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Review

Omega-3 Fatty Acids as a Putative Treatment for Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a global public health epidemic. In the US alone, more than 3 million people sustain a TBI annually. It is one of the most disabling injuries as it may cause motor and sensory deficits and lead to severe cognitive, emotional, and psychosocial impairment, crippling vital areas of higher functioning. Fueled by the recognition of TBI as the ''signature injury'' in our wounded soldiers in Iraq and Afghanistan, and its often devastating impact on athletes playing contact sports, interest in TBI and TBI research has increased dramatically. Unfortunately, despite increased awareness of its detrimental consequences, there has been little progress in developing effective TBI interventions. Recent evidence, however, strongly indicates that nutritional intervention may provide a unique opportunity to enhance the neuronal repair process after TBI. To date, two omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have the most promising laboratory evidence for their neuro-restorative capacities in TBI. Although both animal models and human studies of brain injuries suggest they may provide benefits, there has been no clinical trial evaluating the effects of n-3 fatty acids on resilience to, or treatment, of TBI. This article reviews the known functions of n-3 fatty acids in the brain and their specific role in the cellular and biochemical pathways underlying neurotraumatic injury. We also highlight recent studies on the therapeutic impact of enhanced omega 3 intake *in vivo*, and how this may be a particularly promising approach to improving functional outcome in patients with TBI.

Key words: encephalopathy; omega 3 fatty acids, plasma membrane; therapeutic approaches to CNS injury; traumatic brain injury

Introduction

Traumatic brain injury (TBI) remains a significant cause of death and permanent disability in the United States. Drawing data from hospitalizations and emergency department visits only, the Centers for Disease Control and Prevention (CDC) estimates that 1.7 million people in the United States sustain a TBI each year. Approximately 15%–20% of U.S. soldiers in Iraq and Afghanistan also experience a TBI while deployed, making TBI one of the most common injuries among military personnel.[1] It is estimated that 1.6–3.8 million sports-related TBIs occur in the United States annually, including those not treated by a health care provider.[2,3] Seventy-five to eighty percent of TBIs, however, are mild, involving only a brief alteration in consciousness or mental status.[4] Emerging research on the long-term effects of mild traumatic brain injury (mTBI) has drawn intense media attention and even Congressional scrutiny.

Repetitive head impacts add another level of complexity to the characterization of TBI because the emergence and duration of pathogenic events can overlap. This is particularly relevant in athletes and military personnel. Recent evidence suggests that chronic repetitive subconcussive head impacts may also result in cumulative long-term deleterious effects.[5] Therefore, the summed effects of both concussive and subconcussive injuries may better represent the more complicated clinical landscape for TBI.

TBI represents both an acute and chronic process. Although the immediate consequences of brain injury can be devastating, long-term health disorders associated with TBI include post-traumatic stress disorder (PTSD), neurodegenerative diseases (Alzheimer's disease or Parkinsonism), neurocognitive deficits, psychosocial health problems (e.g., binge drinking, major depression, impairment of social functioning and ability to work, suicide), epilepsy, pain, and other alterations in personality or behavior.[6–8]

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TBI is a multifaceted disease with prolonged secondary pathogenesis and long-lasting adverse neurological sequelae that remain a clinical challenge to manage. Interventions targeting the acute phase of TBI, such as prevention of hypoxia and excitotoxicity, will differ from those targeting the chronic phase of TBI. Phase III clinical trials thus far have failed to yield an effective pharmacological strategy for neuroprotection in TBI, and this may be partly due to the use of drugs that target only a single pathophysiological pathway rather than the multiple mechanisms involved in secondary injury post-TBI.[9] Targeting the multiple pathways that contribute to a deleterious secondary cascade may result in more successful clinical outcomes.

A growing body of preclinical data has shown that nutritional intervention, such as dietary supplementation with n-3 (also known as omega-3) fatty acids, may be of therapeutic benefit in acute injury to the brain.[10–13] Omega-3 fatty acids have long been known to play a restorative role in several pathways implicated in traumatic insult to the brain.[12,14–17] Emerging clinical evidence from both animal models and human studies of other brain injuries continue to suggest that they may provide benefits; however, there has been no human trial evaluating the effects of n-3 fatty acids on resilience to or treatment of TBI,[17–19] though there have been case studies on the use of omega-3s in the acute phase of severe head injury.[188,189] This article reviews the physiological functions of n-3 polyunsaturated fatty acids (PUFAs) in the central nervous system (CNS), and their uniquely protective role against subcellular mechanisms of degeneration induced by traumatic injury to the brain. We also discuss select studies on the therapeutic effects of n-3 PUFAs *in vivo*, and how omega-3 supplementation could potentially improve behavioral and cognitive outcomes in patients with TBI.

