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PREVENTION OF HEAD TRAUMA: IS THERE A ROLE FOR NUTRITIONAL SUPPLEMENTATION?

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- Sports-related concussions are a growing public health concern, with ~1.6-3.8 million occurring in the United States annually. However, considering sports-related concussions alone neglects the importance of sub-concussive head impacts sustained in contact sports.
- The concussive and sub-concussive impacts sustained throughout long-term contact sports participation may lead to long-term neurological impairments and an increased risk of developing neurodegenerative diseases.
- In addition to being unsuccessful, pharmacological interventions aimed at mitigating the damage associated with head trauma have solely focused on treatment and not prevention. A common problem for targeted drug therapy lies within the notion that drugs are often designed to treat one specific process related to the pathological events of injury. With head trauma, the injury cascade is multifaceted, and thus interventions that target multiple pathologies are warranted.
- A prophylactic strategy that enhances both neuronal membrane integrity as well as the post-injury metabolic cascade would be invaluable. This type of intervention would not only mitigate the deleterious effects of concussion, but also provide enhanced protection from sub-concussive impacts.
- Promising pre-clinical investigations of several nutritional supplements including creatine, curcumin and docosahexaenoic acid (DHA) have emerged as viable alternatives to pharmaceuticals to protect against the deleterious effects of sub-concussive and concussive injuries. Biologically, nutritional supplements may act to mitigate neurological damage via multiple mechanisms within the complex neurochemical and neurometabolic consequences that occur with concussive and sub-concussive impacts.

INTRODUCTION

It is estimated that 1.6-3.8 million sports-related concussions occur each year in the United States. However, those numbers likely underestimate the total number of sports-related concussions that occur as many injuries may go undetected and/or not be reported to the appropriate medical personnel. A type of mild traumatic brain injury (mTBI), a concussion results from either direct or indirect biomechanical forces acting on the head or neck. While the overt pathological consequences of traumatic brain injury (e.g., hemorrhage or edema) are not detectable following concussion, advanced technologies can identify quantifiable neuronal damage associated with concussion. Furthermore, emerging evidence suggests that sub-concussive impacts, in the absence of a concussion diagnosis, result in measurable pathophysiological changes as demonstrated by advanced imaging (Koerte et al., 2015) and fluid biomarker quantification (Zetterberg et al., 2013). Moreover, sub-concussive head trauma associated with contact sport participation may also have important implications regarding long-term brain health (Bailes et al., 2013).

To date, much of the research aimed at attenuating the pathophysiological response to injury has focused on post-injury pharmaceutical intervention. The shortcomings of that strategy are evident in that it first neglects those concussions that go unreported and secondly it does not address the evidence linking sub-concussive impacts to long-term brain health. The pathophysiology of mTBI is complex and pharmaceutical interventions often target one aspect of the multifaceted injury cascade. Though most of the current evidence has been limited to animal models, nutritional supplementation strategies aimed at mitigating the deleterious effects of head trauma, both concussive and sub-concussive, have shown considerable promise. Therefore, the purpose of this Sports Science Exchange article is to highlight some of the nutritional supplementation interventions that have been used prior to injury. However, before discussing these interventions, a brief review of pathophysiology is needed.

PATHOPHYSIOLOGY OF BRAIN INJURY

In sport, the forces that result in a concussion are heterogeneous in nature. This is very different from the comparatively homogeneous animal models of experimental TBI and mTBI. Despite the impracticalities of simulating sports-related concussion in the laboratory, animal models of injury have provided key insights regarding the pathophysiology discussed herein. Following head injury, both the structural and biochemical organization of the brain is affected (Barkhoudarian et al., 2016; Giza & Hovda, 2014). Gross manifestations of severe brain injuries such as hemorrhage or edema are not present following sports-related concussion. Instead, the cellular pathophysiological changes manifest as functional disturbances (Giza & Hovda, 2014).

Initially, the rotational and linear forces of insult induce vulnerability to the structural integrity of the neuronal cell membrane. This mechanical insult causes a sudden flux in ionic gradients (i.e., efflux of potassium and influx of sodium and calcium) across the neuronal cell membrane. As membrane potential is altered, excitatory neurotransmitters are indiscriminately released resulting in rapidly spreading depolarization.

