Diet and Nutrition in Critical Care
DOI 10.1007/978-1-4614-8503-2_114-1

Severe Head Trauma and Omega-3 Fatty Acids

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Abstract

Severe traumatic brain injury (TBI), with its diverse heterogeneity and prolonged secondary pathogenesis, remains a clinical challenge. 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. 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. A combination of targets controlling aspects of neuroprotection, neuroinflammation, and regeneration is needed. Omega-3 fatty acids (ω-3FA) offer the advantage of this poly-target approach. Although further clinical trial research is needed to establish the true advantage of using ω-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 ω-3FA to optimize the nutritional foundation of severe TBI patients. Administration of substantial and optimal doses of ω-3FA early in the course of TBI, even in the prehospital or emergency department setting, has the potential to improve outcomes from this potentially devastating public health problem. With evidence of unsurpassed safety and tolerability, ω-3FA should be considered mainstream, conventional medicine, if conventional medicine can overcome its inherent bias against nutritional, non-pharmacologic therapies.

List of Abbreviations

ω-3FAs	Omega-3 polyunsaturated fatty acids
ω-6FAs	Omega-6 polyunsaturated fatty acids
AA	Arachidonic acid
ALA	Alpha-linolenic acid
APP	β-Amyloid precursor protein
BDNF	Brain-derived neurotrophic factor
CaMKII	Calcium/calmodulin-dependent kinase II
COX	Cyclooxygenase
CREB	cAMP-responsive element binding
CT	Computerized tomography
DAI	Diffuse axonal injury
DHA	Docosahexaenoic acid
DHA-Alb	DHA complexed to albumin
EPA	Eicosapentaenoic acid

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DOI 10.1007/978-1-4614-8503-2_114-1

FDA	Food and Drug Administration (United States)
GCS	Glasgow Coma Scale
GRAS	Generally recognizable as safe
H/I	Hypoxic–ischemic
ICP	Intracranial pressure
ICU	Intensive care unit
IL-6	Interleukin-6
IL-1β	Interleukin-1 beta
IND	Investigational new drug
LOX	Lipoxygenase
LTB_4	Leukotriene B4
Mg	Milligrams
MRI	Magnetic resonance imaging
NPD_1	Neuroprotectin D1
PE	Phosphatidylethanolamine
PEG	Percutaneous endoscopic gastrostomy
PGE_2	Prostaglandin E2
PLA_2	Phospholipase A2
PS	Phosphatidylserine
RXR	Retinoid X receptors
SCI	Spinal cord injury
SIR-2	Silent information regulator 2
SOD	Superoxide dismutase
Syn-1	Synapsin I
TBI	Traumatic brain injury
TNF-α	Tumor necrosis factor alpha

Introduction

Omega-3 polyunsaturated fatty acids (ω-3FAs), particularly docosahexaenoic acid (DHA), are structural components of cell membranes, highly concentrated in the brain and retina. Emerging science on the ability of ω-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 clinical experience and case reports. TBI has long been recognized as a leading cause of traumatic death and disability (Selassie et al. 2008). 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 (Coronado et al. 2012). TBI, most often from falls, vehicle accidents, and violence, accounts for almost one third of all injury-related deaths, and males sustain traumatic brain injuries more frequently than do females (Faul et al. 2010). TBI is a major healthcare 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 (Reilly 2007). Some consider TBI a global public health epidemic (Rodríguez-Rodríguez et al. 2013).

DOI 10.1007/978-1-4614-8503-2_114-1

Classification of TBI

TBI is usually classified by one of three main systems: (1) clinical indices of severity, used most often in clinical research to compare patients among centers; (2) pathoanatomic type, used most often to describe injuries for acute management; and (3) physical mechanism (i.e., causative forces associated with the injury), used most often in the biomechanics and prevention fields (Saatman et al. 2008). Mechanistically and anatomically, TBI is divided into closed and penetrating head injuries, closed being a blunt or nonpenetrating injury versus a penetrating, or open, head injury. In penetrating head trauma, a foreign object penetrates the cranium and traverses through the brain parenchyma leading to physical disruption of neurons and fiber tracts, all of which are exacerbated by ischemia and hemorrhage (Ling et al. 2009). A third mechanistic injury has been described that combines characteristics of the other two, that being a blast TBI. When a person has a close exposure to an explosive device, such as soldiers serving in recent military operations in Iraq and Afghanistan, or civilians exposed to terrorist bombings around the world, blast injuries to the brain are a serious concern and may have multiple mechanisms of causing damage. The primary mechanism of damage is caused by over-pressurization or shock waves that transverse the brain itself. There may be secondary injury that occurs from matter thrown by the explosion typically causing a penetrating injury (e.g., fragmentation wound). A tertiary injury results when the patient is thrown by the explosive blast and strikes an object such as a wall or the ground (blunt trauma or traumatic amputation). And a quaternary injury is from factors not included in the first three, such as burns or toxic fume inhalation.

TBI may also be classified using mild, moderate, and severe categories. The Glasgow Coma Scale (GCS), the most commonly used system, grades a person's level of consciousness on a scale of 3–15 based on verbal, motor, and eye-opening reactions to stimuli. A GCS of 13 or above is considered mild, 9–12 moderate, and below 9 severe. Due to numerous problems, including timing of when the GCS is determined, the GCS grading system has limited ability to predict outcomes. Because of this, other classification systems are also used, but currently, there is no consensus. The use of neuroimaging as a method of classification (Maas et al. 2010) and the duration of loss of consciousness (LOC), posttraumatic amnesia (PTA), and other concussion symptoms are examples (Hayden et al. 2007).

Severe TBI

Severe TBI occurs when the injury causes the patient to be obtunded or comatose (i.e., presenting with a GCS score of 8 or less). Such injury is typically associated with significant neurological injury, often with abnormal neuroimaging (e.g., head CT scan revealing skull fracture, intracranial hemorrhage, and early diffuse cerebral edema), and these patients require advanced medical care (Ling et al. 2009). Classically, TBI is described as occurring in two 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.

Primary Injury. 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

DOI 10.1007/978-1-4614-8503-2_114-1

structure as it moves during the sudden stopping of the body in motion. The brain often strikes both in the direct and opposite planes of motion against the inner bony table. This is the coup–contrecoup pattern, where contusions to the brain are seen at the site of skull impact and 180° opposite the site of impact (Ling and Marshall 2008).

