Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)

They act as potent modulators of muscle protein metabolism. They incorporate into cell membranes to enhance muscle protein synthesis, blunt protein breakdown, and resolve systemic inflammation, making them highly synergistic with dietary protein intake.

1. Enhancing Muscle Protein Synthesis (MPS)

When combined with protein and amino acids, EPA and DHA increase the anabolic response of skeletal muscle.

- **Membrane Fluidity:** EPA and DHA integrate directly into the phospholipid bilayers of the muscle cell membrane. This alters membrane fluidity and elasticity, improving the environment for embedded receptor proteins to function properly.
- **Anabolic Signaling**: Incorporation of these omega-3s is linked to the downstream activation of key protein-synthesizing pathways (such as Akt/mTOR), helping stimulate new myofibrillar protein synthesis.

2**. Attenuating Muscle Protein Breakdown**

Muscle wasting and catabolism are largely driven by inflammatory cytokines and protein-degrading enzymes.

- Inflammation Resolution: EPA and DHA are precursors to specialized pro-resolving lipid mediators (SPMs) like resolvins and protectins. These compounds actively resolve inflammation rather than simply blocking it, which protects muscle tissue during recovery.
- Downregulating Degradation: EPA has been shown to attenuate the expression of catabolic factors (like atrogin-1) and suppress the activity of the ubiquitin-proteasome pathway, preserving lean muscle mass.

3. Application and Dosing

- **Synergy with Protein**: Studies indicate that combining omega-3 fatty acids (n-3 PUFAs) with protein provisions—particularly in clinical recovery and older populations—maximizes protein adequacy and prevents muscle loss.
- **Clinical Guidelines**: Specialized nutrition in ICU settings, such as guidelines by European Society for Clinical Nutrition and Metabolism, suggest adding EPA and DHA alongside progressive protein provision to combat muscle catabolism. [1]
- **Typical Dosages**: Experts and health organizations suggest a combined daily baseline of 250 mg to 500 mg of EPA and DHA. However, higher therapeutic doses (1 to 3 grams per day) are frequently evaluated in studies for anti-inflammatory and protein-sparing effects in muscle wasting conditions.

Nutrition and Traumatic Brain Injury: Improving Acute and Subacute Health Outcomes in Military Personnel.

Institute of Medicine (US) Committee on Nutrition, Trauma, and the Brain; Erdman J, Oria M, Pillsbury L, editors.

Washington (DC): National Academies Press (US); 2011.

Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA)

Polyunsaturated fatty acids are classified as n-3 (omega-3) or n-6 (omega-6) depending on whether their first double bond is located on the third or sixth carbon from the terminal methyl group (Jones and Kubow, 2006). More than 80 percent of dietary polyunsaturated fatty acids consumed in the United States consist of the 18-carbon, 2 double bond, n-6 (18:2, n-6) linoleic acid, with an average intake of about 17 g/day (IOM, 2005). The major dietary n-3 fatty acid is alpha-linolenic acid (ALA) (18:3, n-3), which is derived from certain nuts and vegetable oils (Kris-Etherton et al., 2000). Although the long-chain n-3 fatty acids eicosapentaenoic acid (EPA) (20:5, n-3) and docosahexaenoic acid (DHA) (22:6, n-3) can be synthesized from linolenic acid, the efficiency (yield) of the enzymatic reactions involved is rather low (Jones and Kubow, 2006).

Epidemiological studies have indicated that Inuit populations in Greenland whose diets contain a high level of fish (and concomitant high levels of EPA and DHA) have low incidences of cardiovascular disease and rheumatoid arthritis, conditions with a significant inflammatory etiology (Dyerberg, 1993). Several mechanisms affected by n-3 fatty acids may account for these findings. Polyunsaturated fatty acids serve as the precursor molecules for eicosanoids. The primary precursor is arachidonic acid (20:4, n-6), which is enzymatically transformed into inflammatory prostaglandins or leukotrienes that contain two and four double bonds, respectively. Prostaglandins and leukotrienes synthesized from n-3 fatty acids contain three and five double bonds, respectively, and are less biologically active (Jones and Kubow, 2006). Dietary fish oil supplementation reduces synthesis of inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) (Endres et al., 1989). Supplementation with n-3 fatty acids likewise reduces reactive oxygen species (ROS) production by leukocytes (Massaro et al., 2008). EPA and DHA are also the precursors for resolvins, which bring about a programmed resolution of the inflammatory process (Schwab et al., 2007), and DHA serves as the precursor for synthesis of protectins that have anti-inflammatory and neuroprotective activities (Serhan, 2006).

Go to:

EPA AND DHA AND THE BRAIN

Long-chain polyunsaturated fatty acids are important structural components in cell membrane phospholipid bilayers, with EPA and DHA concentrated in synaptic membranes in the brain and in the retina (Dyall and Michael-Titus, 2008). Variations in the ratio of n-3:n-6 composition may affect membrane fluidity, thickness, or other characteristics, as well as influence how proteins embedded in the membrane move and function (Lauritzen et al., 2001). There is evidence that n-3 fatty acids protect normal mitochondrial function and reduce excitotoxicity (reviewed in Dyall and Michael-Titus, 2008). Human studies (years 1990 and later) addressing the influence of EPA/DHA on resilience or treatment of central nervous system (CNS) injuries or disorders, such as stroke, epilepsy, and subarachnoid hemorrhage, are presented in Table 13-1. Likewise, Table 13-1 also lists animal studies on the effects of EPA/DHA on TBI.

