Review

Concussions, Traumatic Brain Injury, and the Innovative Use of Omega-3s

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Traumatic brain injury (TBI), with its diverse heterogeneity and prolonged secondary pathogenesis, remains a clinical challenge. Clinical studies thus far have failed to identify an effective treatment strategy when a combination of targets controlling aspects of neuroprotection, neuroinflammation, and neuroregeneration is needed. Omega-3 fatty acids (n-3FA) offer the advantage of this approach. Although further clinical trial research is needed, there is a growing body of strong preclinical evidence and clinical experience that suggests that benefits may be possible from aggressively adding substantial amounts of n-3FA to optimize the nutritional foundation of TBI, concussion, and postconcussion syndrome patients. Early and optimal doses of n-3FA, even in a prophylactic setting, have the potential to improve outcomes from this potentially devastating problem. With evidence of unsurpassed safety and tolerability, n-3FA should be considered mainstream, conventional medicine, if conventional medicine can overcome its inherent bias against nutritional, nonpharmacologic therapies.

INTRODUCTION

Omega-3 polyunsaturated fatty acids (n-3FA) are structural components of cell membranes, particularly docosahexaenoic acid (DHA), which is most concentrated in the brain and retina. Emerging science on the ability of n-3FA to be beneficial to the nervous system during and after acute traumatic brain injury (TBI) is acknowledged, mainly in preclinical studies but now in growing clinical experience and case reports.

TBI has long been recognized as a leading cause of traumatic death and disability. TBI is caused by a bump, blow, or jolt to the head or a penetrating head injury that disrupts the normal function of the brain. Over 3.5 million known TBIs occur annually, approximately 52,000 deaths, and more than 300,000 hospitalizations in the United States alone [1]. TBI is often classified using mild, moderate, and severe categories. It is believed that 80%–95% of all TBI are mild, often labeled as a "concussion" and are not seen in hospital settings [1]. TBI, most often from falls, vehicle accidents, contact sports, and violence, is a major health care concern, constituting a major cause of death and disability not just in the United States but throughout the world. Motorbikes are major causes, increasing in significance in developing countries as other causes reduce. Some consider TBI a global public health epidemic [2].

Classically, TBI is described as occurring in 2 phases or on the basis of the pathophysiologic mechanism. The primary or initial injury occurs as a direct result of the traumatic event itself. A secondary injury, or phase, occurs from multiple neuropathologic processes that can continue for days to weeks following the initial insult. The primary injury is immediate and not amenable to treatment, only prevention. If severe enough, death can occur almost instantaneously. The damage that occurs from the primary injury is complete by the time medical care can be instituted. High-speed collisions with very rapid deceleration are particularly injurious, but sports-related injuries also can be devastating. Because the neuronal structures reside in a fluid-filled compartment, they often lag behind the bony structure as it moves during the sudden stopping of the

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I am a consultant to Nordic Naturals; however, no mention of any products is included in this article.

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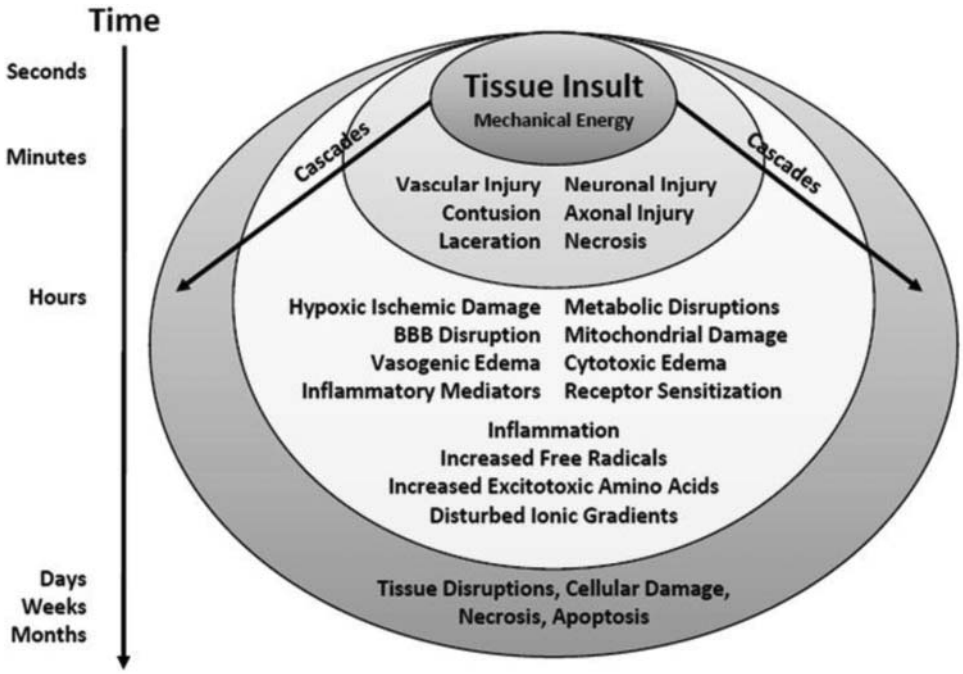

