 1967). While it has been estimated that cerebral ketone metabolism can provide 60% of the human brain's metabolic needs, ketones can only provide 15-25% of the rat brain's energy (Dahlquist and Persson, 1976; Ruderman et al, 1974). It is possible that this reflects a species difference in capacity for ketone metabolism, but may equally be explained by the duration of the starvation or magnitude of ketosis achieved.

Conditions of starvation induce changes in plasma levels of substrate and in transporter expression and the magnitudes vary with age. In normally fed adult mammals, ßOHB metabolism comprises < 3% of total cerebral metabolism and is present in low circulating concentrations (0.1 mmol/ L) with negligible uptake into the brain (Hawkins et al, 1971). However, plasma ketone levels can be increased four- to fivefold within 2 days via ketogenesis associated with starvation or administration of a ketogenic diet resulting in 4.9-fold and 1.5-fold increase in cerebral uptake of ketones in PND20 and adult rats, respectively (Dahlquist and Persson 1976; Hawkins et al, 1971). Ketogenesis after 48 h of starvation among PND57 rats showed a 95% increase in arterial ßOHB levels versus only an 81% increase among PND85 rats (Dahlquist and Persson, 1976). Similarly, there is a significantly greater production of ketones among 5-year-old children (28.6%) versus 10-year olds after 24 h of fasting (Saudubray et al, 1981). Starvation studies have revealed that the ability to generate ketones endogenously is inversely proportional to age even after weaning.

In addition to the changes in substrate supplies, starvation also has been shown to alter the uptake of ketones in an age-dependent manner. Adult rats on a ketogenic diet for 1 week can achieve 2mmol/L plasma ßOHB levels within 24h, which is sustained for 7 days. Despite the same plasma concentration of ßOHB at these time points, the permeability of ^{14}C-D-ßOHB was two times greater at 7 days than 24h, suggesting that adult cerebral uptake of ßOHB changes with time in the presence of ketones (Moore et al, 1976). PND57 rats show 61% greater cerebral uptake of b-OHB after 48h of starvation compared with PND85 animals (Hawkins et al, 1971; Dahlquist and Persson, 1976). It has also been reported that at the same plasma level of ßOHB, PND35 rats show a 1.7-fold greater brain uptake index than PND50. Some of this age difference in uptake may be attributed to transporter expression or even transporter function. Collectively, these results from both cerebral development and starvation provide insight into the brain's capacity to adjust to physiologic changes in substrate availability. The age-dependent nature of these changes emphasizes the potential of alternative substrates as therapeutic options for the younger developing brain.

2. KETONES AND BRAIN METABOLISM AFTER INJURY

In the last 10 years the number of publications with the topic of ketones and the brain has almost doubled from the previous decades. There have been increased interest in the effects of ketone metabolism on brain tumors (Stafford et al, 2010; Mukherjee et al., 2002; Seyfried

et al., 2003; Zhou et al., 2007), Alzheimer's disease (Van der Auwers et al., 2005; Reger et al., 2004), Parkinson's disease (Kweon et al, 2004; Tieu et al., 2003), hypoxia/ischemia (Suzuki et al., 2001,2002; Masuda et al., 2005; Ritter et al., 1996) and traumatic brain injury (TBI; Prins et al., 2004, 2005). Despite the evidence for greater uptake and metabolism of ketones by the younger brain, most of the research focus has been centered on the effects on the adult brain.

2.1 Neuroprotective Properties of Cerebral Ketone Metabolism

The increasing potential utility of cerebral ketone metabolism has directly resulted from the growing evidence for multiple neuroprotective mechanisms. Ketone metabolism has been shown to improve cellular bioenergetics, antioxidant effects, ani-inflammatory traits, and anti-apoptotic properties (Maalouf et al., 2009; Veech et al., 2004). Administration of ketones has been shown to prevent ATP decline following cellular oxidative challenges (Hace et al., 2009), inhibitors of mitochondrial respiration in hippocampal neurons (Kim et al., 2010), and from ischemia in the younger brain (Suzuki et al., 2001, 2002).

