Use of Omega-3 Fatty Acids in Traumatic Brain Injury

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Abstract

Clinical studies thus far have failed to identify an effective treatment strategy for Traumatic brain injury (TBI), 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 which suggests that benefits may be possible from aggressively adding substantial amounts of n-3FA to optimize the nutritional foundation of TBI, concussion, and post-concussion syndrome patients. Early and optimal doses of n-3FA, even in a preventive setting, have the potential to improve outcomes without significant side-effects. With evidence of unsurpassed safety and tolerability, n-3FA should be considered in the acute care and surgical setting, if conventional medicine can overcome its inherent bias against nutritional, non-pharmacologic therapies.

Key Words: Omega-3; Decosahexanoic Acid; DHA; TBI; Brain Injury; Concussion; Neuroregeneration; Neuroinflammation; Neuroprotection

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 TBI's 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 healthcare concern, constituting a major cause of death and disability not just in the United States, but throughout the world. Motor bikes 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 two phases, or on the basis of the path physiologic 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 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 degrees 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. (Figure. 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 two 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, beyond the scope of this review. A critical balance exists between repair and pro-inflammatory factors that determine the outcome of neurodegenerative processes. Acute inflammation in the brain is characterized by rapid activation

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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 (IL-6), which is produced during astrogliosis, and interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α), 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 changing entirely 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 it be in the form of neurofibrillary tangles (NFTs), neuropil threads (NTs), or glial tangles (GTs), is a defining feature of Chronic Traumatic Encephalopathy (CTE) [8]. CTE in a retired professional American football player was first recognized in 2002 by Bennet 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 post injury. Such chronic impairment of glymphatic pathway function after TBI may be a key factor that renders the post-traumatic 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 (post-concussive symptoms, e.g., memory disturbances, depression, headache) [12].

**The Role of Omega-3 Fatty Acids in the Brain**

It is well recognized that n-3FAs 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 (PUFAs) 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. (Figure. 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 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, 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 over dominant 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 was high in fiber, rich in fruits, vegetables, lean meat, and fish, 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 two-series prostaglandins and thromboxanes, prostaglandin E2 (PGE2); and leukotriene B4 (LTB4). These eicosanoids enhance vascular permeability, increase local blood flow, increase infiltration of leukocytes, and enhance production of other pro-inflammatory cytokines [18].

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, 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 polymorph nuclear leukocytes (PMNs) 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, at the least, the opportunity, to modulate the inflammatory aspect of the secondary injury phase of TBI [20].

While 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 (PS) and phosphatidylethanolamine (PE) [21]. DHA signalolipidomics is directly affected by the dietary supply of DHA. When mobilized from the cell membrane by phospholipase A2 (PLA2), DHA regulates unique cellular and molecular signaling pathways. Whereas eicosanoids are derived from 20-carbon chain AA and EPA, docosanoids, including neuroprotectin D1 (NPD1) 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 Pufas and TBI**

EPA and DHA have the ability to impact all the main mechanisms of the secondary injury phase of TBI; have neuroregenerative properties; is 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 n-3FA have the potential for improvement in the outcomes of TBI [24,25], stroke model [26], and spinal cord injury (SCI) [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 two 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 (PEG) 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 PEG tube. 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 9,756 mg EPA, 6,756 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. While these doses were used in adults, in pediatric patients, lower doses should be considered. Most importantly, 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 (www.brainhealtheducation.org): concentrated fish oil in triglyceride form providing approximately 3000 mg of n-3FA per dose is consumed three times a day for a minimum of one week before decreasing to twice a day and eventually once a day. Anecdotally, this loading dose approach provides a more immediate benefit improving mood, calmness, headaches, and

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**Figure 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 [35]
cognitive function and the large doses in the beginning act to overcome the relative deficit of n-3FA in most people. One open label study evaluating pre- and post therapy supplementation for five weeks using electroencephalogram (EEG) 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 EEG, evoked response, and heart rate variability variables in five of seven patients. [Lewis, submitted for publication]

Potential Harmful Effects

Due to the known anti-thrombotic action of these compounds, it is commonly believed they may increase the risk of excessive bleeding or even hemorrhagic stroke. Theoretically, the biochemistry of n-3FAs tells us 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 anti-thrombotic 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 [31]. 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 [32]. 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 they are safe, do not increase the risk of intracranial hemorrhage, and decreases the rate of deep vein thrombosis and pulmonary embolism [33]. 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 anti-clotting 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 ICU patients on potent pharmaceutical blood thinners that increase the risk far greater than that of n-3FA.

Conclusions and Future Directions

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 as 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, and instead a combination of targets controlling aspects of neuroprotection, neuroinflammation, and regeneration is needed. n-3FA offer the advantage of this poly-target 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 TBI patients. Numerous university athletic programs and professional sports teams are reported to be using n-3FA and the omega protocols with their athletes for the prevention of brain injuries. 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, even prophylactically in those at greater risk of a brain injury, such as soldiers and athletes, has the potential to improve outcomes from this potentially devastating public health problem [19]. 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” [34]. 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, non-pharmacologic therapies.

References