To restore resting membrane potentials and ionic concentration gradients the neuron relies on large amounts of energy in the form of adenosine triphosphate (ATP) to power the sodium-potassium (Na^+/K^+) ATPase pumps. Immediately following injury, cellular metabolic needs are met via upregulation of the glycolytic pathway. However, decreases in cerebral blood flow following injury result in decreased oxygen and glucose availability, eventually creating a mismatch between the supply and demand for ATP within the brain. The energy crisis within the neuron is worsened via a concurrent cellular influx of calcium which is sequestered in the mitochondria and contributes to impairment of the mitochondria's ability to generate ATP via oxidative phosphorylation. Reliance upon anaerobic oxidative pathways to meet the ATP demands of the cell results in an acute accumulation of lactate and local acidosis and a depletion of phosphocreatine (Barkhoudarian et al., 2016; Giza & Hovda, 2014). While lactate can be a fuel source for neurons to help meet ATP demands, to sustain this process mitochondrial function and aerobic pathways are once again necessary (Barkhoudarian et al., 2016).

The energy crisis results in an eventual metabolic depression which may last days past the initial injury. Furthermore, sustained ionic imbalances alter the redox state of the cell creating an environment ripe for the increased production of reactive oxygen species (ROS) and resultant oxidative stress which reduces the antioxidant capacity of the cell allowing cellular damage, primarily in the form of lipid peroxidation (Giza & Hovda, 2014).

No injury would be complete without an inflammatory response, and mTBI is no exception as there is evidence of a local immune response following experimental head injury (Giza & Hovda, 2014). Post-injury, microglia, the resident immune cells of the brain, are found to be activated. Further evidence of an immune response is observed via upregulated pro-inflammatory genes and an increase in the number of pro-inflammatory cytokines. The post-injury inflammatory response may be neuroprotective in nature. However, prolonged neural inflammation may be responsible for long-term complications from mTBI and perhaps repetitive sub-concussive injuries alsoκ result in prolonged neural inflammation.

CREATINE AND BRAIN INJURY

Creatine (Cr; N-aminoimimomethyl-N-methylglycine) is endogenously synthesized from glycine, arginine and S-adenosyl-L methionine in the kidneys, liver, pancreas and to a lesser extent, the brain (Braissant et al., 2001), and also consumed in the diet (i.e., meat and fish). In conjunction with the post-injury energy crisis, the tight coupling of Cr to the creatine kinase/phosphocreatine system may be the cause of the decrease in brain Cr that is observed following a sport-related concussion which appears to be dependent on severity (Vagnozzi et al., 2013). Prophylactic treatment with Cr in animal models of TBI has resulted in the maintenance of energy homeostasis as measured by reduced free fatty acid formation, lactate accumulation, and decreased oxidative stress which occurs subsequent to the energy crisis (Scheff & Dhillon, 2004; Sullivan et al., 2000). Scheff and Dhillon (2004) fed male Sprague-Dawley rats a diet consisting of 0.5 or 1% creatine monohydrate (CrM) for 2 wk prior to injury (moderately controlled cortical contusion). Lower levels of both free fatty acids and lactate were observed in animals fed CrM. Further, a dose-dependent effect was observed such that those animals fed the higher dose (1%) exhibited greater neuroprotection. Sullivan et al. (2000) reported similar results regarding energy homeostasis, but also reported lower production of ROS in animals fed CrM. In that study, animals were fed diets similar in Cr content but the diets were initiated at different pre-injury time intervals. Those fed for a longer period of time were afforded greater protection, primarily as evidenced by tissue sparing. Despite evidence supporting the potential neuroprotective properties of Cr, no studies to date have examined Cr supplementation prior to sports-related concussion or other mTBI/TBI in humans.

While the total body Cr pool can be increased through the ingestion of foods high in Cr, additional intake of foodstuffs may be of concern for athletes, due to the increased caloric intake. Supplementation with CrM is known to increase brain Cr content. For example, supplementation with 20 g of CrM in a single bolus dose has been reported to increase the total brain Cr pool, which was augmented when the supplementation period was extended (Dechent et al., 1999). These authors fed young healthy volunteers either 20 g of CrM in a single bolus or 20 g of CrM spread out into 4 x 5 g doses/day for 4 wk. Though both groups increased total brain Cr content, those ingesting CrM for the longer period had larger increases.