Fig. 1. The primary injury of TBI is caused by a transfer of mechanical injury to the brain tissue. This is followed by the secondary injury that occurs over minutes to hours to days and even weeks and months. It is characterized by numerous metabolic and biochemical cascades that may cause more damage than the initial tissue insult itself.

body in motion. The brain often strikes both in the direct and opposite plane of motion against the inner bony table. This is the coup–contre-coup pattern, where contusions to the brain are seen at the site of skull impact and 180° opposite the site of impact [3].

The secondary injury of TBI is a prolonged pathogenic process leading to cell death and worsening damage to the brain far beyond the primary injury (Fig. 1). The secondary injury phase of TBI consists of ischemia, excitotoxicity, and intracellular biochemical cascades; axonal injury; cerebral edema; and inflammation and regeneration. The importance of the secondary injury has gained widespread recognition as a potential target of therapeutic intervention. Although much has been learned about the molecular and cellular mechanisms of TBI in the past 2 decades, these advances have failed to translate into a successful clinical trial and no significant improvement in treatment beyond the acute setting [3].

Neuroinflammation is complicated and beyond the scope of this review. A critical balance exists between repair and proinflammatory factors that determine the outcome of neurodegenerative processes. Acute inflammation in the brain is characterized by rapid activation of the innate immune cells of the central nervous system, microglia, and astrocytes [4]. Once activated, astrocytes, the most abundant cells in the brain, release various growth factors, cytokines, and chemokines that function as neuromodulators to regulate inflammation. Common cytokines produced in response to brain injury include: interleukin-6, which is produced during astrogliosis, and interleukin-1 beta and tumor necrosis factor alpha, which can induce neuronal cytotoxicity [5]. Overturning the long-held concept of the absence of lymphatic vasculature in the central nervous system, it is now known that the brain is directly connected to the peripheral immune system via the glymphatic pathway, entirely changing the way the neuro-immune interaction is perceived [6].

The concept that TBI can lead to neurodegenerative changes was first introduced in 1926 by neurologists Osnato and Giliberti [7]. Affected individuals often exhibit disordered memory and executive functioning and behavioral and personality disturbances (e.g., apathy, depression, irritability, impulsiveness, and suicidality). Upon autopsy, the presence of hyperphosphorylated tau protein deposition, whether in the form of neurofibrillary tangles, neuropil threads, or glial tangles, is a defining feature of chronic traumatic encephalopathy (CTE) [8]. CTE in a retired professional American football player was first recognized in 2002 by Omalu et al. when autopsying the brain of a deceased player [9].

Nearly lost in the discussions of CTE has been the role of sustained or chronic neuroinflammation, even though this association has been well established pathologically since the 1950s. It has been widely believed that the accumulation of toxins and pathological proteins were an issue of overproduction rather than poor clearance from the brain. The recent discovery of the glymphatic pathway facilitating the clearance of β-amyloid and tau from the brain may overturn that belief [6]. After TBI, however, glymphatic pathway function was reduced

by ~60%, with this impairment persisting for at least 1 month postinjury. Such chronic impairment of glymphatic pathway function after TBI may be a key factor that renders the posttraumatic brain vulnerable to tau aggregation and the onset of neurodegeneration [10].