The Role of n-3 Fatty Acids in the Brain

The most important n-3 fatty acids for human health and nutrition are docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA). Omega-3 fatty acids must be obtained from diet, and are highly enriched in algal oil, krill, and cold water fish.[20,21,190] Poultry and eggs also provide small quantities of EPA and DHA,[22] while nuts, soybean, canola, and flax seed oils are major dietary sources of ALA.[23] Humans can also convert a limited amount of ALA into EPA and DHA, but synthesis of EPA and especially DHA from ALA is insufficient to supplant dietary intake.[24]

The human brain consists of 60% lipid by dry weight, and docosahexaenoic acid is one of the most abundant fatty acids found in the solid matter of the brain.[25] DHA is a primary structural component of the mammalian cerebral cortex, and comprises 50% of neuronal membrane phospholipids.[26] Omega-3 fatty acids are essential for maintaining membrane fluidity,[27] which in turn impacts neuronal cell adhesion, axon guidance, synapse maintenance, dendritic formation, and the speed of neurotransmission.[28–30] DHA, for instance, is the longest and most unsaturated fatty acid found in biological membranes, with a structure that is tremendously flexible and therefore versatile.[31] It is capable of undergoing rapid interconversions between multiple torsional states, and is unique in its ability to significantly alter membrane order and fluidity, phase behavior, elastic compressibility, ion permeability, and fusion.[32–39] Not surprisingly, then, this highly adaptable PUFA is particularly enriched in membranes which require rapid vesicle formation and release, such as rod outer segments in the retina and neuronal synapses.[40] The ability of DHA to readily undergo such complex yet minimal energy-requiring conformational changes is thought to be one of the main reasons why it is so abundant in the brain.[31 40]

Due to its steric incompatibility with cholesterol and sphingomyelin, DHA also forms distinct lipid microdomains within the inner leaflet of the bilayer.[41] Such segregation is known to modulate the activity of various receptors, ion channels, G-proteins, and other membrane-bound proteins.[42] At physiological concentrations, for instance, DHA can potently and irreversibly inhibit ion flux through voltage-gated K^+ channels in olfactory neurons.[43] Both DHA and EPA have additionally been shown to inhibit hippocampal neuron membrane excitability, whereas saturated and mono-unsaturated fatty acids do not.[44] Finally, a positive linear relationship also exists between the activity of the sodium-potassium pump (Na^+K^+ATPase) and the membrane concentration of DHA.[45] The mammalian brain has both the highest concentration of DHA as well as the highest activity rate of the sodium-potassium pump, and though the activity of Na^+K^+ATPase accounts for some 20% of the general basal metabolic rate, it accounts for approximately 60% of energy utilization in the brain.[45]

An additional proposed reason for why omega-3 PUFAs are so essential to and enriched in the brain is their unique transformation into neuroprotective metabolites, which are critical in the defense against oxidative stress, tissue inflammation, and maintenance of synaptic integrity.[46–48] For example, during tissue stress, both EPA and DHA are thought to be released from membrane phospholipids and converted into compounds called ''resolvins,'' which actively promote resolution of inflammatory processes, such as via downregulation of NF-κB and clearance of neutrophils.[49–51]

Nonmembrane bound (i.e., unesterified) DHA also regulates ion channel activity, as well as the expression of genes involved in control of signal transduction, synaptic plasticity, and cytoskeletal assembly.[23,29,52,53] In response to oxidative stress, free DHA may be used to synthesize neuroprotectin D1 (NPD1) via 15-lipoxygenase-1. NPD1, in turn, protects cells by upregulating anti-apoptotic proteins such as Bcl-2 and Bcl-xL, while downregulating pro-apoptotic proteins such as Bax and Bad. NPD1 synthesis can also be triggered in response to neurotrophins, ischemia, and reperfusion.[47]

Omega-3 polyunsaturated fatty acids are also ligands for retinoid X receptors (RXR) in the brain, which play a crucial role in neuronal growth and proliferation during fetal development, and in the morphological differentiation of catecholaminergic neurons.[54,55] RXR and related retinoic acid receptors are also highly expressed in the hippocampus, which may prove pertinent to understanding the functional role of omega-3s, particularly DHA, in the adult brain.[23,56]

