

Supplement Considerations In Concussion, Mild Traumatic Brain Injury and Post Concussion Syndrome (PCS)

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Neuronal Alterations Following Traumatic Brain Injury

Concussion and mild traumatic brain injury (mTBI) are the result of rapid deceleration of the brain with the skull that imparts shearing or torsional forces to neural tissue followed by metabolic and mechanical changes (2). The changes have been reported to include:

1. **Initially - disruption of the neurofilaments and microtubules** that provide a framework for axonal transport. This compromises anterograde and retrograde transport of molecular proteins to and from the cell body (somata).
2. **Proteolysis** - Axonal transport can also be affected by delayed, progressive injury secondary to proteolysis.
3. **Neural Membrane Disruption and Inflammation** - that leads to ionic shifts and an increase in intracellular glutamate and calcium. High intracellular glutamate is known to be toxic to brain cells. Some cells may ultimately undergo caspase-mediated apoptosis as a result of these cellular changes. Inflammatory cascades also contribute significantly to further brain cell dysfunction. Neuroinflammatory cascades play a significant role in the pathogenesis of disease following concussion and possibly repetitive subconcussive injury.
4. **Two Major Glucose Metabolism Alterations** - including hyperglycolysis and oxidative dysfunction with increase ROS.

5. **Mitochondrial injury** can also lead to failure in adenosine triphosphate (ATP) generation and an increase in reactive oxygen species. Decreased ATP production is thought to hinder nerve cell repair ability.
6. **Reduced Cerebral Blood Flow** – due to vasoconstriction (1)

Summary:

Diffuse axonal injury is well documented and is sometimes visible on MRI because of eventual cell death. Diffuse axonal injury is considered instrumental in causing cognitive sequelae, such as memory difficulties and concentration problems. The changes involve initial depolarization of neuronal membranes and the release of excitatory amino acids, particularly glutamate, which produces fluxes of calcium and potassium ions across neural and vascular tissue resulting in a hypermetabolic glycolytic state as the neurons attempt to restore equilibrium. There follows a calcium ion-induced vasoconstriction that reduces cerebral blood flow and glucose delivery with a resultant metabolic depression (brain energy demand not adequately met, which may last for days). These changes appear to render neural tissue more susceptible to further injury (2)

Preclinical and Human Supplementation Studies of Importance

Omega-3 Fats

Omega-3 polyunsaturated fatty acids are important structural components of all cell membranes modulating membrane fluidity, thickness, cell signaling, and mitochondrial function.

EPA and DHA are highly enriched in neuronal synaptosomal plasma membranes and vesicles, with DHA being the predominant omega-3 fat in neuronal membranes.

Neuronal DHA, in turn, influences the phospholipid content of the plasma membrane increasing phosphatidylserine and phosphatidylethanolamine production and promoting neurite outgrowth during both development and adulthood

Animal models show that fish oil effectively reduces post-traumatic elevations in protein oxidation resulting in stabilization of multiple molecular mediators of learning, memory, cellular energy homeostasis and mitochondrial calcium homeostasis as well as improving cognitive performance

DHA has provided neuroprotection in experimental models of both focal and diffuse traumatic brain injury

Studies in other models of neurologic injury have revealed a variety of potential mechanisms of neuroprotection, in addition to DHA and EPA's well-established anti-oxidant and anti-inflammatory properties.

Some studies show DHA provided prophylactically may reduce extent of brain damage in traumatic brain injury models

Curcumin

Curcumin is highly lipophilic and crosses the blood-brain barrier enabling it to exert a multitude of different established neuroprotective effects

Animal models show that curcumin supplementation results in significant reduction of neuroinflammation via inhibition of the pro-inflammatory molecules interleukin 1 β and nuclear factor kappa B (NF κ B). More importantly, the reduced neuroinflammatory response mitigated post-traumatic reactive astrogliosis and prevented upregulation of the water channel aquaporin 4, thus reducing the magnitude of cellular edema

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Animal studies demonstrate that curcumin is capable of significantly reducing post-traumatic elevations in lipid peroxidation and protein oxidation, as well as disturbances in plasma membrane turnover and phospholipid metabolism. Additionally, it has prevented reductions in proteins important for learning, memory, and synaptic transmission; and promoted cellular energy homeostasis. Post-traumatic administration of a curcumin supplement also improved injury-associated behavioral impairment, thereby suggesting that curcumin-induced normalization of multiple molecular systems may help preserve neuronal structure and function during the post-injury period.

