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Chapter 11

Nutrition in Traumatic Brain Injury: Focus on the Immune Modulating Supplements

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Additional information is available at the end of the chapter

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1. Introduction

The hypermetabolic nature of post-traumatic brain injury (TBI) state makes adequate nutritional support critical. Maintenance of adequate nutritional intake has been shown to have a significant impact on outcomes after TBI. [1] While pre-injury and immediate post-injury malnutrition has been associated with lower survival after TBI, much remains to be learned about the role and optimization of nutritional support beyond the initial phases of recovery. One of the most rapidly evolving aspects of clinical investigation in this general area is focusing on the effects of immune-modulating nutrition on TBI outcomes. The secondary injury phase following brain trauma is characterized by neuroinflammation, free radical generation, excitatory toxicity, and oxidative stress. [2] In this chapter we will present our current state of understanding of immune-nutrition for TBI, highlighting modern clinical practices and emerging trends. Many nutritional supplements have shown promise in preclinical and animal trials, particularly in the area of neuroprotection prior to injury, but human clinical trials have been largely disappointing or nonexistent.

2. General overview of nutritional support following TBI

Trauma, including TBI, is associated with transient immune-suppression and high rates of nosocomial infection. Gastrointestinal mucosal health quickly deteriorates following trauma and stress.[3] Immune-modulating nutrition has been associated with lower complication and infection rates in surgical and critically ill patients and is recommended in SCCM and ASPEN guidelines for select patients including trauma patients. [4] These guidelines make broad

recommendations for the initiation and management of enteral nutrition in critical illness and should serve as the evidence-based foundation for nutritional support programs. Early administration of enteral feeding, combined with immune-modulating nutrient supplementation, has been shown to promote both the structural integrity and immunological function of the gastrointestinal mucosa. Target caloric and protein intake goals should be calculated for each patient, accommodating fully for any baseline increases in nutritional needs due to the metabolic stress of injury. The general initial nutritional strategy should include the provision of more than 50 percent of the estimated total energy expenditure and 1–1.5 g/kg protein within 24 hours of injury. [5] The provision of these requirements by the enteral rather than the parenteral route is always preferred.

3. The immune-enhancing paradigm

Immune-enhancing nutritional ingredients will be the focus of the subsequent sections of this chapter. Specifically, we will discuss the use of omega-3 fatty acids, dietary nucleotides, arginine, glutamine, and various antioxidants in TBI. General principles of the immune-enhancing paradigm focus on aggressive supplementation of immune-modulating ingredients with the aim of promoting healing of injured brain tissue and minimizing loss of parenchyma in the area of penumbra—the threatened but still viable tissue around the periphery of acute brain injury[6]. Many immune-modulating strategies (including steroid administration in CRASH I) have been trialed, frequently without demonstrating benefit[7]. Protocols for the timing, dosage, and route for many of these immune-modulating elements are yet to be clearly defined, and the authors will focus on the most up-to-date evidence regarding the basic science and clinical research on this topic.

4. Omega-3 fatty acids

Omega-3 fatty acids (n-3FAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to be of potential value in the management of patients with TBI. Present in dietary intake, n-3FAs are commonly found in fish oils and are associated with a wide range of possible health benefits. The human brain is composed of 60% lipid by dry weight, with DHA representing one of the most abundant fatty acids found in the brain. [2] N-3FAs contribute to membrane fluidity and thus affect many different aspects of neuronal development and physiology, including cell adhesion, axon guidance, synaptic integrity, and neurotransmission. [2] Additionally, n-3FAs may also play a role in defense against oxidative stress and inflammation.

Biological pathways

N-3FAs have been shown to mitigate the consequences of several key pathologic cellular pathways associated with TBI, including oxidative stress, apoptosis, inflammation, and neuronal excitotoxicity. [2]

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- In response to disruption of neuronal membranes, arachidonic acid is released and converted to pro-inflammatory prostaglandins. N-3FA derivatives, on the other hand, inhibit activation and migration of inflammatory cells. Physiologically, n-3FAs also suppress T-cell activation and natural killer cell activity and decrease the total number of circulating leukocytes. [2]
- In the setting of acute oxidative stress, DHA has been demonstrated to lessen the burden of lipid and protein peroxidation. Its metabolites can also modulate expression of tissue repair signals, upregulate anti-apoptotic proteins, and downregulate pro-apoptotic proteins. [8]
- The excitotoxic neurotransmitter glutamate is released following TBI, leading to a disproportionate influx of calcium into neurons and subsequent cell death. [2] *In vitro*, DHA has been shown to decrease calcium influx and thus lessen the burden of glutamate cytotoxicity.

Cumulatively, the effects of n-3FAs on TBI-related cellular processes may promote cell survival and viability, highlighting the potential role of n-3FAs in improving neurological outcomes.

Animal studies

Animal studies investigating the role of n-3FAs in experimental TBI models have produced encouraging results.