By far, the most devastating complication of the primary injury in an acute TBI is the development of an intracranial hematoma. Early diagnosis and aggressive, often surgical, management may decrease or prevent some of the secondary problems from occurring. Computerized tomography (CT) scans are routinely used to identify intracranial hemorrhage and are essential to surgical planning (Lee and Newberg 2005). While magnetic resonance imaging (MRI) may be more sensitive, conventional CT scans are far more available and cost effective for detecting acute subarachnoid or acute parenchymal hemorrhage (Yealy and Hogan 1991) (Fig. 1).

Secondary Injury. 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 (Michael-Titus and Priestley 2014). Secondary injury may include damage to the blood–brain barrier, ischemia, hypoxia, intracranial hypertension, hypercarbia, hyponatremia, seizures, neuroinflammation, free radical overload, and excitotoxicity (Saatman et al. 2008) (Fig. 2).

Four categories of mechanisms can be defined in the secondary injury phase of TBI: (1) ischemia, excitotoxicity, and intracellular biochemical cascades, (2) axonal injury, (3) cerebral edema, and (4) inflammation and regeneration. Within each category, a constellation of mediators of secondary damage, neuroprotection, repair, and regeneration exist (Kochanek et al. 2007).

Ischemia. Besides the obvious causes of ischemia, underlying biochemical mechanisms leading to ischemia may also exist such as a reduction in vasodilatory response to nitric oxide and prostaglandins (Armstead 1999). In blast TBI, cerebral vasospasm is not uncommon even weeks after the injury (Armonda et al. 2006). The result of cerebral blood flow compromise results in metabolic responses such as increased anaerobic metabolism, and biochemical responses such as intracellular accumulation of calcium, activation of nitric oxide synthesis, and production of free radicals. These mechanisms begin to occur within minutes of the injury and progress hours and days following the insult culminating in cell injury and tissue death (Williams et al. 2013). Glutamate

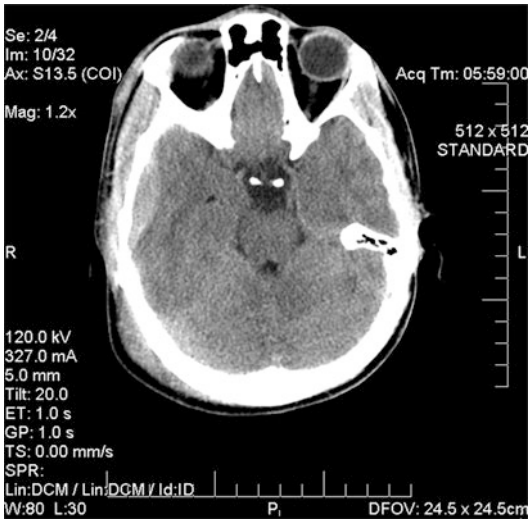

Fig. 1 Computerized tomography (CT) in the acute setting. CT scan of the patient approximately 2 h after the motor vehicle accident and before neurosurgery. Note the moderate-sized panhemispheric right subdural hematoma, a small right temporal epidural hematoma, subarachnoid hemorrhage, and 3-mm right to left shift of the midline (Lewis et al. 2013)

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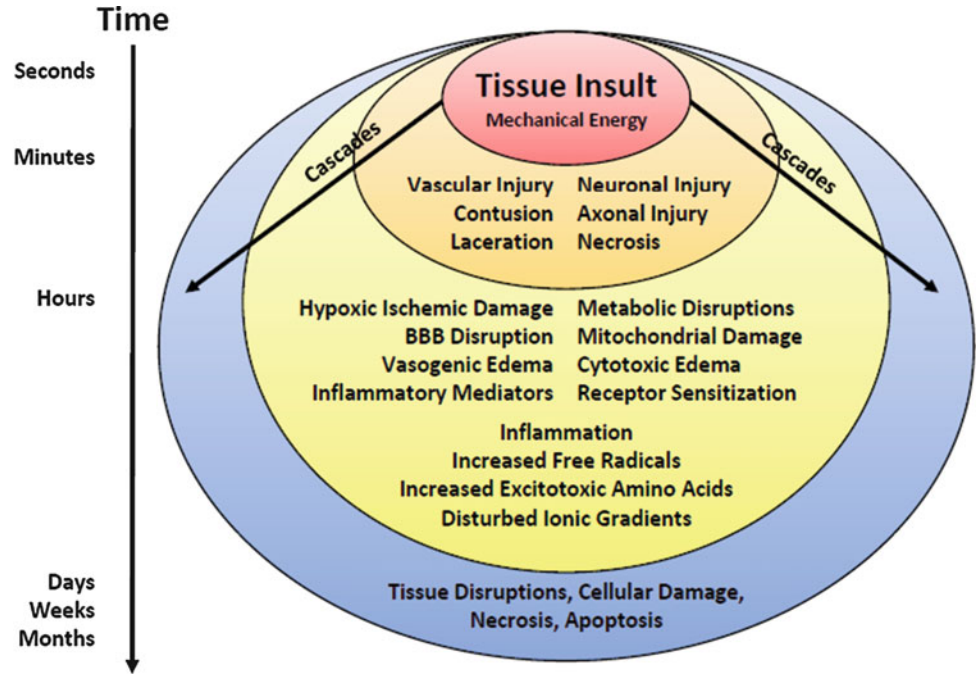

Fig. 2 Summary of the secondary injury following the initial TBI. The primary injury of TBI is caused by a transfer of mechanical injury to the brain tissue. This is followed by the secondary injury that occurs over minutes to hours to days and even weeks and months. It is characterized by numerous metabolic and biochemical cascades that may cause more damage than the initial tissue insult itself

overflow from damaged cells leads to excitotoxicity, affecting neurons and glia. The influx of calcium through glutamate receptors and voltage-gated calcium channels activates calcium-dependent proteases such as phospholipase A2 (PLA_2) which degrade membrane phospholipids, leading to the release of fatty acids, principally arachidonic acid (AA), an omega-6 fatty acid (ω-6FA), and DHA, an ω-3FA. Posttraumatic fatty acid alterations involve the release of both autodestructive and neuroprotective cascades (Michael-Titus and Priestley 2014).