Resveratrol

Resveratrol shown to cross the blood-brain barrier and improve outcomes in animal models following multiple acute neurological insults including stroke, global cerebral ischemia, spinal cord injury, and traumatic brain injury (TBI).

Resveratrol has also been demonstrated to slow the development of chronic neurodegenerative disease in animal models.

Although many of resveratrol's therapeutic benefits are classically attributed to its potent anti-oxidant effects, numerous studies have identified additional mechanisms of neuroprotection.

In adult rodents, administration of resveratrol resulted in reduced levels of oxidative stress and lipid peroxidation and stabilized endogenous anti-oxidants following TBI.

Other studies have demonstrated that resveratrol treatment reduces brain edema and lesion volume, as well as improves neurobehavioral functional performance following TBI. The molecular mechanisms underlying the aforementioned neuroprotection remain largely unknown.

Creatine

Mild TBI reduces brain creatine and phosphocreatine levels in rodent models, suggesting that resulting impairments in the maintenance of cellular energy may play a role in the evolution of secondary brain injury. Creatine is used to enhance ATP production. In the CNS, maintenance of cellular ATP levels is necessary for proper development and provides the cellular energy required to maintain the various cellular processes necessary for proper neuronal structure and function; including the maintenance of neuronal membrane potential, ion gradients underlying signal propagation, intracellular calcium homeostasis, neurotransmission, intracellular and intercellular signal transduction and neuritic transport.

More recent evidence also suggests that creatine may serve as a neuronal co-transmitter augmenting post-synaptic GABA signal transduction.

Studies of patients with CNS creatine deficiency and/or murine models with genetic ablation of creatine kinase have consistently demonstrated significant neurological impairment in the absence of proper creatine, phosphocreatine, or creatine kinase function; thus highlighting its functional importance.

Preclinical studies in a variety of experimental models have suggested that dietary creatine may provide neuroprotection in animal models of chronic neurodegenerative disease, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. The neuroprotective effects may also be conferred in acute neurological injuries, such as TBI

In rodents, pre-traumatic dietary supplementation with creatine monohydrate significantly reduced the magnitude of cortical tissue damage and the concentration of two biomarkers of cellular injury, free fatty acids and lactic acid, following experimental injury.

It was further elucidated that creatine-mediated neuroprotection is in part mediated by the maintenance of cellular ATP levels and improvements in mitochondrial bioenergetics; including increased mitochondrial membrane potential and reductions in mitochondrial permeability, reactive oxygen species, and calcium levels

In humans, studies utilizing nuclear magnetic spectroscopy have demonstrated that creatine supplementation does indeed increase cerebral creatine and phosphocreatine stores.

Several studies have suggested that creatine supplementation may also reduce oxidative DNA damage and brain glutamate levels in Huntington disease patients.

Another study highlighted that creatine supplementation marginally improved indices of mood and reduced the need for increased dopaminergic therapy in patients with Parkinson's disease. Together, these data suggest that dietary creatine supplementation may effectively increase CNS creatine/phosphocreatine stores and may modulate human neurological disease.

Human Pediatric Evidence – Preliminary results obtained in a pediatric population have suggested that post-traumatic oral creatine administration (0.4 g/kg) given within four hours of traumatic brain injury and then daily thereafter, may improve both acute and long-term outcomes. Acutely, post-traumatic creatine administration seemed to reduce duration of post-traumatic amnesia, length of time spent in the intensive care unit, and duration of intubation. At three and six months post-injury, subjects in the creatine treatment group demonstrated improvement on indices of self care, communication abilities, locomotion, sociability, personality or behavior and cognitive function when compared to untreated controls. Further analysis of the same population, revealed that patients in the creatine-treatment group were less likely to experience headaches, dizziness and fatigue over six months of follow-up. Creatine treatment appeared to be well tolerated and there were no significant side effects reported; which was consistent with other human studies utilizing higher dosages.

Green Tea

Antioxidant Epigallocatechin-3-gallate (EGCG) is capable of crossing the blood-nerve and blood-brain barrier, and exerting neuroprotective benefits in animal models of peripheral nerve injury, spinal cord trauma, and ischemic stroke.

