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Review

Vitamins and nutrients as primary treatments in experimental brain injury: Clinical implications for nutraceutical therapies

Cole Vonder Haar[a,1], Todd C. Peterson[b,1], Kris M. Martens[a], Michael R. Hoane[c,*]

[a]University of British Columbia, Vancouver, BC, Canada
[b]Stanford University, Palo Alto, CA, USA
[c]Southern Illinois University, Carbondale, IL, USA

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ABSTRACT

With the numerous failures of pharmaceuticals to treat traumatic brain injury in humans, more researchers have become interested in combination therapies. This is largely due to the multimodal nature of damage from injury, which causes excitotoxicity, oxidative stress, edema, neuroinflammation and cell death. Polydrug treatments have the potential to target multiple aspects of the secondary injury cascade, while many previous therapies focused on one particular aspect. Of specific note are vitamins, minerals and nutrients that can be utilized to supplement other therapies. Many of these have low toxicity, are already FDA approved and have minimal interactions with other drugs, making them attractive targets for therapeutics. Over the past 20 years, interest in supplementation and supraphysiologic dosing of nutrients for brain injury has increased and indeed many vitamins and nutrients now have a considerable body of the literature backing their use. Here, we review several of the prominent therapies in the category of nutraceutical treatment for brain injury in experimental models, including vitamins (B_2, B_3, B_6, B_9, C, D, E), herbs and traditional medicines (ginseng, *Gingko biloba*), flavonoids, and other nutrients (magnesium, zinc, carnitine, omega-3 fatty acids). While there is still much work to be

Abbreviations: FDA, U.S. Food and Drug Administration; TBI, traumatic brain injury; NAM, nicotinamide; PARP, poly(ADP-ribose) polymerase-1; NAD+, nicotinamide-adenine dinucleotide; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; PLP, pyridoxal 5′-phosphate; MWM, Morris water maze; MAP-2, microtubule associated protein-2; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; α-T, α-tocopherol; CNS, central nervous system; Nrf2, nuclear factor (erythroid-derived 2)-like 2; 7,8-DHF, 7,8-dihydroflavone; TrkB, tyrosine kinase receptor B; BDNF, brain derived neurotrophic factor; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein; GAP-43, growth associated protein 43; TLR4, toll-like receptor 4; MAPK, mitogen-activated protein kinases; ALC, acetyl-L-carnitine; acyl-CoA, acyl-coenzyme A

*Correspondence to: Restorative Neuroscience Laboratory Department of Psychology, Life Science II, MC 6502 Southern Illinois University, Carbondale, IL 62901, USA. Fax: +618 453 3563.
E-mail address: mhoane@siu.edu (Michael R. Hoane).
[1]These authors contributed equally to this work.

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done, several of these have strong potential for clinical therapies, particularly with regard to polydrug regimens.

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Contents

1. Introduction

Traumatic brain injury (TBI) affects 2.5 million individuals in the United States every single year and an estimated 1–2% of the population currently lives with chronic impairments due to TBI (Thurman et al., 1999; Zaloshnja et al., 2008). In addition to the personal costs associated with brain injury, there is a considerable financial burden associated with primary care, rehabilitation and loss of productivity due to ongoing problems (Humphreys et al., 2013). Despite the scope of the problem, over 30 years of animal research into the mechanisms and consequences of TBI have failed to yield any successful pharmaceutical agents to treat brain injury in humans. The many unsuccessful clinical trials have caused the field to reconsider several factors involved in clinical and preclinical experimental design. One particular problem with drugs that failed clinical trials is that they were too specific in their treatment targets. This has resulted in a large push in recent years to assess combination therapies, targeting multiple mechanisms of action (Margulies et al., 2015). As nutritionally-based therapies supplement basic biological function and have therapeutic action in the injured brain, these therapies may eventually represent an important component of combination therapies.

In the clinic, major changes in nutritional status have been observed after TBI. The combination of alterations in blood flow, excitotoxicity, free radical damage and altered global and regional metabolic rates has been identified as a major contributor to secondary damage from brain injury (Vespa et al., 2005). This metabolic crisis in the early stages of TBI can be detrimental to outcomes and recent studies have shown that supplementing basic nutrition can significantly improve functional outcomes in patients (Horn et al., 2015; Taha et al., 2011). The guidelines for hospital management of TBI, provided by the Brain Trauma Foundation only include minimal standards for nutritional supplementation, suggesting that patients be placed on full nutritional replacement within 72 h (Bratton et al., 2006). Of note is that standard nutritional replacement is typically formulated to contain carbohydrates, fats and proteins, with no vitamins or other minerals. Deficiencies in nutrition may further exacerbate TBI symptoms and the depletion of bioactive vitamins, minerals and other compounds may make it difficult for the body to process other pharmaceutical compounds, a phenomenon observed in experimental brain injury (Anderson et al., 2015; Kalsotra et al., 2003).

In this paper, we provide an overview of the overlooked area of nutritionally-based therapies in TBI, focusing on findings at the preclinical level. These therapies, collectively referred to as nutraceuticals, have historically been highlighted as preventative measures for chronic diseases (Lassi et al., 2014; Moyer, 2014; Schleicher et al., 2013). However, in recent years, many vitamins, minerals and essential nutrients have risen to prominence as potential primary therapeutics

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