Axonal injury, often called diffuse axonal injury (DAI), is a frequent result of traumatic acceleration/deceleration or rotational injuries resulting in extensive lesions in white matter tracts. Rapid deceleration, most commonly a result of high-speed motor vehicle accidents, causes shearing, inflicted as tissues of differing densities slide over other tissues, stretching axons, especially at junctions between white and gray matter (Meythaler et al. 2001). Classically considered a result of the physical shearing during the primary injury, it is now understood that much of DAI occurs through secondary biochemical cascades in response to the primary injury, hours to days after the initial injury. Axons are normally elastic, but when rapidly stretched they become brittle, and the axonal cytoskeleton can be broken (Hemphill et al. 2011). Ultimately, death of the axon is brought on by the neurochemical pathology as described in the previous paragraph. The axon degrades causing it to draw back toward the cell body and form a bulb. This bulb is called a retraction ball, the hallmark of diffuse axonal injury (Smith and Meaney 2000). Because DAI progresses over hours to days, often it is not found on CT scans done in the emergency setting (Fig. 1). Among patients with DAI, 50–80 % demonstrate a normal CT scan in the acute setting (Wasserman et al. 2012). DAI is most likely to be diagnosed with MRI days to weeks following the TBI. Abnormal MRI signals, bright on T2-weighted images in characteristic multifocal locations, leave little doubt about the diagnosis of DAI (Fig. 3).

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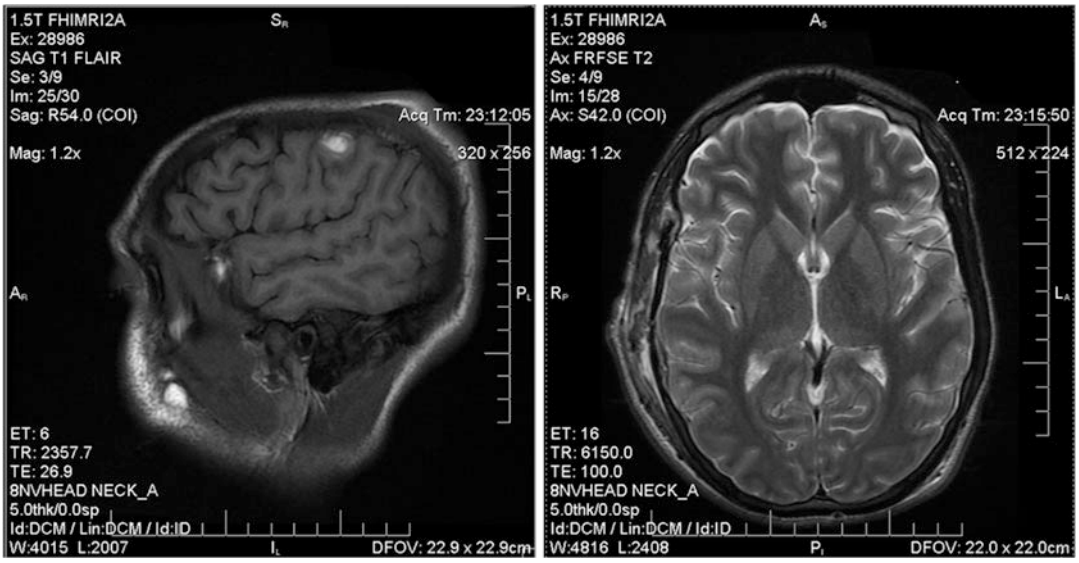

Fig. 3 MRI showing diffuse axonal injury damage 10 days after TBI. T2-weighted magnetic resonance imaging (MRI) on hospital day 10. Note the right cerebral convexity subdural hemorrhage, right postcentral gyrus and left temporal lobe parenchymal petechial hemorrhage, and small superior vermian subarachnoid hemorrhage in the image on the *right*. In addition, multiple zones of abnormal fluid-attenuated inversion recovery signals consistent with diffuse axonal injury (DAI) are present on both images (Lewis et al. 2013)

Table 1 Design of a "perfect" TBI drug

Impacts all four main mechanisms of the secondary injury phase
Has neuroregenerative properties
Beneficial impact on cardiovascular and mental health
Effective in treating long-term effects of TBI (post-concussive symptoms)
Well studied as a substance in the scientific literature
Strong safety profile
Readily available in oral, enteral, and intravenous forms
Can be given to patients across the trauma spectrum; from pre-hospital emergency medical services to acute and intensive care to chronic and rehabilitation phases following injury
Can be used prophylactically prior to injury in populations at risk of TBI

Cerebral edema is a hallmark finding in severe TBI, often resulting in intracranial hypertension unless aggressively managed, commonly through surgical and intensive care means. Intracranial hypertension as a result of edema can compromise cerebral blood flow and result in secondary ischemia or devastating herniation syndromes. In most TBI, cytotoxic (cellular) and vasogenic cerebral edemas occur together. Vasogenic edema forms in the extracellular space due to a breakdown of the blood–brain barrier. Osmotic swelling also may contribute to extracellular cerebral edema (Kochanek et al. 2007). It may be rapid and extensive. Cellular edema, however, may be of greatest importance. Swelling of neurons and astrocytes can occur following the breakdown of sodium and calcium pumps on cell membranes. Excess glutamate uptake coupled to glucose utilization causes sodium, calcium, and water to accumulate exacerbating intracellular edema (Rosenberg 1999). Cerebral edema and intracranial hypertension are the main targets of concern and intervention in the acute intensive care setting (Table 1).

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Neuroinflammation is complicated and beyond the scope of this chapter. Inflammation is essential following any injury, yet may be detrimental if not properly modulated or appropriate in response to the size of the injury. 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 (Streit et al. 2004). 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. Although the proinflammatory cytokines may cause cell death and secondary tissue damage, they are necessary to repair the damaged tissue. For example, TNF-α contributes to tissue growth at later stages of inflammation (Ramesh et al. 2013).

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 (Ling and Marshall 2008).