Epigallocatechin-3-gallate also displays neuroprotective properties in animal models of chronic neurodegenerative diseases including amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease.

Epigallocatechin-3-gallate's neuroprotection has largely been attributed to its potent antioxidant and anti-inflammatory properties; however, a number of studies have identified additional neuroprotective mechanisms.

Vitamin E and Vitamin C

Vitamin E is a potent, lipid-soluble, anti-oxidant that is present in high concentrations in the mammalian brain.

In several animal models of brain injury such as ischemic stroke, subarachnoid hemorrhage and Alzheimer's disease, administration of alpha-tocopherol or its potent derivative alpha-tocotrienol has been shown to lessen oxidative stress and neuropathology.

Other laboratory studies have demonstrated that pre-traumatic alpha-tocopherol supplementation reduces TBI-induced increases in lipid peroxidation and oxidative injury and impairments in spatial memory.

Additional studies in transgenic mouse models of Alzheimer's disease have further demonstrated that pre- and post-traumatic vitamin E supplementation reduces lipid peroxidation, amyloidosis, and improves cognitive performance following repetitive concussive brain injury.

One other point of consideration is that in neurodegenerative disease states like Alzheimer's disease and Parkinson's disease, where there are high levels of reactive oxygen species generation, vitamin E can tend to become oxidized itself. For maximal effectiveness and to maintain its antioxidant capacity, vitamin E must be given in conjunction with other anti-oxidants like vitamin C or flavonoids. These various factors might account for the null effects of alpha-tocopherol supplementation in patients with MCI and Alzheimer's disease in some studies.

Human TBI – emerging evidence has suggested that daily intravenous administration of vitamin E following TBI significantly decreases mortality and improves patient outcomes when assessed at discharge and at two and six month follow-up time points. Importantly, no increase in adverse events was detected. This study also identified that high dose vitamin C administration following injury stabilized or reduced peri-lesional edema and infarction in the

majority of patients receiving post-injury treatment. Like vitamin E, vitamin C, also known as ascorbic acid, is a potent anti-oxidant present in high concentrations in the CNS. Given these similarities in action, it has been speculated that combined vitamin C and E therapy may potentiate CNS anti-oxidation and act synergistically with regards to neuroprotection.

Vitamin D

Research shows that cells in the brain not only possess the hydroxylase responsible for vitamin D activation, but that multiple regions in the brain abundantly express the nuclear vitamin D receptor. Binding of vitamin D to its nuclear receptor, in turn, leads to its association with other transcription factors, such as retinoic acid receptor. Subsequently this complex binds to vitamin-D response elements in genomic DNA, thus augmenting gene transcription. Vitamin D-induced alterations in gene transcription are now believed to modulate a myriad of neuronal properties including proliferation, differentiation and maintenance of calcium homeostasis.

Population based studies have suggested that vitamin D deficiency in the elderly is indeed associated with an increased prevalence of Parkinson's disease dementia, Alzheimer's disease, increased stroke risk and a higher prevalence of MRI findings suggestive of primary cerebrovascular lesions. The association between vitamin D deficiency and elevated stroke risk or other cardiovascular disease has been confirmed in other studies. Furthermore, a randomized controlled trial has suggested that post-ischemic administration of vitamin D may improve endothelial cell function.

In vitro and *in vivo* studies have suggested that vitamin D supplementation with progesterone administration may significantly enhance neuroprotection. Vitamin D deficiency may increase inflammatory damage and behavioral impairment following experimental injury and attenuate the protective effects of post-traumatic progesterone treatment. Progesterone is one of the few agents to demonstrate significant reductions in mortality following TBI in human patients in preliminary trials and phase III multi-center trials currently in progress (1)

CDP Choline and Lecithin

Cholinergic dysfunction is thought to underlie the memory impairment in patients with Alzheimer's disease, and thus, it is of interest that concussion patients show deficits in attention, and memory for new information (2).

Human studies in young and older subjects demonstrate that supplementation with CDP-choline and/or lecithin increase brain levels of acetylcholine. Both CDP-choline and phosphatidylcholine (found in lecithin) cross the blood-brain barrier (facilitated by the choline transporter) and are subsequently incorporated into neuronal membranes as part of their phospholipid structure. The choline in brain phospholipids serves a choline pool for incorporation into acetylcholine synthesis.