Effects of n-3 Fatty Acid Deprivation

Chronic dietary deprivation of n-3 fatty acids in animals leads to: 1) decreased mean cell body size in neurons of the hippocampus, hypothalamus, and parietal cortex; 2) reduced complexity of dendritic arboritizations on cortical neurons; and 3) significant deficits in spatial learning and memory.[57–61] In contrast, increased brain levels of DHA in adult mice enhances hippocampal neurogenesis as evidenced by an increased number of proliferating neurons, increased neurite outgrowth, and increased density of dendritic spines, all of which correlate with markedly improved performance in spatial learning tasks.[62] In addition to serving as building blocks for membrane synthesis and modulating gene expression during neurogenesis, n-3 fatty acids are also involved in regulating

neurotransmitter receptor levels and activity.[58,59] Increased intake of n-3 PUFAs in a rat model of cerebral hypoperfusion, for instance, enriched the density of serotonergic and muscarinic acetylcholine (ACh) receptors in the dentate gyrus and CA3 regions of the hippocampus, and increased binding to muscarinic receptors.[63] Performance on memory tasks was also improved in these rats.[64]

Rodents subjected to chronic omega-3 fatty acid deficiency also suffer from impaired attention and poor performance on shock avoidance, olfactory learning, exploratory, and flexibility behavior tasks.[65–68] Cholinergic pathways and ACh release are critical for arousal, attention, learning, and memory,[69–73] as is dopamine neurotransmission, which is also altered by dietary restriction of n-3 polyunsaturated fats.[74–77] Dopaminergic neurons in the mesolimbic system are critical for motivational behavior and emotional functions, while mesocortical dopaminergic neurons are key players in cognitive functions such as working memory.[78] The vesicular storage pool of dopamine in both of these systems is depleted in n-3 PUFA-deficient animals, resulting in diminished dopamine release and impaired performance on cognitive tasks.[76,77,79] The density of D2 dopamine receptors is also notably reduced in the frontal cortex of omega 3-deprived, aging rats.[75]

Neurotherapeutic Effects of n-3 Fatty Acids *in Vivo*

Dietary supplementation has considerable influence on DHA content in the brain.[80,81] Though previous studies in mammals have focused heavily on chronic dietary deficiency, DHA has been shown to be neuroprotective in nondeficient animal models as well.[14,82] In rats that had not been deprived of dietary fatty acids prior to traumatic axonal insult, for instance, DHA supplementation significantly ameliorated secondary mechanisms of injury and reduced the number of damaged axons.[82]

Through mechanisms that are still incompletely understood, dietary supplementation with omega-3 fatty acids has been shown to decrease the production of reactive oxygen species (ROS) significantly and to improve cognitive function *in vivo*.[83,84] In rat-based models of ischemic injury, for instance, chronic administration of DHA reduced levels of lipid peroxidation byproducts and enhanced antioxidant activity in the brain.[83,85,86] Likewise, treatment at the onset of reperfusion has been shown to dramatically reduce infarction and increase scores on behavioral assessments.[87] Moreover, rats with traumatic spinal cord injuries have demonstrated significantly reduced inflammatory markers, along with increased neuron and oligodendrocyte survival and locomotor performance following a single dose of intravenous DHA post-compression or hemisection.[88,89] When acute I.V. injection of DHA was followed with daily dietary supplementation, these therapeutic effects were sustained throughout the entire study duration of 6 weeks.[89] No significant improvement in outcome, however, was seen if intravenous DHA treatment was delayed until 3 hours post-injury, or if DHA was administered for 1 week through diet alone.

Recent reports have shown that omega-3 PUFAs may have a trophic effect on neurites as well, inducing more rapid and robust outgrowth of new fibers in animals fed a DHA-enriched diet after peripheral nerve transection.[90] Accelerated functional recovery and axonal regeneration secondary to upregulated n-3 PUFAs have also been observed in mice with acute traumatic injury to the sciatic nerve.[91] Similarly, in animal models of TBI, decreased levels of β-amyloid precursor protein, a marker of axonal injury, were observed after 1 month of dietary supplementation with DHA.[14,15] Decreased axonal injury counts and apoptotic markers as well as improved memory have also been documented in rats with traumatic brain injuries when given prophylactic DHA for 30 days.[82]

