Nutritional role in concussion management and recovery

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Background

- Good nutrition is important for maintenance of mental and physical health.
- Nutrition is particularly important when recovering from physical trauma, such as concussion.
- When a concussion occurs, the brain requires extra energy in the form of nutrition to heal the injury.
biomechanical forces cause immediate release of neurotransmitters and disruption of ionic equilibrium across membranes.

- indiscriminate flux of ions (potassium efflux and calcium influx) through previously regulated ion channels
- Na/K/ATPase-dependent pump has to work in overdrive to reestablish equilibrium
- ATP (energy) is depleted
- Lactate= bioproduct of energy utilization; increases→ influx of Ca++→ vasoconstriction→ decrease cerebral blood flow→ decreased energy, increased reactive oxygen species

transient elevation in cerebral glucose metabolism, followed by a prolonged period of glucose metabolic depression

increase in flux of glucose through the pentose phosphate pathway, decreased Mg++, free radical production, and activation of PARP (poly ADP ribose polymerase) via DNA damage.

PARP-mediated DNA repair process can deplete nicotinamide and GAPDH activity (glyceraldehydes 3 phosphate dehydrogenase, a key enzyme in the glycolytic pathway).

Result: increased cell death and behavioral dysfunction.
Appetite may decrease

- Offer small, frequent meals
- Do not skip meals, especially breakfast
- Power snacks, such as fruit, 100 percent fruit juice, smoothies and trail mix (dried fruit, nuts, dark chocolate).
- Focus on good hydration
Use of supplementation

- As posted on the Food and Drug Administration (FDA) web site, “There is simply no scientific evidence to support the use of any dietary supplement for the prevention of concussions or the reduction of postconcussion symptoms that would allow athletes to return to play sooner”

- Numerous supplements, including omega-3 fatty acids (O3FA), curcumin, resveratrol, melatonin, creatine, and *S. baicalensis* as well as vitamins C, D, and E, have shown promising results in animal studies to aid in the recovery of traumatic brain injury by acting on one or more aspects of the neuromolecular cascade.

- Most nutritional recommendations for concussion are theoretical and extrapolated from animal models.
Omega 3 Fatty Acids

- Research has shown that supplementation with O3FA before sustaining a concussion can protect against reduced plasticity of neurons and impaired learning by normalizing levels of proteins associated with neuronal circuit function, cognitive processing, synaptic facilitation, neuronal excitability, and locomotor control.
- Can reduce biological markers of brain injury and cellular apoptosis.
- Can protect against oxidative stress created from a concussion.
- Can help maintain genomic stability and cellular homeostasis as well as decrease the amount of injury the brain requires/utilizes.
- There have not been any human studies with a high level of evidence to confirm these.
- Multiple animal studies show benefit with postconcussion and pretreatment dosing of fish oil.
  - 10 mg/kg of EPA and DHA per day in a 2:1 ratio or 10 mg/kg/d of DHA alone seem to be sufficient if started immediately after a concussion (within 24 h).
- Currently, there are two double-blind randomized control trials examining O3FA supplementation and concussions. Both of these studies are in progress and do not have any preliminary data to share.
The most prominent O3 PUFA in the mammalian brain is DHA (97%)
- highly concentrated in gray matter
- flexible structure
- contributes to the fluidity and function of neural and synaptic membranes.
- essential for normal neurologic development
- reduces synthesis of inflammatory cytokines
- has roles in neuronal differentiation, regulating gene expression, learning and memory, and neuronal plasticity
- improves neuronal function by supporting synaptic membrane fluidity and function, and regulating gene expression and cell signaling
- DHA must be supplemented as it is not produced by the human body.