FAILURE TO FIND THERAPEUTIC INTERVENTIONS FOR TBI

The most definitive strategy to avoid short- or long-term detrimental effects of all TBI, mild to severe, is through primary prevention or avoidance of the injury in the first place. However, once a TBI occurs, the secondary injury represents a window of opportunity for therapeutic intervention with the potential to prevent and/or reduce brain damage and improve long-term patient outcome. To date, however, promising preclinical results have not been translated into successful clinical trials [11]. This may be due to the fact that most interventions target a single biochemical cascade rather than multiple mechanisms of injury.

Approaches that target multiple aspects of TBI are needed. The Western medical system evolved around the epidemiological triad of acute infectious diseases: one host–agent–environment and subsequently one drug to cure. Pharmaceuticals by nature are aimed at disrupting single enzymatic processes. TBI is too complicated for such a narrow approach. What is needed is a broad-spectrum, more holistic approach. Interventions targeting all aspects of the secondary injury, plus repair, regeneration, and protection of the brain are desperately needed. Effective interventions should also treat persistent symptoms associated with the long-term effects of TBI (postconcussive symptoms; e.g., memory disturbances, depression, headache) [12].

THE ROLE OF OMEGA-3 FATTY ACIDS IN THE BRAIN

It is well recognized that n-3FA are important for proper neurodevelopment and function. Linoleic acid (a short-chain n-6FA) and alpha-linolenic acid (ALA; a short-chain n-3FA) are fatty acids that cannot be made *de novo*, must be consumed in the diet, and are therefore considered essential. They are precursors for the synthesis of longer, more bioactive polyunsaturated fatty acids such as the n-6FA, arachidonic acid (AA), and the n-3FAs, eicosapentaenoic acid (EPA) and DHA. However, n-6FA and n-3FA compete for the same elongation and desaturation enzymes and the conversion of ALA to EPA and DHA in humans is negligible (Fig. 2). Therefore, EPA, and DHA in particular, should be consumed directly in the diet [13].

The age-old saying, "You are what you eat," holds true here. The composition of neuronal cell membranes is directly

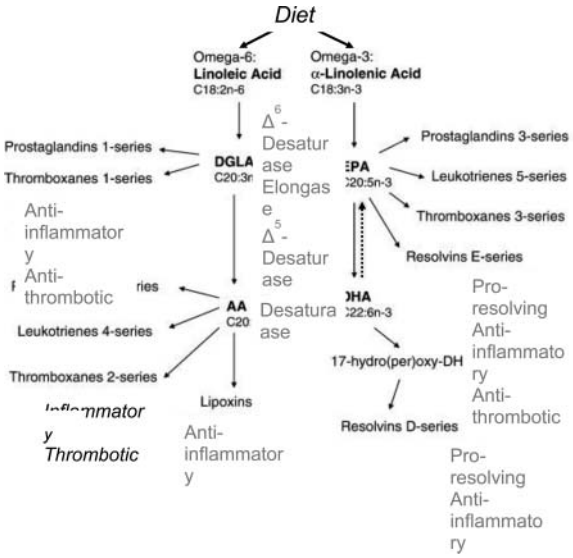

Fig. 2. Omega-6s and omega-3s compete for the same elongation and desaturation enzymes. However, very little ALA is converted ultimately to DHA mainly because the amount of omega-6s in the typical Western diet overwhelms the pathways favoring the synthesis of arachidonic acid. Note the pro-inflammatory and anti-inflammatory mediators.

reflected by the dietary intake of n-3FA and n-6FA. The ratio of n-6 and n-3 FAs affects the physiological functions of the brain and changes in cell permeability and synaptic membrane fluidity and has a major influence on the activity of neurotransmitters [14]. Unfortunately, today's Western dietary intakes result in an overdominant intake of pro-inflammatory n-6FA, creating a relative deficiency of immune-modulating n-3FA. The evolutionary human diet, up until the last century, had a relatively even AA:DHA ratio of approximately 1:1 and was high in fiber and rich in fruits, vegetables, lean meat, and fish and thus provided a more balanced ratio between n-6FA and n-3FA [14]. That ratio is now approximately 22–25:1 with n-6FA dominating [15]. The estimated per capita consumption of soybean oil, the most common source of n-6FA in the Western diet, increased greater than a 1000-fold from 1909 to 1999 in the United States, now contributing almost 8% of all calories consumed [16]. Excessive consumption of AA displaces DHA from membrane phospholipids reflected directly in the composition of neuron membrane phospholipids overwhelmingly favoring AA-derived inflammatory processes [17].