Polyunsaturated fatty acids in humans, particularly DHA, serve an essential role in nervous system development and are required for proper synaptogenesis, neural membrane synthesis, and the building of functionally critical circuits within the brain.[92] DHA deficiency is associated with aging and neurodegenerative conditions such as Alzheimer's disease,[92] while DHA consumption has been shown to improve performance on visuospatial learning and memory tasks in patients with age-related cognitive decline.[93] There is additional evidence in humans that dietary supplementation with omega-3 fatty acids improves functional recovery in subarachnoid hemorrhage and stroke.[94–97]

The impact of omega-3 PUFAs on prevention and recovery from stroke remains an intense area of inquiry, though the association between consumption of fish and fish oils and decreased risk of cardiovascular disease was first noted over 50 years ago.[98] Higher consumption of fish and n-3 fatty acids is correlated with a reduced risk of thrombotic stroke,[99,100] thus omega-3 PUFAs, in particular DHA, are now being investigated as putative ''nutraceuticals'' for treatment of cerebral ischemia.[101,102] Though the mechanisms by which omega-3s are protective against ischemic insult to the brain are not fully understood, neuroinflammation and programmed cell death are two well-known events underlying the pathophysiology of stroke.[103,104] DHA has previously been shown to be metabolized into neuroprotective mediators known as docosanoids, the most extensively studied of which is 10,17S-docosatriene, also referred to as the aforementioned NPD1.[48,105] NPD1 is a potent inhibitor of proinflammatory cytokine expression and apoptosis, as well as ischemia-reperfusion mediated infiltration by leukocytes.[46,101,106,107] DHA also has antioxidant activity and mitigates peroxidative damage of lipids and proteins in the brain.[23] In congruence with these findings, other studies have demonstrated that DHA can attenuate neuronal death and cognitive and locomotor impairments in animal models of ischemia-reperfusion injury to the brain.[108–110] Given that the same inflammatory, apoptotic, and oxidative stress mechanisms are implicated in traumatic injury to the brain, it can be reasonably hypothesized that accumulation of omega-3 fatty acids in the brain might also be neuroprotective in TBI.

Omega-3 Fatty Acids and the Pathogenesis of TBI

TBI results in a diffuse, progressive process of axonal destruction, demyelination, and neuronal cell death, not only at the site of impact but also in the surrounding parenchyma.[111] Injury first occurs due to the direct physical forces associated with traumatic insult, but is then followed by a secondary wave of disruption in the subsequent hours and days due to inflammatory responses, excitotoxicity, and oxidative stress.[19,112,117,119] Omega-3 fatty acids mitigate the consequences of several key pathological pathways in TBI, such as mitochondrial malfunction, apoptotic cell death, glutamate-triggered excitotoxicity, and injury-induced oxidative stress and inflammation.[83,85,86,92,113,114,118] Omega-3 fatty acids may therefore play a critical role in the restoration of cellular energetics and repair of neuronal damage after TBI.

The production of pro-inflammatory prostaglandins is stimulated by and derived from the release of arachidonic acid (AA) secondary to disruption of neuronal cell membranes.[112,113] Also released from neuronal membranes under pathological conditions,[185] however, is DHA, which makes up 30% of the dry weight of the brain.[22, 25, 26,186] Whereas arachidonic acid is rapidly

converted into potent inflammatory mediators such as prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acids, DHA and its derivatives function in a neuroprotective capacity instead, antagonizing the pro-death signaling pathways initially triggered by AA.[92,113] The metabolism of two omega-3 fatty acids, EPA and DHA, specifically leads to the production of docosanoids (also known as ''neuroprotectins'') and resolvins, which not only inhibit the activation and migration of inflammatory cells, but upregulate anti-apoptotic cascades and expression of receptor families significantly involved in tissue repair as well.[114,187] These mechanisms, in turn, result in increased cell survivability and improved neurological outcome.[12,14–17]