Bailes and Mills found that DHA supplementation for 30 days following impact acceleration injury was associated with less diffuse axonal injury.
Risk of O3FA supplementation

— Side effects
  — Belching
  — bad breath
  — “fishy burp”
  — Heartburn
  — Nausea
  — loose stools

— Risk
  — There is more of a theoretical than practical risk of bleeding in athletes.
Nicotinamide/Vit B3

Nicotinamide, or vitamin B3, is a precursor of nicotinamide adenine dinucleotide (NAD+).
- NAD is essential for cellular health and energy conversion.
- Lower levels of NAD are associated with concussions as the brain taps its supplies to deal with them.
- Regulates some of the cell's metabolic, stress, and immune responses to physiological or pathological signals.
- Found in dairy milk, yeast, and beer.

A human trial of nicotinamide riboside supplementation in American football athletes is being conducted (NCT02721537). It is using Functional MRI to evaluate if NAD+ changes in a double blinded placebo controlled trial.
- Trial is using 750 mg/day for 12 weeks.

Promising animal studies are available.
Risk of Nicotinamide

- **Side effects**
  - Flushing
  - Nausea/upset stomach
  - Diarrhea

- **Risks (generally only at very high doses)**
  - Can increase liver damage
  - Can stomach ulcers
  - Increase glucose levels in DM
  - Hypotension
Riboflavin/Vitamin B2 and Magnesium

- Magnesium (Mg): essential mineral that helps stability of all polyphosphate compounds in cells. It binds to ATP to make ATP biologically active and is therefore essential for mitochondrial membrane stability and coupling of oxidative phosphorylation.

- The low Mg levels effectively unblock NMDA receptor channels, allowing for greater influx of Ca2+ causing deleterious intracellular damage.

- Studies in both animals and humans have shown that Mg depletion is significant after TBI and remains low for up to 4 d, which causes cells to be less capable of providing sufficient energy for repair and restoration, inducing apoptosis.

- Riboflavin is a major co-factor in oxidative metabolism.

- Riboflavin administration significantly improves behavioral outcome and reduced lesion volume, edema formation, and the expression of GFAP after traumatic frontal cortex contusion injury.

- Both are known for supplementation for migraine patients. Used together posttraumatically, have been found to reduce headaches.

- Administration of Mg plus riboflavin may provide better therapeutic action than each substance alone.
Riboflavin/Vitamin B2 and Magnesium
Risks and potential dosing

- Magnesium oxide: 400-500mg/day
  - Side effects
    - Abdominal cramping
    - Vomiting
    - Diarrhea
    - Low BP

- Riboflavin: 400mg/day
  - Side effects
    - Diarrhea
    - Excess urination
    - Dark yellow/orange urine
N-Acetyl Cysteine

- An animal study on the effects of NAC revealed significant behavioral recovery after TBI when NAC was administered within 60 min of injury.

- In humans, a double-blind placebo-controlled clinical trial in 80 soldiers who sustained a mild traumatic brain blast injury showed that more blast-injured soldiers were symptom free at day 7 compared with placebo.
  - Study dosing was a 4-g loading dose, 4 g daily (in two divided doses of 2 g morning and night) for 4 d, then 3 g in two divided doses of 1.5 g morning and night, best initiated within 24 h

- NAC is one of the only supplements to have clinical trials, though it is blast injuries not SRC.
N-Acetyl Cysteine Risk

- Side effect
  - Nausea
  - Vomiting
  - Diarrhea
  - Constipation

- Has major interaction with nitroglycerin causing vasodilation
Resveratrol

- Found in abundance in red wine, plants, and nuts
- Has been shown to have antioxidant effects. Exerts neuroprotective effects in degenerative neurological diseases
- Can increase cell survival by suppressing apoptosis that are mediated by a pathway induced by glutamate toxicity as well as improve motor performance, visual spatial memory, and behavior
- There is one human trial currently ongoing at the University of Texas Southwestern Medical Center. -The REPAIR study
  - double-blind, placebo-controlled randomized control trial measuring cognitive performance with ImPACT testing and axonal injury via magnetic resonance imaging in boxers. This study has been completed, but there has not been any data published.
- Study Dose: 500 mg/kg single dose at the time of the injury and then daily for 30 days
- No known side effects
Vitamins C and E

- Vitamin E: decreased functional neurological deficits and microscopic brain damage as well as a decreased amount of oxidative stress and amyloid accumulation

- Vitamin C as a free radical scavenger, also transforms vitamin E to its active form → decreased oxidative stress

- Vitamins C and E supplementation has been studied in humans who have sustained sTBI.