AA, the primary n-6FA in the brain, is metabolized by cyclooxygenase and lipoxygenase enzymes to pro-inflammatory eicosanoids. Eicosanoids are key mediators and regulators of inflammation involved in modulating the intensity and duration of inflammatory responses. AA is the major precursor for eicosanoid mediators such as 2-series prostaglandins and thromboxanes, prostaglandin E2, and leukotriene B4. These eicosanoids enhance vascular permeability, increase local blood flow, increase infiltration of leukocytes, and enhance production of other pro-inflammatory cytokines [18].

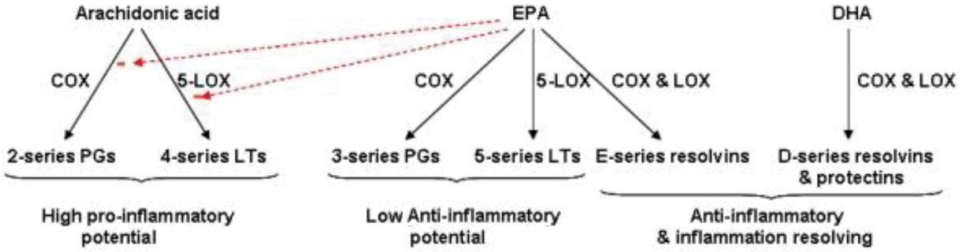

Fig. 3. The downstream biochemical pathways of AA, EPA, and DHA result in stimulation of pro-inflammatory 2-series prostaglandins and 4-series leukotrienes; anti-inflammatory 3-series prostaglandins and 5-series leukotrienes; E- and D-series resolvins; and neuroprotectins [37].

In contrast, n-3FA are anti-inflammatory. EPA is also a substrate for the cyclooxygenase and lipoxygenase enzymes that produce eicosanoids, but the mediators produced are biologically different from the AA-derived mediators. EPA-derived eicosanoids antagonize the action of eicosanoids derived from AA and thus can decrease AA-derived cyclooxygenase activity and inhibit the formation of these pro-inflammatory eicosanoids and cytokines [19]. EPA and DHA also give rise to E-series and D-series resolvins and protectins (Fig. 3). E- and D-series resolvins decrease accumulation of polymorphonuclear leukocytes and attenuate pro-inflammatory signaling. Resolution of inflammation via E- and D-series resolvins is required to shut off ongoing inflammatory processes and limit tissue damage. The anti-inflammatory effects of n-3FA suggest a therapeutic value or, at the least, the opportunity to modulate the inflammatory aspect of the secondary injury phase of TBI [20].

Though EPA is well known for its beneficial vascular properties, very little is found in brain tissue. DHA, on the other hand, is highly concentrated in the central nervous system and is essential for proper neuronal and retinal function. DHA is present in high concentrations in neurons where it is esterified to neuronal cell membrane phospholipids in phosphatidylserine and phosphatidylethanolamine [21]. DHA signalolipidomics is directly affected by the dietary supply of DHA. When mobilized from the cell membrane by phospholipase A2, DHA regulates unique cellular and molecular signaling pathways. Whereas eicosanoids are derived from 20-carbon chain AA and EPA, docosanoids, including neuroprotectin D1 proteins, are derived from the 22-carbon DHA in response to cellular stress and elicit neuroprotection [22]. DHA also promotes neurite growth, increased neurite branching, and subsequent synaptogenesis, resulting in enhanced synaptic function and improving neuronal repair after injury [23].