The antioxidant effects are achieved through several possible mechanisms including (1) decrease ROS production in juvenile mice (Sullivan et al., 2004) and in dissociated neonatal cortical cells (Maalouf et al., 2007), (2) increased glutathione levels and glutathione peroxidase activity in adult rats (Jarrett et al., 2008; Ziegler et al., 2003), (3) increase uncoupling protein expression in juvenile mice(Sullivan et al., 2004), (4) direct scavenging properties of ketones in cultured hippocampal neurons (Haces et al., 2008), (5) the effects of acetate on neurotransmission (Juge et al., 2010).

Ketones have also been shown to decrease cell death in response to various pathological challenges. Adult rats given the ketogenic diet +TBI were shown to have lower levels of Bax mRNA, Bax protein and cytochrome c release than standard fed TBI animals with consequent 8% less apoptosis at 72hrs post injury (Hu et al., 2009a,b). Similar 3-week ketogenic fed young rats showed increased Bcl-2 expression and 50-70% decrease in infarct volume after focal ischemia (Puchowicz et al., 2008). PND21 rats on the KG diet for 4 days prior to insulin-induced hypoglycemia also showed significantly less neuronal death than standard fed rats (Yamada et al., 2005).

Evidence for ketogenic anti-inflammatory effects has emerged in both models of traumatic brain injury and ischemia. Adult head injured rats on the ketogenic diet showed decreased in wet weight/dry weight ratio at 3 days post injury (Hu et al., 2009a,b). PND56 mice infused with ßOHB after middle cerebral artery occlusion showed significant decrease in edema (Suzuki et al., 2002). The anti-inflammatory effects of ketone metabolism do not appear to be restricted to the brain as hindpaw swelling after thermal nociception testing was also decreased in juveniles and adults on the KG diet (Ruskin et al., 2009). There are important age related differences in cerebral maturation of bioenergetics, free radical defenses, cell death mechanisms and swelling that can contribute to differential responses to potential ketogenic therapy. These changes emphasize the continued need to examine the numerous effects of ketone metabolism within different chronological age groups.

2.2 Age and Ketone Use After Traumatic Brain Injury

While the normal developmental changes associated with cerebral substrate metabolism are established after weaning, the response of the brain to injury continues to show relevant age differences. There are age-related differences in ketogenesis, induction of transporter expression and cerebral uptake of ketones after brain injury. The same age differences in the rates of ketosis that have been observed following starvation are also seen among traumatic brain injured (TBI) animals on the KG diet (Figure 1). PND35 rat placed on the KG diet

immediately after injury show 3-fold increases in plasma ßOHB within 6 hrs. PND75 rats do not show significant increases in plasma ßOHB until 24hrs. The age differences in the rates of ketogenesis have significant impact on approaches for therapeutic interventions. While enteral delivery of ketones to the younger brain after injury maybe sufficiently raise plasma ketones within an appropriate therapeutic window, more rapid forms of administration are likely required for the adult brain after injury.

Similar to ketogenesis, the normal age differences in substrate transporters and metabolism are exacerbated by brain injury. While the expression of primarily neuronal ketone transporter (MCT2) has been shown to be elevated in PND35 rats compared to PND75 rats, TBI induces further 60% increase of MCT2 in the endothelia of PND35 rats and only 25% in adult rat brains (Prins and Giza, 2006). The expression of the primary endothelial ketone transporter (MCT1) was also increased 2.3-fold in PND35 rats at 24hrs post-injury, but not in PND75 rats (Prins et al., 2007). The mechanism for the tranporter induction is currently unknown, but the greater expression of the transporters is likely to contribute to the age differences in ketone uptake after injury.