- At high dosages, vitamin E can cause hemorrhage when taking more than 800mg/d in adolescents

- Vitamin C has little danger in high dosages
  - May cause nausea, diarrhea, kidney stones, and gastritis when taking >2g/d
Vitamin D

- Recently, cells in the CNS have been shown to have vitamin D receptors that modulate gene transcription responsible for neuronal proliferation and maintenance of calcium homeostasis.

- By itself, vitamin D has not shown great promise for traumatic brain injuries, though in combination with progesterone, there are some promising results.

- Consider replacing vitamin D in athletes with low levels (<32 ng/mL)
  - 50,000IU weekly
  - 5,000IU daily
Melatonin

- Known to regulate circadian rhythms-- In patients with severe TBI, melatonin production was attenuated overnight and the timing of melatonin secretion was delayed
  - lack of normal sleep could be problematic for effective concussion healing and recovery
- a versatile hormone having antioxidative, antiapoptotic, neuroprotective, and anti-inflammatory properties
- Restores levels of oxidative stress markers, mitigate the damage of reactive oxygen species, and decrease the release of pro-inflammatory cytokines
- The only double-blind, placebo-controlled randomized trial taking place is examining the use of melatonin in children who have encountered a concussion and are having subsequent sleep issues. This clinical trial is ongoing with a planned end date in 2019 (Play Game Trial). They are looking at the therapeutic potential for neurobehavioural conditions (e.g. chronic pain, headaches, anxiety, etc.) in TBI
Melatonin Dosage and Risk

- Dose of 0.5mg-5 mg initially to advance the internal clock (usually late afternoon/early evening, such as 8:00 PM) and, after realignment, a maintenance dose just before normal bedtime is reasonable

- Risks
  - Nightmares
  - Headache
  - short-term feelings of depression
  - daytime sleepiness
  - Dizziness
  - stomach cramps
  - irritability
Curcumin/Turmeric

- Animal-based studies have shown that supplementation with curcumin before sustaining a concussion resulted in improved balance as well as transduction and monitoring of cellular energy.

- Supplementation after a concussion has been shown to improve cell membrane function, restoration of homeostasis, neuronal plasticity, synaptic plasticity, and neuronal signaling as well as significantly reduced neural inflammation by decreasing the levels of microglia and macrophages that aid in neuronal apoptosis.

- Curcumin protects the brain from lipid peroxidation and nitric oxide-based radicals and is found to improve cognition.

- There have been no human trials to date and currently there are not any human trials in the process of evaluating the effects of curcumin and concussion.

- Dose: 500mg/day of turmeric.
Creatine

- Known for aiding in muscle mass growth with weight lifting.

- Biochemically, creatine works in the CNS by donating a phosphoryl group to ADP to make ATP to help replenish energy stores → reduction of mitochondrial permeability, free oxygen radicals, and calcium levels.

- The predominant role of creatine is to maintain energy homeostasis by keeping cellular ATP levels constant in cells with high and fluctuating energy demands, such as those found in muscles and the brain.

- It is known that creatine levels in the brain decrease after sustaining a concussion.

- There have been two human-based randomized prospective studies using creatine supplementation in children after sustaining a moderate to severe TBI. Improved cognition, communication, self-care, personality, and behavior and significantly decreased headaches, dizziness, and fatigue.