The Role of Omega-3 Fatty Acids in the Brain

It is well recognized that ω-3FAs are important for proper neurodevelopment and function. Linoleic acid (a short-chain ω-6FA) and alpha-linolenic acid (ALA; a short-chain ω-3FA) are fatty acids that cannot be made de novo and must be consumed in the diet, therefore considered essential. They are precursors for the synthesis of longer, more bioactive polyunsaturated fatty acids (PUFAs) such as the ω-6FA, arachidonic acid (AA), and the ω-3FAs, eicosapentaenoic acid (EPA) and DHA. However, ω-6FA and ω-3FA compete for the same elongation and desaturation enzymes, and the conversion of ALA to EPA and DHA in humans is negligible. Therefore EPA, and DHA in particular, should be consumed directly in the diet (Salem et al. 2001) (Fig. 4).

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 ω-3FA and ω-6FA. The ratio of ω-6 and ω-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 (Farooqui 2012). Unfortunately, today's Western dietary intakes result in an overdominant intake of proinflammatory ω-6FA creating a relative deficiency of immune-modulating ω-3FA. The evolutionary human diet, up until the last century, had an AA:DHA ratio of 2–1:1, was high in fiber and rich in fruits, vegetables, lean meat, and fish, and thus provided a more balanced ratio between ω-6FA and ω-3FA (Farooqui 2012). That ratio is now approximately 22–25:1 with ω-6FA dominating (Lewis et al. 2011). The estimated per capita consumption of soybean oil, the most common source of ω-6FA in the Western diet, increased greater than a 1,000-fold from 1909 to 1999 in the United States, now contributing almost 8 % of all calories consumed (Blasbalg et al. 2011). Excessive consumption of AA displaces DHA from membrane phospholipids reflected directly in the composition of neuron membrane phospholipids overwhelmingly favoring AA-derived inflammatory processes (Bradbury 2011).

AA, the primary ω-6FA in the brain, is metabolized by cyclooxygenase (COX-1 and COX-2) and lipoxygenase enzymes to proinflammatory eicosanoids. Eicosanoids are key mediators and

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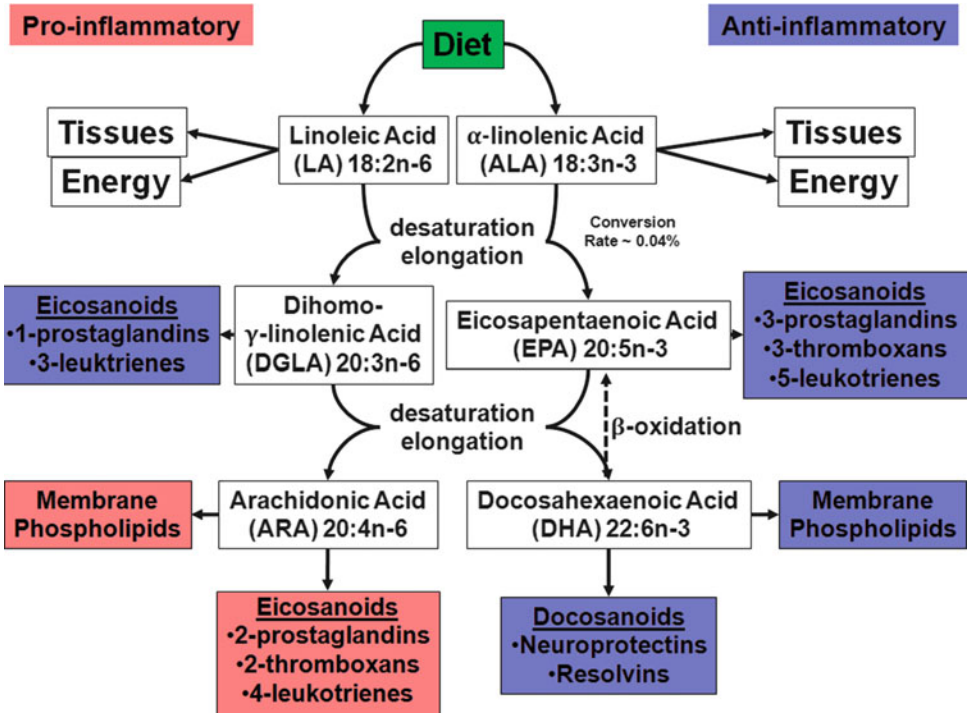

Fig. 4 Biochemical pathways of elongation and desaturation of omega-3s and omega-6s. Omega-6s and omega-3s compete for the same elongation and desaturation enzymes. However, very little ALA is converted ultimately to DHA mainly because the amount of omega-6s in the typical Western diet overwhelms the pathways favoring the synthesis of arachidonic acid. Note the proinflammatory and anti-inflammatory mediators

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 (PGE_2), and leukotriene B4 (LTB_4). Animal studies have shown a direct correlation between the dietary intake of AA and the quantity of PGE_2 produced (Calder 2010). These eicosanoids enhance vascular permeability, increase local blood flow, increase infiltration of leukocytes, and enhance production of other proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, and are associated with increased levels of silent information regulator 2 (SIR-2) and decreased markers of altered energy metabolism (Bailes and Mills 2010).

In contrast, ω-3FAs are anti-inflammatory and antiapoptotic and decrease coagulation factors and vascular resistance. 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 proinflammatory eicosanoids and cytokines (Lewis et al. 2011). EPA and DHA also give rise to E-series and D-series resolvins and protectins. E- and D-series resolvins decrease accumulation of polymorphonuclear leukocytes (PMNs) and attenuate proinflammatory signaling (Kohli and Levy 2009). Resolution of inflammation via E- and D-series resolvin decrease is required to shut off ongoing inflammatory processes and limit tissue damage (Calder 2010). The anti-inflammatory effects of ω-3FA suggest a therapeutic value, at the least, the opportunity, to modulate the inflammatory aspect of the secondary injury phase of TBI (Fig. 5).