OMEGA-3 POLYUNSATURATED FATTY ACIDS AND TBI

EPA and DHA have the ability to impact all of the main mechanisms of the secondary injury phase of TBI; have neuroregenerative properties; are well-studied as substances in the scientific literature; can be given to a patient during the acute phase of injury (or prior to injury) and continued throughout the patient's entire rehabilitation; and can be used prophylactically prior to injury in populations at risk of TBI. Animal models of neurologic pathology indicate that n-3FA have the potential for improvement in the outcomes of TBI [24,25], stroke model [26], and spinal cord injury [27].

Three case studies are now reported in the scientific literature that can provide clinical guidance. In January 2006, an explosion in the Sago Mine in central West Virginia resulted in 14 trapped miners. Forty hours later, one lone survivor was found and brought to medical care. He had suffered hypoxia and exposure to toxic gases, dehydration, and rhabdomyolysis. The patient demonstrated many classic features of carbon monoxide toxicity, including neurologic, cardiac, and renal dysfunction as well as respiratory failure. In addition to rapid resuscitation, dialysis, and hyperbaric oxygen therapy, starting on hospital day 8, the patient was treated with 21.2 g per day of n-3FA that contributed to his neurological recovery following an initial presentation in deep coma. On day 21, he was transferred to a rehabilitation facility and discharged to home 2 months later [28].

In March 2010, a teenager sustained a severe TBI with diffuse axonal injury from a motor vehicle accident. The attending neurosurgeon's impression was that the injury was likely lethal. Believed to be in a permanent vegetative state, a tracheotomy and percutaneous endoscopic gastrostomy tube were placed for custodial care and enteral feedings were started on day 10. The next day, the patient began receiving almost 20 g total n-3FA daily via his percutaneous endoscopic gastrostomy based on the clinical results of the Sago Mine survivor's experience. On day 21, he was weaned off the ventilator and transported to a specialized rehabilitation institute. He was discharged to home 4 months after the injury [29].

When this case was reported on CNN's *Sanjay Gupta MD*, the mother of an 8-year-old girl requested her comatose daughter be given high-dose fish oil 82 days following a near-drowning accident in August 2012. The patient had sustained severe anoxic brain injury in the setting of prolonged cardiac and

respiratory arrest. The patient was discharged to home 1 month later [30]. In none of these 3 case reports were any side effects noted. Despite these case reports and anecdotal evidence, there is a complete lack of clinical trials for the use of n-3FA in human TBI.

SUGGESTED PROTOCOLS FOR USING OMEGA-3S FOR TBI AND CONCUSSIONS

Because of the complex heterogeneity of TBI and without definitive clinical trial evidence, there is no way to know whether n-3FA will help in any particular case of TBI. Growing clinical experience by numerous providers is that the brain needs to be saturated with high doses of n-3FA in order for the brain to have the opportunity to heal. Without an optimal supply of omegas, healing is less likely to happen. It is well recognized that n-3FA are not a drug and not a cure and every situation is different. Clinically, some patients respond better than others. However, there is no downside to providing optimal levels of nutrition in order to give a patient the best opportunity to regain as much function as possible following a TBI.

The dose that was used for the March 2010 case [29] was a concentrated liquid, one tablespoon (15 ml) twice a day for a total of 30 ml per day in the feeding tube followed by a saline flush providing 9756 mg EPA, 6756 mg DHA, and 19,212 mg total n-3FA daily. This case received this dose for about a year without any problems or side effects. Though these doses were used in adults, in pediatric patients, lower doses should be considered. Most important, weekly analysis of the AA:EPA ratio should be monitored to determine the appropriate dosage to avoid theoretical possibility of bleeding. When that ratio drops below 1.0, the dosage should be decreased as needed and intermittent monitoring continued [30].