CDP-choline supplementation has been shown to activate the synthesis of structural phospholipids in the brain and other neuronal membranes, increase cerebral metabolism and acts on the levels of various neurotransmitters. Human trials reveal that it is effective in cases of senile cognitive impairment (e.g., Alzheimer's disease), slowing the evolution of the disease, and in the management of Parkinson's disease. Further, CDP-choline also has been shown experimentally to increase noradrenaline and dopamine levels in the central nervous system. Due to these pharmacological activities, CDP-choline has a neuroprotective effect in situations of hypoxia (oxygen starvation) and ischemia, as demonstrated that CDP-choline restores the activity of mitochondrial ATPase and of membrane sodium-potassium ATPase, inhibits the activation of phospholipase A², which otherwise triggers the formation of inflammatory prostaglandin-2 production. CDP-choline also has been shown to accelerate the resorption of cerebral edema in various experimental models. In studies carried out on the treatment of patients with head trauma, CDP-choline accelerated the recovery from post-traumatic coma and the recuperation of walking ability. Its use achieved a better final functional result and reduced the hospital stay of these patients, in addition to improving the cognitive and memory disturbances which are normally observed after head trauma of lesser severity and which constitute the disorder known as post-concussion syndrome. Of particular note is the fact that CDP-choline is well tolerated by patients and no serious side effects have occurred in any of the groups of patients treated with CDP-choline. Toxicology

studies also indicate that it is a safe intervention and highlight the fact that it produces no adverse effects on the brain's cholinergic system (3,4). Moreover, there is accumulating evidence that cholinergic agents (natural ones include CDP-choline, Huperzine A, Phosphatidylserine) may alleviate some of the cognitive deficits suffered by head-injured patients (2).

Nicotinamide and Tau Protein Integrity

Human Epidemiological Studies suggest that niacin intake is linked to reduced risk of Alzheimer's disease. Animal studies show that niacin supplementation reduces neurofibrillary tangle development in simulated Alzheimer's disease experiments

Nicotinamide administration led to an increase in tau proteins that strengthen microtubules

Nicotinamide slightly enhanced cognitive abilities in normal mice. "This suggests that not only is it good for Alzheimer's disease, but if normal people take it, some aspects of their memory might improve," said LaFerla, UCI neurobiology and behavior professor.

Scientists also found that the nicotinamide-treated animals had dramatically lower levels of the tau protein that leads to the Alzheimer's tangle lesion.

Human Equivalent Dosage: 1000 mg, three times daily (monitor liver enzymes as with nicotinic acid used to lower triglycerides and cholesterol) (5).

References

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Goals of Supplementation in Concussion, mTBI and PCS

1. Decrease Inflammation
2. Increase ATP energy via oxidative phosphorylation
3. Repair plasma membrane
4. Increase and support acetylcholine synthesis (and possibly other neurotransmitters- dopamine, serotonin, nor-epinephrine)
5. Provide increased antioxidant protection
6. Improve cerebral blood flow
7. Stabilize microtubules

Suggested Concussion Supplement Considerations:

- Omega-3 fats (high yield EPA/DHA fish oil) – 3,000 – 5,000 mg per day
- CDP-choline – 500 mg
- Memory Support Complex – (4 capsules per day) each capsule contains CDP- choline (50 mg); Phosphatidylserine (100 mg, 50% grade); Huperzine A (25 mcg); Bacopa Monnieri (50 mg, std to 20% bacosides)
- High Potency Multiple Vitamin and Mineral (including Vitamin C – 1000 mg, Vitamin E – 400 IU, B-50 complex, Vitamin D 1000 IU)
- Curcumin – 480 mg, three times daily
- Creatine Monohydrate (micronized) – 5,000 mg, twice daily
- Lecithin – 10 gm per day (2 tablespoons)

Additional Supplement Considerations

- Alpha-lipoic acid – 600 mg (1-3 times daily)

- Additional Vitamin E and Vitamin C (Vitamin E – 600 IU, Vitamin C – 1000-2000 mg)
- Additional Nicotinamide – 500-1000 mg daily (requires physician monitoring of serum levels of liver enzymes to guard against liver damage)