Brain Disorders & Therapy
ISSN: 2168-975X

Olivera et al., Brain Disord Ther 2015, 4:5
DOI: 10.4172/2168-975X.1000198

Short Communication Open Access

Combination Treatment of Natural Compounds and Integrative Therapies for Mild Traumatic Brain Injury

Anlys Olivera[1#], Heather L Rusch[1,2#], and Jessica M Gill[1*]

[1]National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA
[2]Henry M Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA
[#]First Co-Authours

Introduction

Each year millions of Americans seek acute care for mild traumatic brain injury (mTBI), which is often associated with a range of debilitating sequelae including cognitive, behavioral, emotional, and motor deficits [1]. New evidence indicates that neuroinflammatory responses, excitotoxicity, and oxidative stress may directly contribute to the emergence and maintenance of these chronic postconcussive symptoms (PCS) [2]. In instances of traumatic axonal injury, accumulations of tau and amyloid peptides can form, which may be an early sign of neurodegeneration linked to dementia and Alzheimer's disease [3]. Given the multiple mechanisms underlying PCS, it is reasonable to suggest that successfully preventing or attenuating PCS cannot be accomplished via pharmacological agents with a single mode of action. Herein, we propose that a combination of natural compounds and intergrative therapies with systemic effect may provide a comprehensive treatment strategy for addressing the secondary injury following mTBI.

Omega-3 Fatty Acids

Alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) make up the omega-3 fatty acids, and play a critical role in regulating neuroinflammation, modulating glutamate cytotoxicity, protecting against oxidative stress, and maintaining membrane and synaptic integrity [4]. Omega-3 fatty acids also support the promotion of axonal regeneration and neurogenesis following mTBI through the increase of cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) [5]. In animal models of Alzheimer's disease, supplementation with omega-3 fatty acids was related to increased improvements in global cognition, reduced concentrations of phosphorylated tau, and decreased soluble concentrations and neuronal accumulations of amyloid peptides [6]. These findings are of particular interest to our group because we have linked elevated concentrations of pro-inflammatory cytokines, tau, and amyloid-beta 40/42 to chronic PCS, which may contribute to the formation of neurofibrillary tangles and white matter changes indicative of early onset Alzheimer's disease following mTBI [7].

Curcumin

Curcumin is the active ingredient in turmeric, which has been used for centuries in traditional medicine to treat inflammatory diseases. Curcumin has potent anti-inflammatory and antioxidant effects that contribute to reduced neuronal excitotoxicity, increased neurogenesis, decreased lesion size, and improved cognitive function in animal models of mTBI [8]. As a potent free radical scavenger, studies have shown that curcumin inhibits the formation of reactive oxygen species, superoxide anion and hydroxyl radicals, and enzymes that catalyze pro-oxidant pathways, such as cyclooxygenase [9]. Oxidative stress can damage plasma membrane phospholipids, thereby interfering with the contribution of dietary omega-3 fatty acids to membrane stability. The addition of curcumin can therefore optimize the beneficial effects of dietary omega-3 as a therapeutic agent. Curcumin has also been shown to block the formation of amyloid-beta oligomers, prevent amyloid accumulation, and reverse existing amyloid pathology in animal models of Alzheimer's disease [8].

Resveratrol

Resveratrol is a stilbenoid found in the roots of polygonum cuspidatum, as well as red wine, grapes, berries, and peanuts. Importantly, resveratrol has a good bioavailability and can cross the blood brain barrier, which is an advantage over curcumin. As a potent anti-inflammatory and antioxidant agent, resveratrol has been shown to reduce neuroinflammation and promote neuroprotection in numerous in-vitro and preclinical paradigms by targeting multiple inflammatory pathways, including NF-κB, mitogen-activated protein kinases (MAPK), inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX-2) [10]. Relevant to neurodegenerative processes, resveratrol has been shown to reduce microglial activity and plaque density in animal models of Alzheimer's disease [11]. There is a paucity of research on the role of resveratrol on tauopathies in mTBI; however, its link to reductions in neuroinflammation and oxidative stress provides support for its potential to impede tau accumulation and neurofibrillary tangle formation, especially when part of a combined therapy.

Exercise

Exercise is the single most effective way of enhancing neurogenesis. More specifically, exercise has been found to increase levels of BDNF and glial cell line-derived trophic factor (GDNF), two key growth factors that support the survival of existing neurons and encourage growth and differentiation of new neurons and synapses in the cortex, basal forebrain, and hippocampus—brain regions implicated in executive function, learning, and memory. Moreover, exercise appears to support metabolic pathways that preserve DHA in the plasma membrane, which suggests that a combined treatment of dietary omega-3 fatty acids and exercise has additional therapeutic potential to attenuate the deleterious effects of mTBI on neurodegeneration and cognitive function [12]. Endorphins produced during exercise act as a potent antidote to cortisol, which may help to combat psychological stress associated with mTBI. Additionally, yoga may offer additional benefits of improved emotional regulation and enhanced motor coordination.