CURCUMIN AND BRAIN INJURY

Curcumin, the major yellow pigment and bioactive component of the commonly used spice in Indian and Southeast Asian cuisine, is a pleiotropic molecule (interacts with many molecular targets) that has a long history of medicinal use due to antioxidant and anti-inflammatory properties (Gupta et al., 2012). The high content of polyunsaturated fatty acids (PUFAs) makes the brain particularly susceptible to lipid peroxidation in the presence of ROS (Ansari et al., 2008). The anti-oxidative properties of curcumin were perhaps best demonstrated by Wu et al. (2006), who fed male Sprague-Dawley rats a regular diet or a diet high in saturated fat with or without curcumin (500 ppm) for 4 wk prior to TBI (fluid percussion injury). Diets high in saturated fat increase free radical formation and exacerbate the negative effects of TBI on cognition and neuroplasticity. Curcumin supplementation attenuated the damage associated with TBI as evidenced by reduced levels of oxidized proteins and normalized levels of brain-derived neurotrophic factor (BDNF) and its downstream effectors (Wu et al., 2006). BDNF and downstream effectors play a role in cognitive processes, which was supported by better performance in the Morris water maze by rats fed curcumin (Wu et al., 2006).

The anti-inflammatory properties of curcumin are primarily attributed to the ability of curcumin to suppress inflammation by inhibiting IκB Kinase (IKK) signaling complex, thereby preventing the activation of nuclear factor-kappa B (NF-κB) (Jobin et al., 1999). NF-κB regulates the release of many pro-inflammatory cytokines. Cerebral edema, which can occur

following TBI, has been suggested to be a result of activation of the pro-inflammatory transcription factor NF-κB and the pro-inflammatory cytokine interleukin-1ß (IL-1ß) (Laird et al., 2010). To test the hypothesis that curcumin conferred pre-injury protection via attenuating cerebral edema, Laird et al. (2010) injected anesthetized mice with curcumin (75 or 150 mg/kg body mass) 15 min before TBI (controlled cortical impact). Pre-treatment with curcumin attenuated cerebral edema as measured by brain water content, irrespective of dose. However, only the high dose (150 mg/kg) reduced IL-1ß expression. Those data suggested that the anti-inflammatory properties of curcumin as it relates to brain injury are dose dependent. However, the neuroprotective effects of curcumin may not be limited to anti-oxidative or anti-inflammatory properties. Maintenance of energy homeostasis through modulation of the AMP-activated protein kinase (AMPK)/mitochondrial uncoupling protein-2 (UCP-2) pathway may be another potential target for curcumin. An increase in mitochondrial proteins, including AMPK, was reported by Sharma et al. (2009) following a 4 wk diet of curcumin prior to mTBI (mild fluid percussion injury).

Though no studies to date have been conducted in humans, a major hurdle to overcome is the low bioavailability of commercially available curcumin, in the form of turmeric. Poor solubility, low absorption from the gut, rapid metabolism and rapid systemic elimination are all limitations to the therapeutic potential of curcumin (Anand et al., 2007). While high doses of curcumin (10-12 g) have resulted in little to no appearance in the circulation (Lao et al., 2006), various methods have been used to increase the bioavailability of curcumin with varying degrees of success with a number of the unique formulations earning the distinction of generally recognized as safe (GRAS) from the United States Food and Drug Administration.

DOCOSAHEXAENOIC ACID AND BRAIN INJURY

Docosahexaenoic acid (DHA), an omega (ω)-3 fatty acid, is found in most mammalian tissues, but is highly enriched within the mammalian central nervous system (CNS) and is over 100-fold more abundant in the mammalian CNS than eicosapentaenoic acid (EPA), another ω-3 fatty acid. Even in the absence of dietary manipulation, neuronal DHA is found to be significantly reduced following experimental TBI (Wu et al., 2014). In rodents, dietary restriction of DHA elicits a heightened response to experimental TBI as evidenced by neurophysiological and functional disturbances (Desai et al., 2014). Though no precise mechanism has yet been elucidated in support of those findings, the importance of DHA in the CNS cannot be understated.