For concussions and milder cases of TBI when patients are able to swallow on their own, a different protocol with fish oil capsules or liquid equivalent has been used extensively as published by the nonprofit charity Brain Health Education and Research Institute on their website [31]: 5000 mg of concentrated fish oil in triglyceride form providing approximately 3000 mg of n-3FA is consumed 3 times a day for a minimum of 1 week before decreasing to twice a day and eventually once a day. Anecdotally, this tapering provides a more immediate benefit improving mood, calmness, headaches, and cognitive function and the large doses in the beginning act more as a loading dose to overcome the relative deficit of n-3FA in most people. One open-label study evaluating pre- and posttherapy supplementation for 5 weeks using electroencephalogram brain mapping has been completed and submitted for publication. The pilot study showed statistically significant improvement in patient brain auditory-evoked response processing and heart rate variability power and improvements in most electroencephalogram, evoked response, and heart rate variability variables in 5 of 7 patients[32].

POTENTIAL HARMFUL EFFECTS

Due to the known antithrombotic action of these compounds, it is commonly believed that they may increase the risk of excessive bleeding or even hemorrhagic stroke. Theoretically, the biochemistry of n-3FAs tells us that this should be true. However, that has never been shown to be of clinical concern in any clinical trial reported in the literature. In fact, the antithrombotic nature is one of the properties that make n-3FA effective in decreasing mortality, particularly cardiovascular mortality where the effect is more beneficial than statins [33]. Multiple clinical trials have shown that high-dose fish oil consumption is safe, even in patients receiving other agents that may increase the risk of bleeding, such as aspirin and warfarin [34]. Interestingly, it is standard of care that most critically ill and injured patients are put on subcutaneous heparin, or similar, to prevent deep vein thrombosis while immobile. Recently, Farooqui et al. examined the use of blood thinning pharmaceuticals and concluded that they are safe, do not increase the risk of intracranial hemorrhage, and decrease the rate of deep vein thrombosis and pulmonary embolism [35]. Potent blood thinners used in this protocol (heparin and Lovenox) completely block the enzymes responsible for allowing the platelets to clot. n-3FA potentiate the body's natural anticlotting abilities rather than blocking enzymatic processes and add the ability to modulate neuroinflammation, decrease apoptosis, and start synaptogenesis. Ironically, most doctors who will not use n-3FA, citing that high doses of n-3FA decrease the ability of blood to clot and increase a patient's risk of bleeding, immediately put their intensive care unit patients on potent pharmaceutical blood thinners that increase the risk far greater than that of n-3FA.

CONCLUSIONS AND FUTURE DIRECTIONS

Concussions and TBI, with their diverse heterogeneity and prolonged secondary pathogenesis, remain a clinical challenge to clinician, patients, and their families. Current medical management of TBI patients appropriately focuses on specialized prehospital care, intensive acute clinical care, and long-term rehabilitation but lacks clinically proven effective management with neuroprotective and neuroregenerative agents [11]. Clinical studies thus far have failed to identify an effective treatment strategy because they typically have targeted single enzymatic factors in an attempt to identify a pharmacologic target rather than

considering multiple mechanisms of injury with a more holistic approach. The concept of a "magic bullet" focused on a single target is not helpful; instead, a combination of targets controlling aspects of neuroprotection, neuroinflammation, and regeneration is needed. n-3FA offer the advantage of this polytarget approach [27].

Although further clinical trial research is needed to establish the true advantage of using n-3FA, there is a growing body of strong preclinical evidence and clinical experience suggests that benefits may be possible from aggressively adding substantial amounts of n-3FA to optimize the nutritional foundation of concussion and TBI patients. Numerous university athletic programs and professional sports teams are reported to be using n-3FA and the omega protocols with their athletes. However, recovery from TBI may be hindered by our modern, pro-inflammatory diet. An optimal nutritional regimen to overcome the n-6FA dominance must be in place if the brain is to be given the best opportunity to repair itself.

Administration of substantial and optimal doses of n-3FA earlier in the course of TBI, prophylactically, has the potential to improve outcomes from this potentially devastating public health problem. As the father of one severe TBI survivor says, "Conventional medicine only takes survivors of severe TBI so far, often ending at the nursing home door, or heavily medicated at home, facing long empty hours, and overwhelming family resources. Unconventional therapies are not merely a reasonable option, they are a necessity" [36, p. 242]. With evidence of unsurpassed safety and tolerability, n-3FA should be considered mainstream, conventional medicine, if conventional medicine can overcome its inherent bias against nutritional, nonpharmacologic therapies.

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