The nonspecific release of the excitotoxic neurotransmitter glutamate is another destructive event following acute traumatic injury in the brain.[117] Excess glutamate causes overactivation of N-methyl D-aspartate (NMDA) and calcium-permeable AMPA receptors, leading to massive influx of Ca^{2+} and the induction of both programmed and necrotic cell death via calcium-dependent proteases.[19,115–117] DHA has previously been shown to mitigate glutamate cytotoxicity and decrease Ca^{2+} influx *in vitro*,[118] and downregulates the expression of AMPA receptor subunits on the surface of cultured cells.[119] One of the most detrimental consequences of surplus intracellular Ca^{2+}, however, is increased oxidative stress, a key contributor to the pathophysiologic changes that occur after TBI. Influx of excess Ca^{2+} into mitochondria leads to the formation of ROS, which directly damage DNA and proteins. The toxic accumulation of damaged DNA and oxidized proteins further induces programmed cell death.[117] ROS also initiate the process of lipid peroxidation on a catastrophic scale, which not only disrupts the integrity and function of neuronal membranes, but propagates further free radical formation secondary to the propensity of lipoperoxyl byproducts for attacking adjacent fatty acid chains.[113] Moreover, antioxidant defense mechanisms are relatively scarce in the human central nervous system, and the continued production of ROS via lipid peroxidation further depletes endogenous free radical scavengers that have already been overwhelmed.[120] Disruptions in cerebral blood flow likewise result in energy depletion and subsequent collapse of energy-dependent ion transport as well as intracellular Ca^{2+} overload.[19 116] Hence oxidative stress is not limited to the ischemia/hypoxia stage; rather, a second course of oxidative damage (as well as inflammation) is incurred during the reperfusion phase of injury, resulting in additional microvascular damage, secondary ischemia, and neuronal cell death.[121 122]

Clinical Considerations and Future Directions

TBI, with its intrinsic heterogeneity and prolonged secondary pathogenesis, remains a clinical challenge to manage. Clinical studies thus far have not yet identified an effective treatment strategy against secondary injury after traumatic insult to the brain has occurred.[9] This is perhaps due to the fact that the majority of phase III prospective trials targeted single factors rather than multiple mechanisms of injury.[123] NMDA receptor antagonists, for example, were specifically aimed at reducing glutamate excitoxicity but failed to be of significant benefit in human trials.[124,125] Likewise, administration of corticosteroids, well known for their anti-inflammatory effects, has shown no clear improvement in outcome or reduction in intracranial pressure,[126] and one large study revealed that such compounds may in fact increase the risk of death after TBI.[127] Other monotherapies that have been recently and clinically investigated for potential neuroprotection in TBI include: cyclosporin A, progesterone, erythropoietin, and statins.[9,123]

As most drugs aimed at limited pathways of injury have achieved little, if any, success in larger clinical trials, treatments with broader, pleiotropic effects are being increasingly explored. Multi-potential approaches such as dietary supplementation with omega-3 fatty acids, however, have primarily been investigated at only the pre-clinical stage. Two notable exceptions are progesterone and statins. The sex steroid progesterone, unlike corticosteroids, is thought to not only reduce cerebral edema but to also have neuroprotective effects as well, and has been positively correlated with improved functional outcomes at up to 6 months follow-up in two randomized, double-blind, placebo-controlled phase II trials.[128,129] Two multi-center, phase III clinical trials are now currently under way.

In addition to inhibiting cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors, or ''statins,'' exert favorable effects on multiple mechanisms of both acute and secondary injury.[130] Larger phase II clinical trials specifically evaluating the use of rosuvastatin and artovastatin in the treatment of TBI have thus been planned.[123]

Overall, multifunctional compounds such as HMGCoA reductase inhibitors have emerged as one of the most promising lines of defense against the deleterious effects of traumatic injury to the brain.

Like statins, n-3 PUFAs target multiple components of the secondary TBI injury cascade (Fig. 1) and, being an essential part of the human diet, are highly safe and well tolerated.[111,131,132] In contrast to statins and hormone-based therapies, omega-3s are readily taken up by the brain. Unlike hormones, they can be orally administered in addition to the parenteral route.[133,134] The U.S. Food and Drug Administration has furthermore confirmed the overall safety of fish oil, and both DHA and EPA at levels up to 3 g/day are generally recognized as safe.[135] The American Heart Association has furthermore established intakes of 1 g of EPA and DHA from fish or fish oils for patients with cardiovascular disease, and supplements of 2–4 g for subjects with high blood triglycerides.[136] Most clinical studies of DHA have employed a dose of 2–6 g/day, and no consistent adverse events have been observed in humans consuming from less than 1 up to 7.5g/day of DHA.[137]