***Corresponding author:** National Institute of Nursing Research, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892 USA, Tel: +1 646-509-8303; E-mail: gillj@mail.nih.gov

Received November 26, 2015; **Accepted** December 09, 2015; **Published** December 17, 2015

Citation: Olivera A, Rusch HL, Gill JM (2015) Combination Treatment of Natural Compounds and Integrative Therapies for Mild Traumatic Brain Injury. Brain Disord Ther 4:198. doi:10.4172/2168-975X.1000198

Meditation

There is an ever-growing body of scientific evidence to support the vast benefits of meditation, including the possibility of preserving cognition and preventing dementia and Alzheimer's disease. Meditation may decrease stress-induced cortisol secretions, which have neuroprotective effects via elevated BDNF levels. Furthermore, meditation may potentially lower oxidative stress, improve lipid profile integrity, strengthen neuronal circuits, and enhance cognitive reserve capacity, all which provide support for a reduced risk for cerebrovascular disease and age-related neurodegeneration [13]. Mindfulness-Based Stress Reduction (MBSR), one of the most widely used mindfulness programs, has been associated with changes in gray matter volumes in brain regions involved in self-awareness, emotional regulation, learning, and memory. Compassion meditation may help modulate limbic brain structures associated with emotional regulation, and focused breathing exercises before bed may increase melatonin levels, which seem to improve sleep quality. In participants with mTBI, meditation improved mental fatigue, cognitive function, self-efficacy, and quality of life, as well as reduced symptoms of depression [14].

Neurofeedback

Neurofeedback is a type of EEG biofeedback whereby an individual can improve brain function through intensive brain training exercises. Results, although only preliminary, suggest that neurofeedback is linked to increases in cortical grey matter and cortical white matter tracts, as well as improvements in attention, problem solving, and short and long term memory deficits. Several studies indicate that neurofeedback results in greater functional improvement compared with other forms of rehabilitation, including, traditional strategies, computerized tasks, and prescription medication [15]. Neurofeedback may have the potential to reduce outcomes of posttraumatic stress disorder (PTSD) and depression, which is highly comorbid with mTBI [16].

Clinical Relevance

Emerging evidence supports the use of natural neuroprotective compounds and integrative therapies that target multiple mechanisms underlying PCS following mTBI. This short review is in no way comprehensive or inclusive, but provides a foundation for the development of a combined holistic treatment for mTBI and subsequent PCS. For example, probiotics, vitamin D, acupuncture and acupressure are also being used to manage a myriad of symptoms with success like pain, headache, sleep disturbance, and general wellbeing. The proposed therapies may have limitations in efficacy working alone due to oxidative stress and other system compromise. We therefore recommend a combination of therapies, which work synergistically to overcome the restrictions of any one intervention. The natural compounds and integrative therapies proposed are readily available, well tolerated, and offer a gestsalt of health benefits. Moreover, therapy combinations can be customized based on individual peference, injury severity, and symptom presentation. Currently there are no FDA approved treatments for mTBI, as well as insufficient medical recommendations for the prevention of secondary injury and persistent symptoms. This highlights the urgent need to test new therapies for the prevention and treatment of PCS, which severely impacts quality of life.

References

1. Coronado VG, McGuire LC, Sarmiento K, Bell J, Lionbarger MR, et al. (2012) Trends in Traumatic Brain Injury in the U.S. and the public health response: 1995-2009. J Safety Res 43: 299-307.
2. Das M, Mohapatra S, Mohapatra SS (2012) New perspectives on central and peripheral immune responses to acute traumatic brain injury. J Neuroinflammation 9: 236.
3. Johnson VE, W Stewart, Smith DH (2012) Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. Brain Pathol 22: 142-149.
4. Hasadsri L, Wang BH, Lee JV, Erdman JW, Llano DA, et al. (2013) Omega-3 fatty acids as a putative treatment for traumatic brain injury. J Neurotrauma 30: 897-906.
5. Wu A, Ying Z, Gomez-Pinilla F (2004) Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma 21: 1457-1467.
6. Ma QL, Yang F, Rosario ER, Ubeda OJ, Beech W, et al. (2009) Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. J Neurosci 29: 9078-9089.
7. Olivera A, Lejbman N, Jeromin A, French LM, Kim HS (2015) Peripheral Concentrations of Total Tau are Increased in Military Personnel who Sustain Traumatic Brain Injuries during Deployment JAMA Neurology 72: 1109-1116.
8. Wu A, Ying Z, Gomez-Pinilla F (2006) Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol 197: 309-317.
9. Menon VP, Sudheer AR (2007) Antioxidant and anti-inflammatory properties of curcumin. In The molecular targets and therapeutic uses of curcumin in health and diseas. Springer, US.
10. de la Lastra CA, Villegas I (2005) Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications. Mol Nutr Food Res 49: 405-430.
11. Sun AY, Wang Q, Simonyi A, Sun GY (2010) Resveratrol as a therapeutic agent for neurodegenerative diseases. Mol Neurobiol 41: 375-383.
12. Wu A, Ying Z, Gomez-Pinilla F(2013) Exercise facilitates the action of dietary DHA on functional recovery after brain trauma. Neuroscience 248: 655-663.
13. Xiong GL, Doraiswamy PM (2009) Does meditation enhance cognition and brain plasticity? Ann N Y Acad Sci 1172: 63-69.
14. Goyal M, Singh S, Sibinga EM, Gould NF, Rowland-Seymour A, et al. (2014) Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med 174: 357-368.
15. May G, Benson R, Balon R, Boutros N (2013) Neurofeedback and traumatic brain injury: a literature review. Ann Clin Psychiatry 25: 289-296.
16. Neurofeedback and Biofeedback for Mood and Anxiety Disorders: A Review of the Clinical Evidence and Guidelines - An Update (2014) Canadian Agency for Drugs and Technologies in Health Ottawa (ON), USA.