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DIET, KETONES AND NEUROTRAUMA

Mayumi Prins, Ph.D.
UCLA David Geffen School of Medicine, Department of Neurosurgery

SUMMARY

The annual incidence of traumatic brain injury far exceeds the rates of any other disease in the United States, yet progress towards age-relevant therapies, attention to patients needs and research funding have all been minimal. Cerebral metabolism of glucose has been shown to be altered after head injury and increasing cerebral metabolism of alternative substrates (ketones) has been shown to be neuroprotective in several models of traumatic brain injury. This altered dietary approach may have tremendous therapeutic potential for both the pediatric and adult head injured populations.

Keywords

ketones; brain substrate; metabolism; injury; development

Traumatic brain injury (TBI) remains the most under-addressed pediatric health issue in the United States. Each year TBI affects 1.5 million people, almost half of whom are children and young adults. Each year 300,000 children survive TBI and are discharged with life-long disabilities. This silent epidemic is the number one cause of death and disability among children. While age-specific treatment options have yet to be established, improving cellular metabolism with dietary approaches may provide therapeutic options in the near future.

Traumatic brain injury is generated by mechanical forces acting on the brain causing rapid movement of the brain in the skull. These biomechanical forces cause immediate release of neurotransmitters and disruption of ionic equilibrium across membranes. This chaos initiates an immediate but transient elevation in cerebral glucose metabolism, followed by a prolonged period of glucose metabolic depression (Yoshino et al., 1991). The pattern of glucose metabolic changes is similar among postnatal day (PND)17 rats, but the duration of the metabolic depression is significantly truncated (Thomas et al., 2000). During this period of depressed glucose metabolism there is an increase in flux of glucose through the pentose phosphate pathway (Bartnik et al., 2005), decreased Mg^{++}, free radical production, and activation of PARP (poly ADP ribose polymerase) via DNA damage (Hall, 1993). PARP-mediated DNA repair process can deplete cytosolic NAD^{+} (nicotinamide) pool and can decrease GAPDH activity (glyceraldehydes 3 phosphate dehydrogenase, a key enzyme in the glycolytic pathway). Disruption of cellular metabolism results in increased cell death and behavioral dysfunction.

Please address all correspondence to: Mayumi L. Prins, Ph.D., Division of Neurosurgery, UCLA School of Medicine, Room NPI 18-228, Box 957039, Los Angeles, CA 90095-7039, Telephone: (310) 825-0646, Fax: (310) 794-2147, E-mail: mprins@mednet.ucla.edu.

Disclosures

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Dietary supplements have been used to restore energetic and ionic deficiencies after TBI. Post-injury decreases in ATP have been treated with creatine supplementation after controlled cortical impact injury in the adult rodent (Sullivan et al., 2000). Administration of creatine 4 weeks prior to injury decreased contusion volume by 50%, improved ATP and mitochondrial bioenergetics. Similarly, Mg^{++}, which is essential for glycolytic and oxidative enzyme function, decreases after TBI and supplementation with Mg^{++} after injury also improves histology, behavior and edema (McIntosh et al., 1988).

In contrast to dietary approaches to re-establish TBI-induced deficiencies in brain metabolites, diets have also been used to replace or redirect essential brain substrates. TBI-induced impairments of the glucose metabolic machinery may make glucose a less favorable *energy* substrate. In fact, hyperglycemia has been long associated with poor outcome after TBI. Early administration of glucose after severe TBI suppresses ketogenesis, increases insulin and increases lactic acid production (Robertson et al., 1991). TBI patients who were fasted or maintained on a ketogenic-like diet to minimize hyperglycemia showed significantly lower plasma glucose and lactate concentrations, elevated ß-hydroxybutyrate levels and better urinary nitrogen balance compared to standard fed patients (Ritter et al., 1996). Similar plasma substrate changes were observed with 24-hr starvation in the adult rodent after controlled cortical impact injury. The fasted animals showed significant cortical tissue preservation, improved cognitive outcome and improved mitochondria bioenergetics (Davis et al., 2008). The neuroprotection associated with acute starvation was determined to be associated with the ketosis and not hypoglycemia. These studies bring to question the current standards for patient management of plasma glucose levels after TBI and suggest that replacing or redirecting the brain's primary fuel source with an alternative substrate may be beneficial.

Cerebral metabolism of ketone bodies (ß-hydroxybutyrate, acetone and acetoacetate) alters mitochondrial metabolism which improves metabolic efficiency, increases the $\Delta G'$ of ATP hydrolysis, and decreases the production of free radicals (Veech, 2004). These metabolic properties of ketones are thought to contribute to their neuroprotective potential and have recently been applied to the juvenile brain post-injury.

While the adult brain is not static in its fuel options, the ability of the brain to increase reliance on alternative fuel metabolism appears to be age-dependent, even after weaning. This fact has been particularly important following TBI where rapid changes require early intervention. Administration of ketones during this period of glucose metabolic depression has resulted in age-related neuroprotection. Postnatal day (PND) 35 and PND45 rats placed on a ketogenic diet immediately after controlled cortical impact injury showed 58% and 39% reduction in cortical contusion volume at 7 days, respectively (Prins et al., 2005). PND35 rats were also shown to have improved motor and cognitive performance (Appelberg et al., 2007). PND65-75 and PND17 rats failed to show ketogenic neuroprotection after injury. The lack of neuroprotection among PND17 animals may be due to the fact that both glucose and ketones are essential substrates for brain development, unlike post-weaned age groups where ketones serve as an alternative substrate. In contrast to PND17, the cerebral uptake of ketones may be insufficient during the acute post-injury period among PND65-75 rats. Recent studies have shown an age-dependent increase of both monocarboxylate transporter (MCT)2 and MCT1 expression after TBI in the ipsilateral cortical microvasculature (Prins and Giza, 2006; Prins et al., 2007). The greater magnitude of MCT1 and 2 expression in the juvenile brain at 6 and 24 hrs post-injury may contribute to a greater and more rapid ketone uptake during the critical early changes after TBI.

The ketogenic diet is composed of various types of fatty acids (FA) which are broken down by the liver and increase plasma ketones. Unlike ketones, FAs are not readily transported

into the brain (with a few exceptions). Dietary administration of omega-3 FA for 4 weeks prior to TBI improved cognitive performance and normalized markers of plasticity (Wu et al., 2004). However, not all FAs are created equal. In order to mimic the typical American fast-food diet, adult rodents were given a high-fat/high sucrose diet 4 weeks prior to fluid percussion injury. Injury alone resulted in impaired cognitive performance and decreased BDNF, synapsin I and CREB. Both the cognitive and molecular markers of plasticity were further worsened on the high fat/high sucrose diet (Wu et al., 2003).

This brief review summarizes the reported effects of dietary approaches, especially ketones, on neurotrauma. Whether ketosis is achieved by starvation or administration of a ketogenic diet, the common underlying conditions of low plasma glucose in the presence of an alternative substrate (ketones) have consistently shown neuroprotective effects after various types of brain injury. If TBI induces altered glucose processing then maintenance of “normoglycemia” may not be the optimal approach. As the evidence accumulates, the current TBI patient management guidelines of plasma glucose regulation may need to be revisited as will the establishment of age-specific guidelines.

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