Potential harmful effects of n-3 PUFAs, however, have been described in the literature. Due to the established anti-thrombotic action of these compounds, for instance, they may increase the risk of hemorrhagic stroke, as suggested by a necropsy-based study of four cases in Greenland.[138] The authors warn, however, that the power of their analysis is weak given the limited sample size, and that their study may have been subject to inadvertent selection bias.[138] In addition, 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.[139–141] The overall clinical data suggests that DHA at doses up to 6 g/day does not have deleterious effects on platelet aggregation or other clotting parameters in normal individuals, and fish oil does not augment aspirin-induced inhibition of blood clotting.[137] Platelet function is, on the other hand, inhibited by DHA consumption in type 2 diabetics, but it is suggested that this may actually be of benefit to these individuals, especially when coupled with the other activities of DHA.[142] Nevertheless, it may be prudent to discontinue high-dose supplementation in the setting of an acute bleeding illness or in patients at high risk for hemorrhagic stroke or, as is frequently recommended with aspirin, warfarin, and clopidogrel, prior to planned invasive procedures with the highest risk for bleeding complications.[143–146]

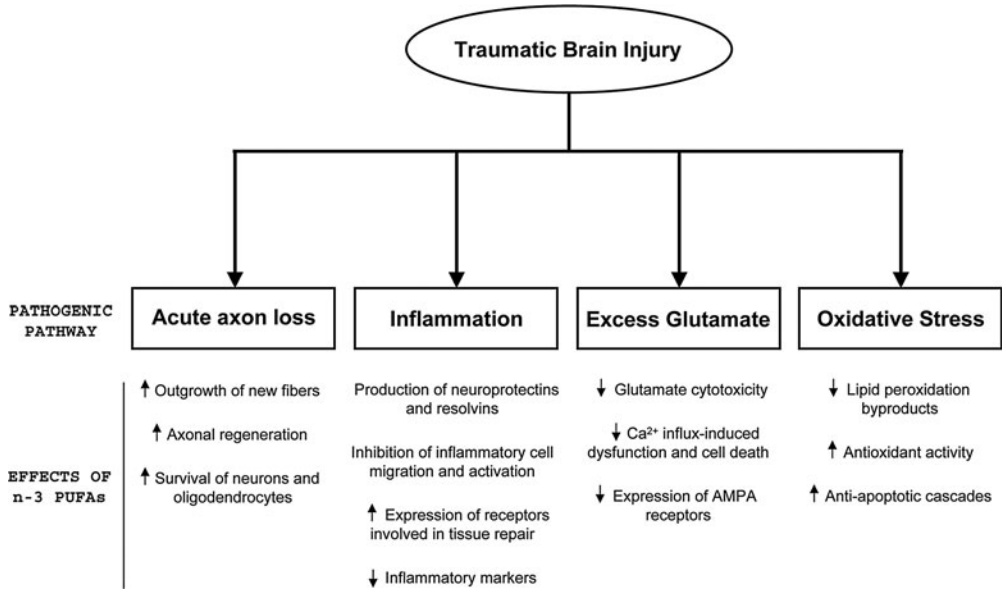

FIG. 1. Therapeutic impact of omega-3 fatty acids on different mechanisms of injury in TBI. Supplementation with n-3 polyunsaturated fatty acids improves cell survival, recovery, and functional outcome after traumatic insult via pleiotropic effects on a variety of pathways.

Despite the accumulation of evidence that DHA has protective antioxidant effects on cells, PUFAs nonetheless have high susceptibility to lipid peroxidation themselves by virtue of having acyl chains with several double bonds,[147] and lipoperoxidation byproducts, such as oxygenated α,ß-unsaturated aldehydes that can be derived from oxidation of DHA, have a potential carcinogenic role.[148] Only one study has examined the formation of such compounds *in vivo,* and reported that plasma levels of 4-hydroxyhexenal (4-HHE), a lipoperoxyl specifically derived from DHA, were significantly increased in 12 men given 0.8–1.6 g/day DHA for 2 weeks.[149] The authors noted, on the other hand, that 4-HHE only represented 0.01% of plasma PUFAs in these men, suggesting that production of 4-HHE only took place to a very low extent.[149] Two studies have examined markers of oxidative stress in patients supplemented with 4 g/day and 6 g/day of DHA for 6 and 8 weeks, respectively, and found that lipid peroxidation was either unaffected or significantly lower in these individuals compared to placebo-treated controls.[150,151] Data on the potentially adverse effects of lipid oxidation following omega-3 fatty acid ingestion otherwise remain highly limited at this time.