- In rat fluid percussion injury (FPI) models, n-3FAs have been shown to decrease oxidative damage as measured by protein oxidation, improve post-traumatic cognitive disability as measured by water maze testing, and normalize dysregulated expression of genes linked to neuronal energy homeostasis. [9, 10]
- In a rat model of controlled cortical impact (CCI), n-3FAs were shown to restore TBI-induced deficits in neuronal dopamine release, important for maintenance of learning, attention, and other neurobehavioral phenomena. [2, 11]
- Finally, in response to impact acceleration TBI in rats, dietary DHA supplementation has been linked to decreased neuronal injury and decreased caspase-3 activity, a marker of apoptosis. [12-14]. Conversely, dietary deficiency of n-3FAs in animal models has been associated with impaired neurogenesis, decreased neuronal size, and neurobehavioral defects. [2] In rat models, n-3FA deficiency has been specifically connected with increased spinal cord vulnerability to neuronal damage, measured by reduced markers of synaptic plasticity and membrane homeostasis in the lumbar spinal cord. [15]

Clinical studies

Despite the laboratory and animal research showing potential benefits of n-3FAs in improving clinical outcomes following TBI, there have been no clinical trials to verify such benefits in human subjects. There have been promising case reports of n-3FA use in TBI and a pilot study which suggested a link between n-3FAs and prevention of post-traumatic psychiatric distress [16, 17], but more robust studies of clinical response will be necessary to ascertain therapeutic benefit. Challenges to conducting effective studies include inconsistent doses and sources of commercially-available n-3FA preparations. Various trials use different doses of n-3FA and the sources are inconsistent as suppliers vary the species of fish used to make fish oils. Low

doses of n-3FA are incorporated in many commercial fish oils but experimental TBI studies typically have focused on higher dose supplementation. [18] Each product also has its own ratio of DHA and EPA. Two prescription n-3FA products are available in the United States, but both primarily consist of EPA.

Clinical Limitations

The clinical use of dietary n-3FAs for TBI has been historically limited by concerns for anti-thrombotic actions, but this concern has subsided with several studies in cardiology patients using combination regimens of fish oil and antiplatelet agents. [19, 20] Other threats to the n-3FA supply, including heavy metal toxicity in some fish oils, also confound the field.

5. Dietary oligonucleotides

Following traumatic brain injury, nucleotides are released into the extracellular space, acting in both an autocrine and paracrine fashion, via nucleotide receptors on neuronal cells. [21] From individual nucleosides to antisense strands and microRNAs, dietary oligonucleotides represent a possible therapeutic means through which the pathophysiological responses and functional outcomes of TBI can be modulated. [22]

Biological pathways

Much work has been done at the single nucleoside level, specifically focusing on the role of adenosine. Adenosine is a purine nucleoside, speculated to play a neuroprotective role in TBI, leading to lower neuronal metabolism and greater cerebral blood flow. [23] Adenosine and its metabolic derivatives have been shown to acutely upregulate after TBI in both animal models and human disease. [24-27] A product of ATP breakdown, cerebral adenosine acts via the purinergic signaling system and may reduce cellular death related to glutamate-mediated excitotoxicity. It also decreases free radical-related/oxidative damage. [28] Although different adenosine receptors have been observed to facilitate both beneficial and deleterious physiologic effects in post-TBI studies, adenosine and its downstream pathways remain clearly linked to the pathophysiology of TBI and represent possible targets for therapeutic modulation. [21, 29-33]

Antisense oligonucleotides, on the other hand, are short synthetic nucleotide strands that can bind to specific messenger RNA (mRNA) targets, making them susceptible to degradation and thus effectively blocking synthesis of corresponding proteins. [34] These nucleotides represent yet another promising avenue through which novel TBI management strategies can begin to utilize more recent biomedical research discoveries.

Animal studies

Animal TBI studies involving oligonucleotide-based therapies have produced some promising results. Oligomeric diets demonstrated potential benefit in rat models of TBI,

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preventing TBI-induced weight loss and thymus atrophy and, by extension, averting immune dysfunction. [35]

In terms of specific nucleosides, adenosine is increased in rat fluid percussion injury (FPI) and controlled cortical impact (CCI) models of TBI, and 2-chloroadenosine, an adenosine analogue, has been demonstrated to confer improved bioenergetic and functional outcomes after FPI. [27] Additionally, in a weight-drop closed head injury (CHI) TBI model, intraperitoneal injection of cytidine triphosphate (CTP) has been shown to decrease neuronal apoptosis and improve motor function post-TBI. [36]

Antisense oligonucleotides have also been studied in animal models of TBI.