There is a large body of evidence suggesting that rodents supplemented with DHA prior to experimental TBI exhibit enhanced resilience to brain injury with functional outcomes mirroring those of biological indicators of injury. Chiefly, pre-injury supplementation with DHA mitigates white matter damage. The mechanism by which the integrity of white matter is preserved is multidimensional and not fully understood, but there is evidence that DHA supplementation bestows metabolic protection via decreasing post-injury calcium influx (Wang et al., 2003) thereby allaying post-injury glutamate cytotoxicity (Wang et al., 2003) and suppressing mitochondrial dysfunction and the eventual development of ROS (Wu et al., 2007).

The neuroprotective effect conferred by DHA supplementation is elicited at varying doses in rodent models of TBI, but the greatest effect is observed at a dose corresponding to 40 mg/kg/day (Mills et al., 2011) which corresponds to a dosage of ~3.6 g/day in a 90 kg athlete. Dietary sources of ω-3 FAs are limited, with cold water algae being the primary producers of DHA and EPA and fish the primary dietary source. Hence, worldwide consumption is low and nutritional supplementation is recommended. Supplementation is easily achieved, as a dose-dependent relationship exists whereby plasma phospholipid DHA concentrations increase up to a dosage of ~2 g/day after which any further increase in dose negligibly increases plasma phospholipid concentration (Arterburn et al., 2006).

Despite the body of evidence suggesting a neuroprotective effect of nutritional supplementation, very few studies to date have been conducted in humans. This may be due to the logistical difficulties of conducting well-designed large-scale studies in athletic populations. To that end, our research group recently investigated the effects of DHA supplementation on a blood biomarker of head trauma in American football athletes (Oliver et al., 2016). While concussions were excluded, it is known that the routine head trauma associated with a season of American football results in detectable neurophysiological damage which can be observed via advanced imaging (Koerte et al., 2015) and blood biomarker quantification (Oliver et al., 2016). In our study, American football athletes were randomly assigned to a control group or DHA of varying doses (2, 4 or 6 g/day). The larger doses were selected based on the size and physical activity levels of the athletes, as both are known to affect circulating fatty acids. Blood was sampled over the course of the season at specific time points corresponding to changes in the number and magnitude of head impacts. Based on our data, we concluded that DHA supplementation, irrespective of dose, attenuated axonal damage which is a characteristic of mTBI. It was also the most sensitive predictor of axonal injury when measured by serum neurofilament light polypeptide (Nf-L) (Zetterberg et al., 2013). However, inference to these data was limited due to several constraints including a small sample size and the inability to monitor head impact via telemetry systems. Additional examination of the data suggested that the low dose treatment group (2 g/day) was associated with the greatest attenuation in head trauma as measured by serum Nf-L (Oliver et al. 2016).

SUMMARY AND PRACTICAL APPLICATION

Athletes participating in contact sports are routinely exposed to impacts that may result in a sports-related concussion. However, even in the absence of a diagnosis, the routine impacts that are sub-concussive in nature also result in neuronal damage which can have long-term effects on brain health. Despite the use of helmets in some contact sports, they do not totally prevent or reduce the effect of impacts. Research has primarily been limited to treatment following injury, but given that sub-concussive impacts result in neuronal damage and the fact that a large

percentage of concussions may go unreported, preventing the deleterious effects of head trauma deserves greater attention. In that regard, nutritional supplementation warrants further study and discussion. Unlike pharmaceutical treatments that may target a single mechanism, nutritional supplementation has the potential to target multiple pathways in the complex secondary events that occur following an injury.

The nutritional supplementation interventions presented here (creatine, curcumin, DHA) have all been studied extensively in animal models. Moreover, an abundance of research exists examining the effect of the nutritional supplementation in humans suffering from other neurological disorders that affect similar pathways associated with sub-concussive and concussive impacts. However, little research exists on the potential of these nutrients to prevent and/or reduce the deleterious effects associated with sub-concussive and concussive impacts. While more research is warranted, the evidence in animal models supports the use of these nutrients for neuroprotection. As always, sports nutritionists, athletes and coaches must ensure that the testing of supplements to be used with athletes passes all required regulations set forth by institutions of oversight.

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