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. Although DHA is present in high concentrations in neurons,

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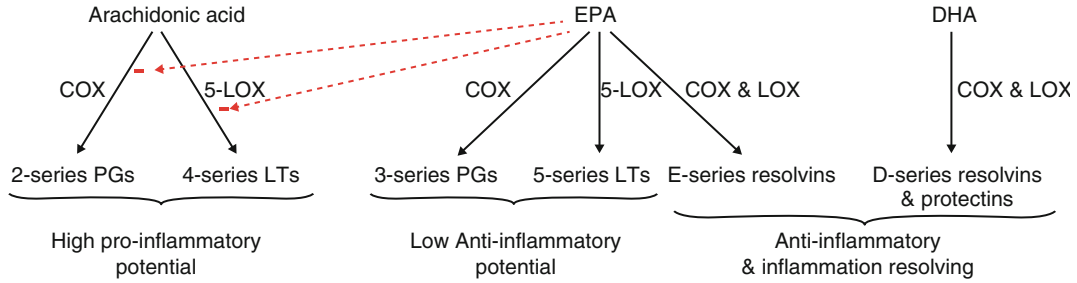

Fig. 5 General overview of the synthesis and actions of lipid mediators produced from arachidonic acid, EPA, and DHA (Calder 2010). The downstream biochemical pathways of AA, EPA, and DHA result in stimulation of proinflammatory 2-series prostaglandins and 4-series leukotrienes, anti-inflammatory 3-series prostaglandins and 5-series leukotrienes, E- and D-series resolvins, and neuroprotectins (Calder 2010)

neurons are incapable of elongating and desaturating essential fatty acids to form DHA. Rather, DHA is synthesized primarily by astrocytes, secreted, and taken up by neurons (Moore et al. 1991) where it is esterified to neuronal cell membrane phospholipids in phosphatidylserine (PS) and phosphatidylethanolamine (PE) (Kim 2008).

When mobilized from the cell membrane by PLA_2, DHA regulates unique cellular and molecular signaling pathways (Kim 2008). DHA signalolipidomics is directly affected by the dietary supply of DHA. Whereas eicosanoids are derived from 20-carbon chain AA and EPA, docosanoids are derived from the 22-carbon DHA and include neuroprotectin D1 (NPD_1). NPD_1 upregulates antiapoptotic proteins (BCL-2 and BCL-X_L) and downregulates proapoptotic proteins (BAX and BAD) in response to cellular oxidative stress and insults. This elicits neuroprotection, probably by improving mitochondrial capacity to handle excessive intracellular calcium concentrations after insult (Bazan et al. 2011). DHA not only protects neurons and astrocytes but also attenuates microglia activation from initiating apoptotic cascades (Williams et al. 2013).

DHA influence on neuronal survival following TBI is key, but research now shows DHA is neurotrophic. DHA promotes neurogenesis, neurite growth, increased neurite branching, and subsequent synaptogenesis, resulting in enhanced synaptic function (Rashid et al. 2013). DHA is converted to an ethanolamide derivative, *N*-docosahexaenoylethanolamine, a DHA-derived structural analogue of anandamide that has a number of bioactive functions. This compound, now referred to as synaptamide, contributes to the neuroprotective effects of DHA by improving neuronal repair after injury (Kim 2013). Additionally, DHA is structurally part of retinoid X receptors (RXR) in the brain, which play a crucial role in neuronal growth and proliferation (Hasadsri et al. 2013). DHA also counteracts the loss of brain-derived neurotrophic factor (BDNF) that can occur as a result of TBI and other stressors. BDNF has been linked to regulation of synaptic plasticity, cognitive function, and neurodevelopment (Wu et al. 2011).

Failure to Find Therapeutic Interventions for TBI

Tremendous advances in surgical and intensive care unit (ICU) management of TBI, including maintaining adequate oxygenation, controlling intracranial pressure (ICP), and ensuring proper cerebral perfusion, have resulted in reduced mortality (Ling et al. 2009). The increasing role of specialized intensive care units with neurologically trained medical and nursing providers using evidence-based clinical management has had a favorable impact on both the consistency and level of

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care. Advances in neuromonitoring, neuroimaging, and early aggressive neurosurgical interventions are important contributors to improved TBI outcome (Ling 2008).

The most definitive strategy to avoid short- or long-term detrimental effects of TBI 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. The understanding of the pathophysiology of TBI has undergone momentous changes in the past decade. To date, however, promising preclinical results have not been translated into successful clinical trials (Xiong et al. 2009). This may be due to the fact that most interventions target a single biochemical cascade rather than multiple mechanisms of injury. More recently, treatments with broader, pleiotropic effects are being explored. Progesterone, unlike corticosteroids, is thought to not only reduce cerebral edema but to also have neuroprotective effects 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. Two multicenter, phase III clinical trials are now currently under way (Hasadsri et al. 2013).

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-minded approach. What is needed is a broad-spectrum, more holistic approach. Progesterone represents a good step in that direction. Progesterone exerts its protective effects by protecting or rebuilding the blood–brain barrier, decreasing development of cerebral edema, downregulating the inflammatory cascade, and limiting cellular necrosis and apoptosis (Stein et al. 2008). However, progesterone must be administered by continuous intravenous infusion over the first 3 days following injury. It cannot be given beyond that period, nor orally, and does not have any neurorestorative properties that may improve neurological function after the patient survives the initial acute phase of TBI.

Interventions targeting all aspects of the four mechanisms of secondary injury, plus repair, regeneration, and protection of the brain, are desperately needed. Mechanisms that are potential drug targets include angiogenesis, axon remodeling, remyelination, neurogenesis, and synaptogenesis. Therapies may also target regeneration by enhancing the ability of pluripotent cells to differentiate into neurons, glia, and vascular endothelium. Effective interventions should also treat the persistent symptoms associated with the long-term effects of TBI (post-concussive symptoms, e.g., memory disturbances, depression, and headache) (Diaz-Arrastia et al. 2014).

Omega-3 PUFAs and TBI

If one were to take a blank sheet of paper and design an intervention for TBI, it is possible it would look similar to omega-3 fatty acids. EPA and DHA have the ability to impact all four main mechanisms of the secondary injury phase of TBI; has neuroregenerative properties; is well known to beneficially impact cardiovascular and mental health; is well studied as a substance in the scientific literature; a safety profile beyond compare such that DHA is added to 100 % of all infant formulations in the United States; is available in oral, enteral, and intravenous forms; can be given to a patient during the acute phase of injury and continued throughout the patient's entire rehabilitation; and can be used prophylactically prior to injury in populations at risk of TBI. It is a ubiquitous substance that has been around longer than mankind that is consumed by people worldwide. Some argue evolution of the human brain could not have occurred without the access

DOI 10.1007/978-1-4614-8503-2_114-1

to EPA and DHA from fish (Bradbury 2011). The FDA recognizes ω-3FA as generally recognizable as safe (GRAS) up to 3,000 mg/day, while the European Food Safety Authority recognizes up to 5,000 mg (EFSA 2012). In 2011, the FDA approved investigational new drug (IND) status for up to 9,000 mg of EPA/DHA (Katz 2011).