- In a rat stab wound model of brain injury, antisense oligonucleotides against a monocyte chemoattractant protein (MCP-1) were able to inhibit inflammatory chemokine production. [37]
- In a rat FPI model, pretreatment with antisense oligonucleotides against a specific N-methyl-D-aspartate (NMDA) glutamate receptor (NMDA-R1) decreased mortality from 50% to 8% and improved behavioral recovery, both likely due to the prevention of glutamate excitotoxicity. [38]
- In a murine weight-drop CHI TBI model, injection of oligonucleotides against acetylcholinesterase (AChE) reduced mortality from 50% to 20% in trauma-sensitive mice, decreased post-TBI neuronal death, and improved neuromotor recovery as measured via a beam test for balance and coordination. [34]

Clinical studies

While no clinical studies have explored the use of oligonucleotide-based therapies for TBI, associations have been made in humans between TBI severity and increased CSF concentrations of adenosine. [23, 27] Clinical concerns of oligonucleotide treatments include the cardiovascular effects of purinergic modulation and the effects of oligonucleotides on other unrelated receptor targets. Certainly the array of cell-based and animal studies highlight clear potential for the translational relevance of dietary oligonucleotides. [33, 34]

6. Arginine

Arginine is a nonessential amino acid and is a component of both enteral and parenteral nutrition formulas. [39] Normally, arginine homeostasis is driven by dietary intake and metabolic degradation, and when its utilization increases during growth, development, or injury, arginine may be recognized as an essential amino acid. [39] Parenteral arginine supplementation in trauma patients has been demonstrated to confer improved wound healing and immune responses and has no known adverse effects as a nutritional supplement. [39] From this background, and given that serum levels of L-arginine and its

metabolites have been shown to be significantly reduced in patients post-TBI, arginine represents a potential dietary adjuvant to enhance TBI therapy. [40]

Biological pathways

L-arginine is the immediate, endogenous precursor of nitric oxide (NO), an important physiological vasodilator. [41] Immediately post-TBI, there is an increase of NO, followed by a sustained decrease which can result in diminished cerebral blood flow (CBF) and consequent hypoperfusion. [42] Additionally, arginine is a precursor for proline and 4-hydroxyproline – both important for extracellular matrix (ECM) remodeling – and for creatine – an important energy source in both muscle and brain tissues that will be discussed independently later in this chapter. [40]

Animal studies

Administration of L-arginine has been shown in both rat and mouse controlled cortical impact (CCI) models to restore CBF and reduce contusion volume post-TBI in a dose-dependent manner. [40, 41, 43-48] It has been also been demonstrated in a rat fluid percussion injury (FPI) model to reduce immunoreactivity for nitrotyrosine, a marker of peroxynitrite ($ONOO^-$) super oxide radicals. [49, 50] While one study failed to confirm that hypertonic arginine produced significant cerebrovascular improvements over hypertonic saline in a rat FPI model, other dose and time studies in rats have even shown that L-arginine is most neuroprotective when 300mg/kg is given as soon as possible after injury. [39, 51] Rats treated with an arginase-specific inhibitor (Nω-hydroxy-nor-arginine) showed significantly reduced contusion volume post-TBI. [45]

Clinical studies and limitations

There have been no clinical studies exploring the potential therapeutic benefits of isolated arginine supplementation in post-TBI patients. Arginine is a common ingredient in commercially-available formulas and in low doses it appears to be safe. Trials of critical care formulas including arginine, fish oil, and various antioxidants appear to be safe and are effective at reducing infection rates in TBI and other critically-ill patients. [52] Although arginine seems to have strong translational promise, a number of potential risks exist before considering hyper-supplementation of arginine. For instance, while some studies have linked L-arginine to reduced neuronal damage, none have been able to demonstrate the same beneficial effects with regards to neurological function. [43] Secondly, the optimal dose of 300 mg/kg in rats is much larger than amounts of arginine found in typical nutritional formulations. [39] Finally, the roles of other arginine derivatives, such as arginine vasopressin, and nitric oxide (NO) signaling remain unclear in post-TBI pathophysiology. [46, 53-64]

7. Glutamine

Glutamine is a non-essential amino acid, widely distributed throughout the body. It is the most abundant free amino acid in circulation. [65, 66] Glutamine synthesis cannot keep up with

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increased requirements such as those experienced during physiological stress, yet it is important for the immune response. Consequently, glutamine supplementation has been shown to decrease infectious complications in trauma patients. [65, 66] The brain serves prominently in glutamine metabolism and is a net producer of the amino acid. [67] In the brain, glutamine is involved in the glutamine-glutamate cycle which functions to conserve the carbon skeletons of neurotransmitters. [67] As part of this cycle, it is synthesized from glutamate and ammonia in astrocytes and also serves as the precursor for glutamate along with alpha-ketoglurate. [67-69]

While glutamate is recognized as an excitotoxic neurotransmitter released after TBI, patients with brain injury are also observed to experience profound hypoglutaminemia. [67, 68, 70-95] While the cause of this hypoglutaminemia is not known, this observed deficiency provides rationale for dietary supplementation.