There are particularly interesting age and species differences in the effects of ketone uptake on brain glucose uptake. In adult rodents, increases in plasma ketones have no effect on cerebral uptake of glucose. However, younger rats infused with ßOHB show a significant reduction in brain glucose uptake in PND20 (Miller et al., 1986) and PND45- 55 (LaManna et al., 2009). Higher order animals and humans all show decreases in cerebral metabolic rates of glucose in response to ketosis regardless of age (Kammula, 1976; Redies et al., 1989, Hassselbalch et al., 1994,1996). Consistent with the age differences in rodents, glucose uptake decreased by an additional 13% only among PND35 TBI animals on the KG diet (Prins and Hovda, 2009). The metabolism of ketones under these circumstances may flood the acetyl-CoA pool, inhibit pyruvate oxidation and thereby decrease glucose uptake via glycolytic inhibition (Randle et al., 1966; Ruderman et al., 1974).

Substitution of cerebral metabolic fuels may be exactly what the younger brain requires after TBI. The rapid brain deformation from TBI initiates a rapid cascade of metabolic changes that ultimately results in a period of glucose metabolic depression in the brain (Yoshino et al., 1991; Thomas et al., 2000; Prins & Hovda, 2009). During this decrease in cerebral glucose uptake, glucose is also diverted to other biochemical pathways (pentose phosphate pathway) (Bartnik et al., 2005) and glycolytic metabolism of glucose is further impaired by low levels of cytosolic NAD^+ (nicotinimide adenine dinucleotide; Figure 2). Given the obstructions and diversion of the brain's primary fuel source, metabolism of ketones should improve cellular energy production, cell survival and functional outcome.

Administration of ketones via the ketogenic diet after TBI has been shown to improve cellular ATP (Ying et al., 2009), decrease contusion volume (Prins et al.,2005; Prins and Hovda, 2009), and improve motor and cognitive performance (Appelberg et al., 2009) in the PND35 rats. More recently, PND35-40 rats on the KG diet after TBI showed decreased edema at 3 days post-injury, decreased cytochrome c release and less apoptosis than standard fed animals (Hu et al., 2009). Collectively, these studies emphasize the promising effects of brain ketone metabolism in the younger brain after traumatic brain injury.

2.3 Age and Ketone Use After Ischemia

In addition to TBI, The beneficial effects of ketone metabolism have also been documented in juvenile models of hypoxia/ischemia. PND35 mice infused intravenously with ßOHB before or after bilateral carotid artery occlusion showed less edema, improved ATP and lower levels of lactate (Suzuki et al., 2001). In a subsequent study, Suzuki et al., (2002) showed infusion of ßOHB after transient middle cerebral artery occlusion to decrease infarct

volume, lipid peroxidation and cognitive deficits. Even 1hr delay of ßOHB infusion provided neuroprotection from transient occlusion. A more recent study has focused on understanding the protective mechanisms of the ketogenic diet for ischemia. PND28 rats were fed the KG diet for 3 weeks prior to or infused intraventricularly for 4 days prior to middle cerebral artery occlusion (Puchowicz et al., 2008). Infusion and diet both resulted in 55-70% reduction in infarct volume, 3-fold increase in HIF1alpha and Bcl-2 proteins and 55% increase in succinate. The authors propose that the elevation in succinate inhibits the enzyme that degrades HIF1alpha thereby increasing neuroprotection.

2.4 Age and Ketone Use After Other Challenges

The effects of ketone metabolism on conditions of hypoglycemia have also been studied in the younger brain. PND21 rats maintained on the KG diet for 4 days prior to insulin-induced hypoglycemia showed significantly less neuronal cell death than standard fed rats (Yamada et a., 2005). The KG fed rats were also able to maintain upright posture, walk and show protective reflexes during tail suspension.

Ketone metabolism has been shown to reduce cerebral inflammation in the younger brains after TBI and ischemia, and more recently shown to reduce peripheral swelling following a model of pain. PND21 and adult rats were given KG diet for 3 weeks before hindpaw thermal nociception testing (Ruskin et al., 2009). Both age groups on the diet showed increased tolerance to pain and reduced peripheral swelling, though the anti- inflammatory response was greater in the juveniles.