Preclinical data generally separate into several categories of interest to include TBI, stroke, and spinal cord injury, as well as post-injury treatment and pre-injury administration.

Gomez-Pinilla and colleagues have shown in several TBI treatment studies that dietary DHA following experimental TBI in rats counteracts broad and fundamental aspects of TBI pathology. In fluid percussion injury studies of rats, they demonstrated that DHA normalized levels of BDNF, synapsin I (Syn-1), cAMP-responsive element-binding protein (CREB), and calcium/calmodulin-dependent kinase II (CaMKII) and improved learning ability. The DHA diet counteracted the reduction of superoxide dismutase (SOD) and SIR-2 that follows TBI. Furthermore, DHA normalized levels of PLA2 and syntaxin-3, which may help preserve membrane homeostasis and function after injury (Gomez-Pinilla 2008). Additionally, the same group found effects of TBI were optimally counteracted by the combination of DHA and exercise (Wu et al. 2013). Shin and Dixon also investigated the supplementation of ω-3FA and found they restored dopamine transmission deficits after TBI (Shin and Dixon 2011).

Perhaps the most compelling experiments in TBI treatment were done by Bailes and colleagues. In two separate experiments using an impact acceleration injury model in rats, four groups of animals were used: two groups that were injured then supplemented with 10 or 40 mg/kg/day of ω-3FA consisting of EPA and DHA for 30 days, an unsupplemented control group that received an injury, and an unsupplemented sham group that was not injured (Mills et al. 2011a). A second study was done using DHA only (Bailes and Mills 2010). In both studies, supplementation significantly reduced the number of β-amyloid precursor protein (APP)-positive axons at 30 days post-injury, in a dose-dependent manner, to levels similar those in uninjured sham animals.

Belayev and colleagues have completed a variety of preclinical studies that administered DHA following experimentally induced ischemia in a rodent stroke model. Animals were subjected to middle cerebral artery occlusion for 2 h. Most recently, they demonstrated that DHA complexed to albumin (DHA-Alb) given 3 h after onset of stroke is highly neuroprotective following focal cerebral ischemia in aged rats (Eady et al. 2014). Infarct volumes were significantly decreased and neurological scores improved. DHA also reduced microglia infiltration and increased the number of astrocytes and neurons. The same group had previously tested young rats with similar results (Belayev et al. 2005). Additionally, this group determined that DHA-Alb therapy is highly neuroprotective in permanent stroke (rather than transient) in rats (Eady et al. 2013). When they used DHA not complexed to albumin, in addition to the previously described findings, they found that DHA also modulates the neuroinflammatory response and triggers long-term restoration of synaptic circuits, even when administered up to 5 h after injury. When investigating the therapeutic window for using DHA-Alb, DHA-Alb led to improved neurological score and significant reductions of infarct volumes (especially in the cortical or penumbral region), even when treatment was initiated as late as 7 h after onset of temporary middle cerebral artery occlusion (Eady et al. 2012).

When Williams et al. evaluated an ω-3FA triglyceride emulsion administered before and after a hypoxic–ischemic (H/I) injury, they found a significantly 43 % reduced total infarct when administered 90 min prior to H/I and 47 % when administered immediately after H/I. In post-H/I experiments, the triglyceride formulation containing only DHA, but not one with only EPA, exhibited neuroprotective effects. The DHA emulsion significantly decreased total infarct volume

DOI 10.1007/978-1-4614-8503-2_114-1

by 51 % when administered at 0 h post-injury, 46 % at 1 h, 51 % at 2 h, and no protective effect at 4 h (Williams et al. 2013). Similarly, Berman et al. found significant improvement in functional outcome with DHA-Alb treatment following H/I in very young rats (Berman et al. 2010) and, when combined with hypothermia, even further functional improvement and reduced brain damage (Berman et al. 2013).

DHA lessens neurological damage following spinal cord injury (SCI) as well. Michael-Titus et al. have conducted a series of SCI experiments. First, they administered DHA 30 min after SCI induced by surgical hemisection in adult rats. One week after injury, they found reduced neuronal cell loss, oligodendrocyte loss, decreased apoptosis, as well as improved functional outcome. In contrast, when the ω-6FA AA was administered after injury, it exacerbated the injury, increased the size of the spinal cord lesion, decreased neuronal and glial cell survival, and worsened functional outcome. Next, the same group used a more severe model of SCI, induced by compression, but also added DHA to the diet for 6 weeks following injury and injection at 30 min. Similar to the previous study, neuroprotection and maintenance of locomotion was greatly enhanced. Additional neuroprotective effect of the DHA-enriched diet, while not apparent the first week, improved functional and histological outcomes even more than bolus alone at 6 weeks. Of note, when DHA was given within an hour of SCI, neuromotor function was maintained but the effect was lost when treatment was delayed 4 h. These findings also support the idea that treatment with ω-3FA represents a promising therapeutic approach for neurotrauma which would be easy to translate to the emergency patient-care arena considering the well-documented safety and tolerability of these compounds (Michael-Titus 2007).

Preclinical studies also have demonstrated that ω-3FA can be protective when administered prior to injury. When fish oil was administered 30 min prior to experimental TBI, it improved functional outcome after TBI and decreased disruption of the blood–brain barrier. If animals were deprived of DHA prior to TBI, decreased brain levels of DHA were associated with poorer sensorimotor outcomes (Russell et al. 2014) When rats were fed fish oil for a longer period of time (4 weeks), a different research group found that in the fish oil group as compared to placebo, spatial learning and cognitive function were significantly better using the Morris Water Maze and had a higher density of hippocampal neurons on autopsy (Wang et al. 2013a). Bailes and colleagues, following their successful treatment experiments, repeated their acceleration injury model in rats using a 30-day pre-injury gavage of DHA with no post-injury supplementation. Again, they found decreased numbers of APP positive axons, most significant at 40 mg/kg/day, in addition to improved Morris Water Maze testing (Mills et al. 2011b).