Animal studies

While many animal studies assess post-TBI glutamatergic signaling, in a rat TBI model, glutamine administration was shown to decrease concentrations of pro-inflammatory cytokines and apoptotic cells in gastrointestinal tissue, thus reducing TBI-associated damage to gastrointestinal mucosa. [65, 66]

Clinical studies

Limited clinical studies have associated glutamine and alanine dietary supplementation with lower mortality rates, shorter hospital lengths of stay, decreased occurrences of pneumonia and stress ulcers, and higher lymphocyte counts in TBI patients. [96] While these results have been linked to an improved immunological response, future basic science and clinical studies are needed to advance our understanding of the translational potential of glutamine as a nutritional adjuvant in TBI therapy.

As a potential limitation of glutamine therapy, glutaminergic signaling has been implicated in basic science studies with post-traumatic epilepsy. [97] Additionally and perhaps of greater relevance, the recent REDOXS (REducing Deaths due to OXidative Stress) trial sought to investigate the effect of nutritional supplementation in critically-ill patients. A randomized trial, the study found that glutamine supplementation actually resulted in increased harm and mortality in critically ill patients and cautiously advocated that administration of glutamine be reserved for burn and trauma patients not in multiorgan failure. [98] Of note, much of the glutamine in that study was administered in parenteral form, and the body of literature using enteral glutamine has shown no such outcome.

8. Antioxidants

Biologic pathways

Reactive oxygen and nitrogen species (ROS/RNS, respectively) play an integral role in brain injury and posttraumatic neuronal degeneration. [99, 100] In the setting of acute traumatic

stress, endogenous protective mechanisms such as glutathione (GSH) and superoxide dismutase (SOD) may become overwhelmed by increased production of free radicals. [99] This is driven in part by influx of excess of intracellular calcium into mitochondria. Lipid peroxidation mediated by oxygen radical species has been suggested as an important factor in posttraumatic neuronal degeneration. [100] In addition to disrupting the membrane phospholipid architecture, lipid peroxidation contributes to the formation of cytotoxic aldehyde-containing byproducts that bind to and impair the function of cellular proteins. [101] The oxidation of DNA and proteins then may trigger programmed cell death. This process is exacerbated during the reperfusion phase of injury, resulting in additional microvascular damage and neuronal cell death.

Clinical studies

Increasing amounts of evidence point to potential effectiveness of antioxidants in modulating the severity of TBI. [99, 100] Specifically, nutritional antioxidants may be critical in attenuating the deleterious effects of oxidative stress in ischemia and reperfusion type injuries. [102] Specific antioxidant agents that have been investigated in the setting of TBI include vitamin E (alpha-tocopherol), glucocorticoid methylprednisolone, tirilazad mesylate, 21-amino-steroids, green tea extract, ginkgo biloba extract, resveratrol, curcumin, and niacin. [100-102] In addition, evidence points to selenium as being an effective inhibitor of ROS-mediated apoptotic neural precursor cell death in TBI. [103] A full discussion of these antioxidants is beyond the scope of this chapter which focuses on immunonutrition, but several antioxidants are worthy of special mention.

Commercially available enteral formulas frequently tout "added antioxidants," but these typically are vitamin C, vitamin E, and beta-carotene. In the setting of TBI, enteral nutrition enriched with antioxidants and neuromodulatory agents seems to have some clinical benefit. [104] Although there were no mortality differences between the control and glutamine/probiotic enteral nutrition regimens, the glutamine/probiotic group demonstrated lower infection rates and infections per patient, as well as shorter intensive care stays and fewer ventilator days. [104]

The finding that plasma vitamin C levels are significantly lower in patients with brain trauma suggests that vitamin C plays a potential role in oxidative stress related to brain injury. [105] In addition to vitamin C, other nutritional factors may play a role in modulating oxidative damage associated with TBI, including vitamin E (alpha-tocopherol), beta-carotene, and coenzyme Q10. [106] Despite promising preliminary animal studies, data showing efficacy of specific or combined micronutrient supplementation in the setting of brain injury remains elusive. [106] A small study examining high-dose vitamin C and vitamin E showed some promise but should be interpreted as preliminary. [107]

It has to be noted that phase III clinical trials of neuroprotective agents in TBI have been somewhat disappointing. [108] In a multicenter trial of tirilazad mesylate in TBI, the experimental group was found to have similar mortality and neurologic recovery rates when compared to placebo. [109] However, a subgroup analysis suggested that tirilazad mesylate may contribute to reduced mortality in male patients with severe head injury accompanied by

traumatic subarachnoid hemorrhage (34% tirilazad group mortality versus 43% placebo group mortality). [109]

One trial of polyethylene glycol (PEG)-conjugated SOD in TBI patients initiated within 8 hours of the injury showed a trend toward improved neurological outcomes. [110] Subsequent larger trials failed to reproduce any beneficial effect however. [111] Another agent, U-83836E, a second-generation lazaroid with non-steroidal structure, has been shown to decrease post-injury lipid peroxidation and protein nitration and enhance preservation of mitochondrial respiratory function and calcium buffering ability in a mouse model, and human studies using this agent may be warranted. [112] Melatonin is another antioxidant agent showing promise in providing neuroprotective benefits based on evidence from rat model of TBI. [111] A number of other promising agents have been investigated, but human evidence continues to be scarce.