High intake of fish oil via heavy consumption of fish may also increase the risk of exposure to environmental toxins and contaminants such as mercury and polychlorinated biphenyls.[152,153] The current body of evidence indicates that the benefits of fish intake generally outweigh the potential risks, except in a few selected species of fish.[154] But the existing recommendations apply only to ingestion of fish rather than supplementation with purified fish oil, testing of select samples of which has revealed very low to negligible levels of mercury and other environmental toxins.[155] Prescription preparations of fish oil additionally undergo even more rigorous purification and are subject to further regulatory processes and quality control in order to achieve FDA approval.[143]

Concern has also been raised regarding the possibility of immunosuppression by n-3 PUFAs due their anti-inflammatory effects. High doses of DHA (≥ 4.9 g/day), for instance, can suppress T-cell activation in humans and inhibit natural killer cell activity as well as decrease the number of total circulating white blood cells.[156–158] Although alterations in certain immune parameters may be of benefit in inflammatory diseases, they are of unknown consequence in healthy individuals. Intake of elevated levels of omega-3s may potentially incur a higher risk of infection, but no increased incidence or rate of infections has been reported thus far in the literature. Studies with sufficient statistical power to specifically examine this possibility, however, have not been conducted.[137]

A recent Cochrane Collaboration review concluded that fish oil supplementation may produce mild gastrointestinal discomfort but are otherwise well tolerated.[159] The most common intolerance encountered to fish oil clinically is a ''fishy'' smell, aftertaste, and eructations.[145,146,160] A practical solution to this problem, particularly in the setting of TBI, could be the use of intravenous as opposed to oral preparations of fish oil. In addition, vitamin E is frequently added to supplements in order to reduce rancidity, maintain freshness, and increase shelf life.[143]

In summary, further clinical studies are warranted to examine closely both the potential benefits and adverse effects of omega-3 fatty acids in the acute phase of human TBI. To date, however, there have been no clinical trials examining nutritional intervention with omega-3s immediately after TBI.[18,19] There is a single report in which oral intake of n-3 and n-6 fatty acids for 90 days augmented immediate memory and attention scores in patients with mild cognitive impairment, as well as immediate and delayed memories in patients with organic brain lesions, including TBI.[161] It should be noted, however, that fewer than 10 patients with TBI were included in this study and all were required to be at least 5 years post-injury. Hence, supplementation was not initiated during the acute period but rather after a sustained, chronic history of neuropsychological decline. Furthermore, no physiological measures of neural activity were performed in these subjects, such as imaging via functional MRI. Finally, this study was performed prior to the validation and widespread use of biochemical markers in biological samples such as urine, serum, and CSF to both monitor and quantify primary and evolving damage in TBI, such as the highly brain-specific protein S100B.[162–165] Serum levels of S100B have recently been shown to

predict CT findings and clinical outcomes in mild traumatic head injury,[166] and are increasingly utilized to help identify, for example, patients who may benefit from early surgical intervention after TBI.[164] Future studies on the neuroprotective potential of n-3 fatty acids for treatment of TBI could therefore examine whether sustained omega-3 administration can reduce levels of biomarkers of structural damage and inflammation, enhance regional brain activity, and improve cognitive function in post-traumatic patients over time.

TBI is an intrinsically multifaceted disease and therefore requires a combinatorial approach to its management. Nutritional interventions targeting key pathological factors in the acute phase will differ from those directed toward the subacute and chronic phase of TBI. Orally administered, omega-3 fatty acids may take days to weeks to get incorporated into cellular membranes to demonstrate the potential benefits. Therefore, intravenous administration of omega-3 fatty acids could be a more suitable intervention to study the immediate potential benefits after TBI, while sustained oral administration may enhance the repair and recovery mechanisms after TBI.

Conclusion

Omega-3 fatty acids restore cellular energetics, reduce oxidative stress and inflammation, repair cellular damage, and mitigate the activation of apoptotic processes after TBI. Simultaneously affecting these well-elucidated key pathological mechanisms associated with TBI, well tolerated, and easy to administer, nutritional interventions using omega-3 fatty acids present a unique advantage and opportunity. Further clinical studies are warranted to examine the potential benefits closely, as well as any drawbacks, of omega-3 fatty acids as an integral component of multidisciplinary treatment to lessen both the primary and secondary effects of TBI.

Author Disclosure Statement

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