With 3 days of pre-stroke treatment, DHA exhibited a neuroprotective effect against ischemic deficits by reduction of behavioral disturbance, brain infarction, edema, and blood–brain barrier disruption (Chang et al. 2013). Berman's work includes pretreatment 90 min prior to H/I injury. They report DHA-Alb pretreatment improves functional outcome and reduces volume loss after H/I injury in neonatal rats (Berman et al. 2009). In another rat H/I study, DHA pretreatment was done 1 h, 3 days, or daily for 6 weeks prior to injury. All three groups resulted in a reduction of blood–brain barrier disruption, brain edema, inflammatory cell infiltration, interleukin-6 (IL-6) expression, and caspase-3 activity and an increase in antioxidative capacity (Pan et al. 2009).

Figueroa et al. have performed several SCI prophylactic studies. When rats were fed an ω-3FA-enriched diet for 8 weeks prior to sham or a contusion SCI operation, the ω-3FA group exhibited significantly better functional outcomes including lower sensory deficits, autonomic bladder recovery, and early improvements in locomotion. They also found SCI triggers a marked DHA deficiency that was associated with dysfunction and corrected with the enriched diet. They

DOI 10.1007/978-1-4614-8503-2_114-1

conclude that ω-3FA prophylaxis confers resiliency to SCI mediated, at least in part, by generating a neuroprotective and restorative neurolipidome (Figueroa et al. 2013).

Omega-3 Use in Human TBI. Unfortunately, there is a complete lack of clinical trials for the use of ω-3FA in human TBI. However, two case studies are recorded that can provide clinical guidance. In January 2006, an explosion in the Sago Mine in central West Virginia resulted in 14 trapped miners. Two days 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/day of ω-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 (Roberts et al. 2008).

The only case report in the literature on the specific use of substantial amounts of ω-3FA following severe TBI occurred 4 years later and was guided by the Sago Mine experience. In March 2010, a teenager sustained a severe TBI in a motor vehicle accident. After prolonged extrication, he was resuscitated at the scene and flown to a Level I Trauma Center. His GCS score was 3. CT scan revealed panhemispheric right subdural and small temporal epidural hematomas and a 3-mm midline shift (Fig. 1). The patient underwent emergency craniotomy and ICP monitor placement. The patient was rated at Rancho Los Amigos Cognitive Scale Level I, and the attending neurosurgeon's impression was that the injury was likely lethal. On hospital day 10, T2-weighted magnetic resonance imaging (MRI) revealed right cerebral convexity subdural hemorrhage and abnormal FLAIR signals consistent with diffuse axonal injury (Fig. 3). 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. The following day, ω-3FAs were added to enteral feedings. With the cooperation of the attending neurosurgeon and hospital pharmacy, the patient began receiving 19,212 mg total ω-3FA daily via his PEG. On day 21, he was weaned off the ventilator and transported to a specialized rehabilitation institute. Notably, the patient attended his high school graduation 3 months after the injury. He was discharged to home 4 months after the injury. The patient remained on this level of ω-3FA for more than 1 year, experienced no adverse effects, and remains on a substantial daily dose to the present (Lewis et al. 2013).

To date, the treating neurosurgeon in the Sago Mine case and the recommending physician in the severe TBI case have treated or recommended similar high doses of ω-3FA to dozens of patients in similar situations. However, no clinical trials using ω-3FA for TBI have been done.

Guidelines and Protocols

Without definitive clinical trial evidence, there is no way to know if ω-3FA will help in any particular case of severe TBI. The clinical experience of the author is that the brain needs to be saturated with high doses of ω-3FA in order for the brain to have the opportunity to heal. Without an optimal supply of omegas, healing is less likely to happen. ω-3FA is not a drug and not a cure. Every situation is different and some patients may 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 in the case that was reported on CNN's Sanjay Gupta MD show (http://www.cnn.com/2012/10/19/health/fish-oil-brain-injuries/) and also published in the *American*

DOI 10.1007/978-1-4614-8503-2_114-1

Journal of Emergency Medicine (Lewis et al. 2013) was Nordic Naturals Ultimate Omega concentrated liquid, one tablespoon (15 ml) twice a day for a total of 30 ml/day in the feeding tube followed by a saline flush providing 9,756 mg EPA, 6,756 mg DHA, and 19,212 mg total ω-3FA daily. The severe TBI case reported received this dose for about a year without any problems or side effects. This dose, sometimes called the Lewis Protocol, was based on the amounts used by for the survivor of the Sago Mine accident and published in the *Journal of the American College of Surgeons* (Roberts et al. 2008). While these doses were used in adults, in pediatric patients, lower doses should be considered. A very rudimentary, untested, and arbitrary rule used by Lewis et al. is to divide the patient's weight in pounds by 5 to give the total number of milliliters total per day. For example, in a 100-lb child, 10 ml twice a day for a total of 20 ml should be considered. This dose has been frequently recommended by the author over the past 4 years without a single clinical report of side effects.

Applications to Critical or Intensive Care

Early nutritional intervention in TBI is underappreciated. Patients not fed within 5 and 7 days after TBI have a two- and fourfold increased likelihood of death, respectively; and decreasing amount of nutrition in the first 5 days is related to increased mortality rates (Härtl et al. 2008). Early enteral nutrition after brain injury can be accomplished by PEG or nasogastric tube, even in the emergency department. Of the 49 total recommendations published by the American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine, only 2 warrant Grade A recommendations, both of which state that immune-enhancing enteral formulations with ω-3FA should be used in critically ill surgical patients (including trauma) (McClave et al. 2009). Similar recommendations exist in Europe (Weimann et al. 2006).

One recent meta-analysis concludes that early initiation of nutritional support for TBI patients can decrease mortality, reduce complications, and facilitate recovery. Wang et al. also conclude that parenteral nutrition appears to be superior to enteral nutrition and immune-modulating formulas seem to be superior to standard formulas in reducing infectious complications (Wang et al. 2013b). One reason why enteral nutrition is favored over parenteral nutrition in current clinical practice may be because of the formulations themselves. The two parenteral nutrition formulations available in the United States are both soybean oil based, whereas in Europe, three formulations currently contain fish oil. As noted previously, soybean oil is a major source of AA, and the proinflammatory properties of AA likely are more harmful than good.