Increasing amounts of evidence suggests that the most effective antioxidative approach to the brain-injured patient should involve combined treatment with mechanistically synergistic antioxidants. [101] Strategies within such a paradigm should include simultaneous scavenging of lipid peroxidation-initiating free radicals, inhibition of lipid peroxidation propagation, and removal of neurotoxic lipid peroxidation products. [101] Clinical trials with multidrug antioxidant regimens are needed before any recommendations can be made.

9. Branched-chain amino acids

Branched-chain amino acids (BCAAs) are essential amino acids that have important roles in energy metabolism and protein and neurotransmitter synthesis. [113] Valine, isoleucine, and leucine comprise the BCAAs, and these entities have important roles in regulating protein synthesis, gluconeogenesis, and energy metabolism as well as functioning as a major source of nitrogen for producing glutamine in the brain. [113] Because of the important baseline functions of these compounds, this would suggest that alterations in BCAA metabolism after TBI may actually play a role in decreased energy production and neurotransmitter synthesis, thereby contributing to TBI pathology. As such, the supplementation of BCAAs or their metabolites may have a role in the reduction of TBI pathology and possibly outcome.

Biologic Pathways

The metabolism of BCAAs is partially regulated by protein synthesis requirements and excess BCAAs are either catabolized or excreted. In terms of catabolism of excess BCAAs, the first step is catalyzed by the branched-chain aminotransferase isoenzymes, mitochondrial BCATm and cytosolic BCATc. The resulting product of this process is glutamate, which is a major excitatory neurotransmitter as well as a precursor of alpha-ketoglutarate. The second, irreversible step in BCAA catabolism is catalyzed by the mitochondrial branched-chain α-ketoacid dehydrogenase (BCKDC) enzyme complex. [114] BCKDC catalyzes oxidative decarboxylation of the BCKA products of the BCAT reaction, forming NADH and the respective branched-chain acyl CoA derivative of each BCAA. [114]

Animal studies

It is well-established that TBI causes cognitive impairment and altered net synaptic efficacy. In one study where brain injured mice or sham-injured mice either consumed water or water containing BCAAs, there was an overall cognitive improvement with a simultaneous restoration in net synaptic efficacy. [115] The major finding of this study was that dietary delivery of BCAAs ameliorates hippocampal-dependent cognitive dysfunction together with a restoration of net synaptic efficacy after concussive brain injury, and in every animal, cognitive improvement occurred only in conjunction with restored net synaptic efficacy. [115]

Clinical studies

Although the literature on this subject is rather sparse, there are some promising results. It has been reported that the levels of all three BCAAs in patients with mild TBI relative to healthy volunteers is decreased. BCAA levels are further reduced in patients with severe TBI compared with all groups. [113] In one study, it was shown that short-term intravenous supplementation of BCAAs in rehabilitation patients with TBI enhances recovery of cognitive function, induces a supraphysiologic plasma content of BCAAs, and increases tyrosine plasma concentration. [116] This study also revealed that plasma amino acid levels remained decreased in the posttraumatic rehabilitation phase (1-22 months). In this study, 40 patients with TBI were randomly assigned either intravenous BCAAs or placebo. Plasma tyrosine concentration improved in the group given BCAA supplementation and overall disability improvement was greater than that noted in the placebo group. The key conclusion of the study was simply that supplementation of BCAAs in TBI restores plasma levels to the normal range without having a negative effect on levels of precursors of brain catecholamines and serotonin. [116]

Another study revealed that BCAA supplementation may aid in recovery from a posttraumatic vegetative or minimally conscious state, thus reducing the risk of the vegetative state persisting over time. [117] This study, also performed by Aquilani et al., supplemented patients for 15 days by intravenous route with either BCAAs or placebo who were either in a posttraumatic vegetative or minimally conscious states. [117] The 15-day period of these trials is too short to draw any meaningful conclusions regarding that adaptation of BCAAs.

Another study sought to assess the impact of plasma BCAA and tyrosine levels following enterally-administered BCAAs; However, enteral administration failed to return plasma BCAA levels to the normal range. [118] In addition, it was found that elevated plasma phenylalanine was associated with decreased ICP and increased jugular venous oxygen saturation (SjvO2), while higher plasma isoleucine and leucine levels were associated with increased ICP and higher plasma leucine and valine were linked to decreased SjvO2. Therefore hyperalimentation with enteral nutrition should be carefully performed to avoid harmful side effects of amino acids while promoting improvements in brain metabolism. [118]

Summary

Although there are a small number of very preliminary but promising studies suggesting that BCAA supplementation may be beneficial to the TBI patient, further studies are needed to

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optimize the route and dosage of supplementation and to better elucidate the side effects of artificial supplementation such that supplementation produces no significant side effects.