- Based on these studies, creatine shows promise for the treatment of concussions; however, given that these studies were evaluating patients with sTBI with a longer time to recovery, it is not known if creatine would improve outcomes in patients with concussions whose symptoms are not protracted.
Creatine Dose and Risk

- Dose: 0.4 g/kg best if given within hours of the injury and split throughout the day
- Traditional supplementation protocols include a short (3-7 days) ‘loading phase’ with high-dose creatine (15-20 g/day split in 2-3 doses) and/or a longer duration ‘maintenance phase’ of 1-3 months (3-10 g/day split in 2-3 doses)

- Risk - mostly can be avoided by maintaining good hydration and splitting the dose into multiple increments
  - muscle cramping
  - Diarrhea/nausea/vomiting
  - Dehydration
  - water retention
  - mood alteration
  - kidney dysfunction
Ketogenic Diet

- 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.

- Increased glucose intake during concussion causes increase in insulin and increase in lactic acid which causes increased symptoms and prolonged energy crisis.

- Cerebral metabolism of ketone bodies (β-hydroxybutyrate, acetone and acetoacetate) alters mitochondrial metabolism which improves metabolic efficiency, increases ATP hydrolysis, and decreases the production of free radicals.

- Oxidative stress is responsible for mitochondrial dysfunction after TBI. Ketones decrease oxidative stress, increase antioxidants and scavenge free radicals.
Ketogenic Diet

- The ketogenic diet is a very low-carb, high-fat diet.
- Involves drastically reducing carbohydrate intake and replacing it with fat. This reduction in carbs puts your body into a metabolic state called ketosis.
- In Ketosis, your body becomes incredibly efficient at burning fat for energy. It also turns fat into ketones in the liver, which can supply energy for the brain.
- The high-fat low-carbohydrate ketogenic diet is already clinically established as a treatment for pediatric epilepsy. The strength of diet therapy is measured by the ratio of grams of fat: carbohydrate + protein, with the “dose” typically ranging from 1:1 to 4:1. In contrast, a standard American diet is roughly equivalent to a 0.3:1 diet ratio.
Glucose

1. Decrease in glucose uptake
2. Decrease in glycolytic processing of glucose
3. Increase glucose use by pentose phosphate pathway
4. Decrease ATP production
5. Increased oxidative damage to proteins, lipids, DNA

TBI Actions (white diamonds)

TCA

Ketone Action Sites (black diamonds)
A. 3 enzymatic steps to enter TCA cycle
B. Reduce NAD couple, which decreases mitochondrial free radical production
C. Increase energy of ATP
D. Increase glutathione peroxidase activity, decreasing cytosolic free radicals
Ketogenic Diet Risk

- Long-term use in the pediatric population has sometimes been associated with growth retardation, kidney stones, bone fractures due to osteopenia, and hypercholesterolemia; short-term side effects include low-grade acidosis, constipation, dehydration, vomiting or nausea, and hypoglycemia.

- There are no human clinical studies or animal studies that have specifically evaluated associations between the use of ketogenic diet and resilience prior to CNS injury.
“Recommendations”

- EPA and DHA: 10 mg/kg of per day in a 2:1 ratio or 10 mg/kg/d of DHA alone up to 2 g/d started within 24 hours
- Nicotinamide: 750 mg/day for 12 weeks
- Magnesium oxide: 400-500mg/day
- Riboflavin: 400mg/day
- N-Acetyl Cysteine: 4-g loading dose, 4 g daily (2 g BID) for 4 d, then 3 g (1.5 g BID), best initiated within 24 h
- Resveratrol: 500 mg/kg single dose at the time of the injury and then daily for 30 days
- Vit D: 50,000IU weekly or 5,000IU daily (for deficient athletes)
- Melatonin: 0.5mg- 5 mg
- Curcumin/turmeric: 500mg/day
- Creatine: protocols include a short (3-7 days) ‘loading phase’ with high-dose creatine (15-20 g/day split in 2-3 doses) and/or a longer duration ‘maintenance phase’ of 1-3 months (3-10 g/day split in 2-3 doses)
Any Questions?!


Resources