In 2006, Heller and his German colleagues report one study evaluating the use of a fish oil parenteral formulation in a total of 661 patients from 82 German hospitals. The retrospective study included 276 patients with abdominal sepsis, 59 after multiple trauma, and 18 with severe head injury. Administration of omega-3 fatty acid may reduce mortality, antibiotic use, and length of hospital stay (Heller et al. 2006). Mayer and Seeger reviewed the literature in 2008 and concluded that enteral nutrition with ω-3FA improved ventilation time in patients with acute lung injury and study reduced mortality in septic patients. They noted that using a high-dose, short-term infusion of fish oil-based lipid emulsion improved immunologic parameters and decreased length of stay in surgical patients by balancing the negative effects of ω-6FA (Mayer and Seeger 2008). More recently, two reviews involving Heller and Mayer provide further evidence that parenteral nutrition with fish oil-based emulsions is not only safe and effective in reducing the infection rate and hospital/ICU stay in surgical and ICU patients but cost effective in Italian, French, German, and UK hospitals (Pradelli et al. 2014).

DOI 10.1007/978-1-4614-8503-2_114-1

Since 2004, European fish oil-based lipid parenteral emulsions have been used at Boston Children's Hospital under investigational new drug status for the treatment of intestinal failure-associated liver disease in infants. Parenteral nutrition is a lifesaving therapy for infants with intestinal failure. The use of parenteral soybean oil is strongly associated with the development of parenteral nutrition-associated liver disease. Without transplant, mortality in this population approaches 100 %. Switching infants to a fish oil-based emulsion results in resolution of cholestasis, reversing of liver damage, and a noticeable impact on decreasing the incidence of morbidity and mortality of this often fatal condition (Chang et al. 2012).

Potential Harmful Effects

Potential harmful effects of ω-3FA have been described in the literature (Hasadsri et al. 2013). By virtue of having several double bonds, ω-3FAs have high susceptibility to lipid peroxidation. However, this has never been shown to be an issue clinically. The development of a fatty liver is often cited as well; however, the experience at Boston Children's Hospital should completely dispel that myth.

Due to the established antithrombotic action of these compounds, it is commonly believed they may increase the risk of excessive bleeding or even hemorrhagic stroke. Theoretically, the biochemistry of ω-3FAs tells us this should be true. However, that has never been shown to be of clinical concern in any of the over 9,000 clinical trials reported in the literature. In fact, the antithrombotic nature is one of the properties that makes ω-3FA effective in decreasing mortality, particularly cardiovascular mortality where the effect is more beneficial than statins (Studer et al. 2005). 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 (Hasadsri et al. 2013). Clinical data suggests that DHA at doses at least up to 6 g/day does not have deleterious effects on platelet aggregation or other clotting parameters, and fish oil does not augment aspirin-induced inhibition of blood clotting.

This point is worth examining further. 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 decrease the rate of deep vein thrombosis and pulmonary embolism (Farooqui et al. 2013). Potent blood thinners used in this protocol (heparin and Lovenox) completely block the enzymes responsible for allowing the platelets to clot. ω-3FAs 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 will not use ω-3FA citing that high doses of ω-3FA decrease the ability of blood to clot and increase a patient's risk of bleeding, yet immediately put their ICU patients on potent pharmaceutical blood thinners that increase the risk far greater than that of ω-3FA.

Applications to Other Conditions

Brain and heart disorders resulting from LC-Omega-3 (EPA+DHA) deficiency are the biggest challenges to the future of humanity. Associated costs are currently bankrupting health care systems and threatening wider

DOI 10.1007/978-1-4614-8503-2_114-1

economic instability worldwide. *Consensus statement*, *Global Summit on Nutrition*, *Health and Human Behaviour*, *March 2011*.

ω-3FAs are important throughout life from the development of the fetus and pregnancy through childhood development, adulthood, and old age. They are a nutritional cornerstone of human health. Extensive research has documented the health benefits of EPA and DHA which include not only a healthy heart but brain and cognitive function, joint mobility, eye health, pregnancy and lactation, healthy skin and hair, and a normally functioning immune response. Despite the great health benefits of omegas, individuals around the world suffer from ω-3FA deficiency, a little-known problem to most people, but one that is counted as the sixth leading cause of preventable death in the United States, among dietary, lifestyle, and metabolic risk factors (Danaei et al. 2009). ω-3FA deficiency stems in large part from the growing unavailability of foods rich in these nutrients, principally fish, and because of the increasing popularity of the Western diet worldwide. There is more scientific evidence behind the cardiovascular benefits of fish oil than any other nutritional supplement. A complete review of ω-3FA is far beyond the scope of this chapter. Hundreds of books, thousands of studies, and tens of thousands of scientific manuscripts have been written. ω-3FAs are the most studied and reported supplement in the literature and second only to aspirin of all substances, pharmaceutical or nutritional.

Conclusions and Future Directions

Severe TBI, with its diverse heterogeneity and prolonged secondary pathogenesis, remains 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 (Xiong et al. 2009). 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. ω-3FAs offer the advantage of this poly-target approach (Michael-Titus 2014).

Although further clinical trial research is needed to establish the true advantage of using ω-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 ω-3FA to optimize the nutritional foundation of severe TBI patients. Recovery from TBI may be hindered by our modern, proinflammatory diet. An optimal nutritional regimen to overcome the ω-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 ω-3FA earlier in the course of TBI, even in the prehospital or emergency department setting, 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 (Goldstein 2012)." With evidence of unsurpassed safety and tolerability, ω-3FA should be considered mainstream, conventional medicine, if conventional medicine can overcome its inherent bias against nutritional, non-pharmacologic therapies.

DOI 10.1007/978-1-4614-8503-2_114-1

Summary Points

- Severe traumatic brain injury (TBI), with its diverse heterogeneity and prolonged secondary pathogenesis, remains a clinical challenge.
- Pharmaceutical targets have focused on narrow targets based on interrupting enzymatic processes during the secondary pathogenesis. Optimal dosing of omega-3s is a broad and holistic approach that can impact neuroprotection, neuroinflammation, and regeneration following TBI.
- Omega-3 fatty acids have been shown effective in preclinical studies to be beneficial in TBI.
- There is a growing body of clinical experience suggesting that benefits may be possible from aggressively adding substantial amounts of omega-3s to saturate the brain of severe TBI patients.
- Omega-3s are well tolerated and have unsurpassed safety and tolerability.
- Administration of omega-3s early in the course of TBI, even in the prehospital or emergency department setting, has the potential to improve outcomes from this potentially devastating public health problem.

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