10. Choline

Immediately following TBI, there is a transient period of excess cholinergic activity which may contribute to excitotoxicity via nicotinic and muscarinic receptor subtypes. However, the chronic phase of TBI is actually associated with decreased brain cholinergic function.

Acetylcholine acts on nicotinic and muscarinic acetylcholine receptors, and previous studies have suggested that TBI-related deficits in alpha-7 n-acetylcholine receptor (α7 nAChR) density may contribute to post-TBI cognitive deficits. [119] If this downregulation of α7 nACh receptors in fact contributes to the cognitive impairment seen as a result of TBI, a therapeutic option includes drugs or compounds that are selective agonists of α7 nAChRs and these may be helpful in ameliorating some measures of cognitive decline. [119]

One such compound that has been shown to bind α7 nAChR is choline. [119] Choline is an essential nutrient available from a wide variety of nutritional sources. It is an important molecule involved in synthesis of structural cell membrane phospholipids, other signaling molecules, and is also a precursor for acetylcholine. [120] As such, it is postulated that dietary choline supplementation may minimize cognitive deficits, reduce brain inflammation, and protect the penumbra.

Biologic pathways

Acetylcholine acts on nicotinic and muscarinic acetylcholine receptors, both of which are prominently located in brain regions that are involved with attention and cognition. [119] As previously stated, choline has been shown to be an agonist at α7 nAChRs, but not other nicotinic receptor subtypes. α7 nAChRs are known to be involved in both excitotoxicity and inflammatory pathways. Once TBI occurs, multiple biochemical pathways, including the aforementioned excitotoxicity and inflammatory pathways, are set into motion which leads to a chronic, neurodegenerative condition.

Animal studies

In one study, dietary choline supplementation was shown to significantly reduce brain injury-induced spatial learning deficits in a rat model. Additionally, the choline-supplemented diet helped reduce brain inflammation and spared cortical tissue. [119]
It is known that administration of cytidine-5'-diphosphate (CDP)-choline functions as a neurostimulant in neurological disorders of memory.[121] As such, its use in TBI was promising. Dixon et al. demonstrated that chronic CDP-choline treatment can attenuate neurological and cognitive performance deficits following TBI in rats. [122] CDP-choline treatment also increased post-injury resistance to the memory-disrupting effects of scopolamine. Exogenous administration of CDP-choline increased ACh release. [122] The mechanism of action is not definitively known, but CDP-choline may attenuate post-injury

functional deficits by several mechanisms, including providing the ACh precursor choline to drive up ACh synthesis, maintaining cell integrity by accelerating membrane formation, and/or stimulating brain metabolism. [122]

Clinical studies

Like with many immunonutrients, a number of large-scale studies have shown no benefit despite promising animal trials. Ruff et al. found that citicoline (an intermediate in the generation of phosphatidylcholine from choline) supplementation in TBI patients did not improve the extent or speed the recovery in patients following acute stroke. [123]

Similarly, Zafonte et al., completed the Citicoline Brain Injury Treatment Trial (COBRIT), a phase III, double-blind study comparing citicoline versus placebo. In this trial, 1213 study participants with complicated mild, moderate, or severe TBI were randomized to receive 2000 milligrams of citicoline or placebo daily for 90 days. The trial ran from 2007-2011 but was terminated early due to futility. The study did not demonstrate any benefits of citicoline treatment. [123]

Summary

Not all promising findings in the preclinical arena have been translated to success in patients. Choline supplementation in TBI rats holds promise. However, these have not held true in the patient models. This creates a need to understand the mechanism of how choline induces positive results in rats. Additionally, there may be other compounds or physiologic conditions that are necessary to allow for the beneficial effects of choline which are as of yet unknown.

11. Creatine

Creatine is a common dietary supplement, frequently used to increase strength and muscle mass. Creatine metabolism plays a key role in ATP turnover in the metabolically active brain. Endogenously expressed, cerebral creatine levels have been observed to decrease after TBI and recent studies have also shown that it provides significant neuroprotection against oxidative stress and ischemia. [124, 125] While investigations of creatine as a nutritional component of TBI therapy have been limited to animal models, much potential exists for clinical research to further define its translational relevance.