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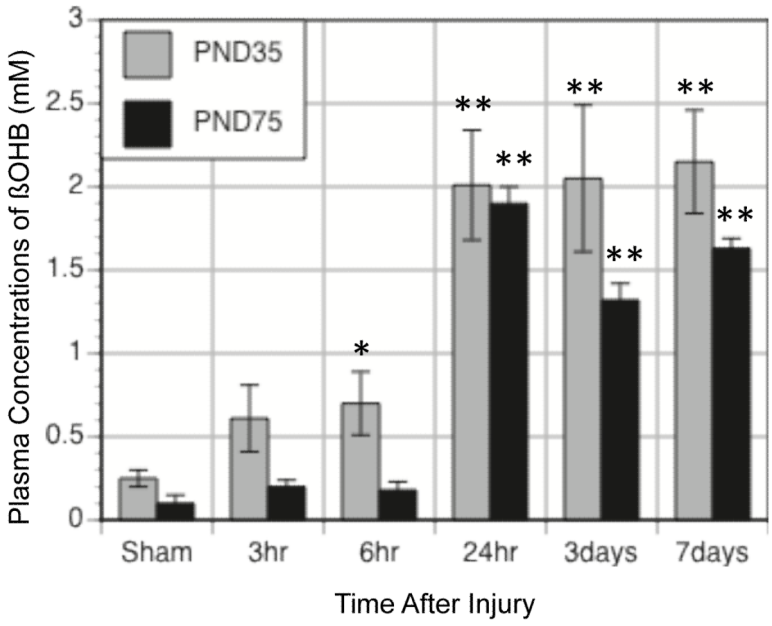

Figure 1.

Changes in plasma concentrations of ßOHB with time after TBI in PND35 (grey bars) and PND75 (black bars) rats maintained on the KG diet after injury. PND35 animals achieve higher levels of ßOHB earlier than PND75 animals. Data is expressed as mean ±sem. *, ** $p<0.05$, 0.01 relative to age-matched sham

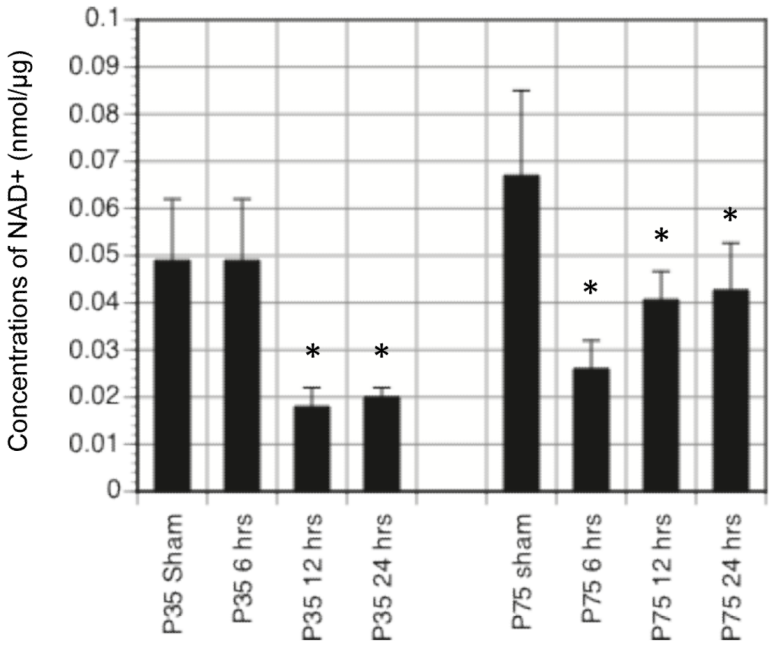

Figure 2.

Concentration of cytosolic NAD+ (nmol/µg) in PND35 and PND75 rats at 6, 12, 24hrs post injury. Animals were given sham or CCI injury and at 6,12,or 24 hrs after injury brains were rapidly removed, the cortical tissue dissected and homogenized ice cold homogenization media (0.25 sucrose, 3mM Tris, pH 7.4,1mM EGTA) with a Dounce homogenizer. The homogenate was centrifuged at 17,000g at 4°C for 10min. The cytoplasmic fraction was removed and analyzed for NAD^+ concentrations (Nisselbaum and Green,1969). Cytosolic NAD^+ decreases significantly after TBI in both age groups and will likely contribute to glycolytic inhibition via GAPDH.