Biological pathways

The mechanisms of creatine-induced neuroprotection seem to be largely related to its effects on mitochondrial bioenergetics, binding to mitochondrial creatine kinase (CK) to exert structural protection allowing the enzyme to maintain its ability to inhibit free radical generation. [126, 127] Creatine supplementation lowers mitochondrial membrane potentials and reduces mitochondrial levels of reactive oxygen species (ROS) and calcium while maintaining the levels of adenosine triphosphate (ATP). [126] Physiologically, these effects result in inhibition of mitochondrial permeability and reduced neuronal loss. [126] Hybrid hydrophobic derivatives of creatine, creatinyl amino acids, have been synthesized with the aim to

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establish better penetration across the blood-brain barrier. *In vivo* these compounds maintain both their neuroprotective abilities and chemical stability. [128]

Animal studies

In experimental mouse and rat TBI models, chronic supplementation of creatine has been shown to decrease the extent of cortical damage by as much as 36% and 50%, respectively. [126] Compared to rats receiving a control diet, rats fed a creatine-enriched diet have also shown decreased levels of neurochemical markers of TBI-induced acute cellular injury.[127, 129] Many of these protective effects were demonstrated to follow a dose-dependent manner and cumulatively provide promising preclinical data to steer pilot clinical studies. [129]

12. Magnesium

Magnesium is essential for maintenance of vital cellular functions, including glycolysis, sustaining membrane structure and function, protein synthesis and DNA replication. [130] Magnesium also plays an important role in central nervous system following injury. It is known that after TBI, the normal homeostatic mechanisms of magnesium are deranged, resulting in a rapid decline in magnesium levels in the brain. [131] This disruption of normal magnesium homeostasis has actually been shown to correlate with the severity of neurologically-mediated behavioral deficits following injury. [132] As such, it has been postulated that magnesium pharmacotherapy may aid in the treatment of various CNS injuries, including ischemia and cortical lesions, and has been found to be effective in some of these arenas. Because of the critical function of magnesium, it is also postulated that manipulation of dietary magnesium may have an impact on the recovery of function following TBI.

Biological pathways

Magnesium plays an important role in homeostatic regulation of key pathways involved in the delayed secondary phase of brain injury. [133] During normal physiological processes, magnesium is a noncompetitive inhibitor of the NMDA receptors, thereby regulating calcium influx. [134] Following acute brain injury, tissue magnesium is depleted, leading to loss of homeostatic control of the NMDA receptors. The ensuing massive influx of calcium leads to neuronal degeneration and cell death. [133]

Animal studies

Previous research has shown that dietary magnesium deficiency prior to injury worsens recovery of function and that systemic administration of magnesium pre- or post-injury significantly improves functional recovery. A number of studies in rats have shown that treatment with magnesium after brain injury did offer neuroprotection. [133, 135-137] Bareyre et al. showed that in addition to beneficial effects on behavioral outcomes, magnesium supplementation in brain-injured rats attenuated cortical histological damage. [138] Magnesium therapy administered up to 24 hours after injury in rats significantly improved motor outcome and behavioral parameters in rats with severe diffuse traumatic axonal brain injury.

[139] Additionally, magnesium supplementation was shown to reduce long-term motor and cognitive deficits after TBI in rats which may result in decreased post-traumatic stress and anxiety. [140]

Clinical studies

Disruption of magnesium homeostasis has been observed in human traumatic brain injury. Despite a number of preclinical studies showing beneficial effects of magnesium supplementation in TBI, mostly in rat models, clinical studies in TBI patients have failed to show a consistent clinical benefit. Temkin et al. showed that continuous infusions of magnesium for 5 days given to patients within 8 hours of moderate or severe TBI were not neuroprotective and may even have a negative effect in the treatment of significant head injury. [141] However, in another prospective clinical trial by Dhandapani et al., magnesium sulfate administered to TBI patients within 12 hours of their injuries produced decreased mortality and improved neurologic patient outcome. [142] There have been a number of studies looking at the role of magnesium supplementation in combination with other pharmacological agents or physiological interventions, such as hypothermia and hyperoxia, again with varied results in both preclinical and clinical trials. A recent meta-analysis of all randomized controlled trials comparing magnesium supplementation in patients following acute TBI shows no evidence to support the use of magnesium beyond standard physiologic replacement. [143]

Summary

The success of magnesium in attenuating the process of neurodegeneration in animal models of brain injury has been widely studied with promising results. Unfortunately, these preclinical successes have not consistently translated into success in humans. Magnesium supplementation in TBI patients has produced varied results, requiring further investigation into not only magnesium supplementation but the secondary parameters that may affect clinical outcome in TBI patients.

13. Vitamin D

Vitamin D hormone (VDH; 1, 25-dihydroxyvitamin D3) is recognized as a neurosteroid with downstream implications in many different CNS signaling cascades. [144] VDH deficiency is associated with dysregulated neuronal physiology and has been demonstrated to both exacerbate TBI and reduce the efficacy of progesterone treatment for TBI. [145-147]. The relationship between VDH and TBI is perhaps most important in aging populations, within which the former is high in prevalence and the latter is rising in incidence. [148, 149]

Biological pathways

With regards to TBI, vitamin D generally acts in an anti-inflammatory manner, by regulating intracellular calcium levels (hence reducing the effects of glutamate excitotoxicity) and enhancing free radical scavenging. [144] Much TBI-related vitamin D research investigates it

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as a combined therapy with progesterone. The two hormones are proposed to act in a synergistic and perhaps compensatory manner, each of them having their own anti-inflammatory and oxidative damage-reducing properties. [144] Together, VDH and progesterone stimulate neural growth in cultured neurons following *in vitro* glutamate excitotoxicity. [145, 147]

Animal studies

In rat cortical contusion injury (CCI) models of TBI, combined therapy consisting of VDH and progesterone resulted in reduced expression of inflammatory genes; protection against cell death and DNA damage; and significant improvement in post-traumatic behavior in VDH-deficient rats. [148, 149]

Clinical studies

Limited clinical trials have shown promising results for VDH and progesterone combination therapy, improving outcomes and decreasing mortality rates after TBI. [144] VDH has a high safety profile and is inexpensive and easily administered. [147] Continued investigations will be critical to further elucidate its specific mechanisms of actions, differences in combination therapy and monotherapy, and potential for use in a therapeutic or preventative manner.

14. Zinc and other trace elements

Trace elements are known to be important modulators of cell physiology and growth, contributing to many key processes such as wound healing and the immune response. [150] Among trace elements, zinc is specifically critical for tissue repair and essential for the function of many enzymes and gene expression. [151, 152] The majority of zinc ions in the brain are bound to proteins while the remaining are sequestered in presynaptic neuronal vesicles. [151] Although neurotoxic at high levels, zinc mediates synaptic transmission and plasticity, and clinical studies have shown that after TBI patients lose excess zinc in urine in proportion to injury severity and are at increased risk for developing zinc deficiency. [152, 153] Dietary zinc regulates intestinal zinc absorption and plays an important role in zinc homeostasis, thus making zinc promising as a possible nutritional adjunct to TBI therapy. [154]

Biological pathways

To a large degree, there is some debate with regards to whether zinc is neuroprotective or neurotoxic. [155] Many studies have demonstrated zinc accumulation after brain injury, associating it with neurodegeneration and deposited aggregates of ubiquitinated proteins and thus linking altered zinc homeostasis to impaired protein degradation. [153, 156-160] Though zinc chelators were able to block these TBI-induced histological changes, they did not lead to improved post-TBI outcomes in rats. [152, 153]

Contrarily, the neuroprotective effects of zinc are also established at the basic science and animal model levels. After mechanical repetitive strain injury (RSI), neuronal-like cells have been shown to develop a cellular zinc deficiency, and zinc deficiency itself has been linked to impaired neuronal stem cell proliferation and compromised cellular repair. [161, 162]

Animal studies

In animal models, zinc reduces the development of behavioral deficits after TBI. [153, 163] Specifically, in a rat controlled cortical impact (CCI) model, zinc supplementation reduced anxiety and cognitive impairments. [153, 161, 163] This supplementation did not lead to increased neuronal cell death. [161] Further evidence of its potential therapeutic benefit comes from the fact that zinc deficiency has been demonstrated to result in increased cell death and altered glial immune responses in several different rat and mouse TBI models. [151, 153, 164, 165]

Clinical studies

Limited preclinical studies show that, after an initial period of total parenteral nutrition, dietary zinc supplementation of 22 milligrams per day using zinc gluconate significantly increases visceral protein mass in post-TBI patients, is associated with improved Glasgow Coma Scores, as well as mortality decrease from 26% to 12%. [153] With the recommended upper limit of dietary zinc being 40 milligrams per day, further clinical studies will clearly define the optimal doses and time windows to improve post-TBI deficits and prevent neurotoxicity and undesired effects to other organs. [153, 166]

Other trace elements

While zinc has been the most thoroughly studied trace element in the contexts of TBI therapy, few studies have investigated the potential roles of others. While most of these elements still present the same concerns of toxicity versus protection, preliminary results seem promising for continued research. [154]

- As described above for zinc, copper deficiency has also been linked to increased neuronal apoptosis in a rat model of TBI. [165]
- To prevent deposition of free iron from heme degradation, administration of heme oxygenase (HO) inhibitors such as tin protoporphyrin or iron chelators have shown to reduce pathophysiologic and neuromotor changes in post-TBI models. [167, 168]
- As mentioned previously in this chapter, selenium, acting as an antioxidant, reduces reactive oxygen species (ROS)-mediated apoptosis of neural precursor cells both *in vitro* and in a mouse model of TBI. [103]

15. Conclusion

TBI represents a heterogeneous pathophysiological process that is clearly a challenge to manage. Multiple clinical studies of nutritional strategies have not defined a specific pathway that can serve as a sole, standalone target in TBI nutritional therapy. Multidimensional treatment plans, perhaps incorporating some of the described nutritional adjuvants, will thus merit more investigations from both the bench and the bedside to elucidate effective strategies to best treat TBI patients. Unfortunately, many strategies that are promising in the lab or in animal models have not borne fruit in clinical trials to date.

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