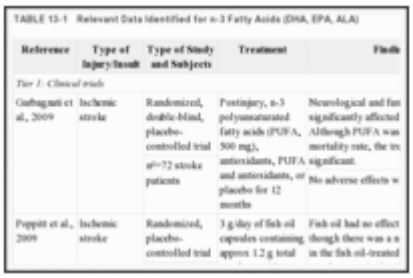

TABLE 13-1 Relevant Data Identified for n-3 Fatty Acids (DHA, EPA, ALA)

Reference	Type of Injury/Insult	Type of Study and Subjects	Treatment	Findi
Tier 1: Clinical trials				
Guthagnati et al., 2009	Ischemic stroke	Randomized, double-blind, placebo-controlled trial n=72 stroke patients	Postinjury, n-3 polyunsaturated fatty acids (PUFA, 500 mg), antioxidants, PUFA and antioxidants, or placebo for 12 months	Neurological and fun significantly affected Although PUFA was mortality rate, the tre significant. No adverse effects w
Poppitt et al., 2009	Ischemic stroke	Randomized, placebo-controlled trial	3 g/day of fish oil capsules containing approx 1.2 g total	Fish oil had no effect though there was a n in the fish oil–treated

TABLE 13-1

Relevant Data Identified for n-3 Fatty Acids (DHA, EPA, ALA).

There are various models that explain the transportation of fatty acids through the blood-brain barrier, most of them involving complexes with albumin and circulating lipoproteins. Other models propose that there are no specific transporters that participate in this process (Hamilton and Brunaldi, 2007).

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USES AND SAFETY

There are insufficient data to correlate reduced concentrations of n-3 fatty acids with functional impairments; therefore, no Estimated Average Requirements (EARs) have been established. An Adequate Intake (AI) for alpha-linolenic acid, based on the average daily intake by apparently healthy people that is therefore assumed to be adequate, has been set at 1.6 g/day for adult men and 1.1 g/day for adult women (IOM, 2005). Any intake of EPA and DHA, which normally accounts for about 10 percent of total n-3 fatty acids in the diet, is considered to contribute to the AI for ALA. The most effective way to increase body stores of EPA and DHA is through increased dietary intake of oil from cold-water fish species and from krill.

Intake of up to 1 g/day of n-3 fatty acids from dietary fish intake is generally regarded as having very low risk, but higher intakes can increase the risk of gastrointestinal upset as well as increases in blood glucose and concentrations of low-density lipoprotein (LDL) cholesterol (Kris-Etherton et al., 2002). Increased intake of n-3 fatty acids will decrease the synthesis of the eicosanoid thromboxane A_2, which promotes platelet aggregation (Kramer et al., 1996). Excessive intake can therefore increase the risk of bleeding, although this was not generally observed in a number of randomized clinical trials of fish-oil supplementation (Huang et al., 2007; Javierre et al., 2006). Environmental contaminants such as mercury and polychlorinated biphenyls can accumulate in certain species of fish, presenting another potential risk. The risk from mercury toxicity can be diminished, however, by avoiding some fish species (e.g., swordfish, mackerel), and ingestion of other contaminants can be diminished by removing the skin and fat from fish before cooking. Alternatively, purified EPA and DHA can be taken in capsule form.

Although increased dietary n-3 fatty acid intake reduces cellular production of ROS, the increased desaturation (double bonds) of these fatty acids increases susceptibility to lipid peroxidation, which may have detrimental effects on specific cellular processes, such as T cell–mediated immune function (Wu and Meydani, 1998). This can be ameliorated, however, by adequate supplementation with the antioxidant vitamin E (Wu and Meydani, 1998).

EVIDENCE SUGGESTING INCREASED RESILIENCE

Human Studies

There have been no human studies examining the role of EPA/DHA in providing resilience to traumatic brain injury (TBI). However, several randomized clinical trials have examined the effect of EPA/DHA on other neurological diseases, such as epilepsy and stroke, with mixed results. In a clinical trial including 942 Japanese hypercholesterolemic patients with stroke, use of EPA (1,800 mg/day for approximately five years) led to a significant reduction of stroke recurrence (Tanaka et al., 2008). Use of n-3 fatty acids also was associated with a lower risk of mortality in stroke patients in a small trial (n = 72) (Garbagnati et al., 2009). In another trial including 102 ischemic stroke patients, however, fish oil supplementation (1,200 mg/day) for 12 weeks produced no significant differences from placebo in any lipids, inflammatory, hemostatic, or composite mood parameters (Poppitt et al., 2009). In a small trial including 51 epilepsy patients, seizure frequency was reduced over the first six weeks of supplementation with n-3 fatty acids (1,700 mg/day), but the protective effect was not sustained thereafter (Yeun et al., 2005). Additional studies (from 1990) addressing the influence of EPA/DHA on other CNS injuries or disorders in humans, such as stroke, epi lepsy, subarachnoid hemorrhage, and Alzheimer's disease are presented in Table 13-1. The occurrence or absence of adverse effects in humans is included if reported by the authors.

Animal Studies

A series of animal studies (Wu et al., 2004, 2007) showed that preinjury intake of an n-3 fatty acid–enriched diet (8 percent of total energy) could counteract some of the damaging effects of TBI by, for example, normalizing levels of molecular systems associated with energy homeostasis (e.g., Sir2α), ameliorating protein oxidation, and improving learning ability (Table 13-1). These results suggest potential neuroprotective effects of n-3 fatty acids on TBI.

EVIDENCE INDICATING EFFECT ON TREATMENT

Human Studies

There have been no clinical trials conducted to determine the efficacy of n-3 fatty acid infusion for treatment of TBI. Nevertheless, n-3 fatty acid infusion into healthy human subjects affects several inflammatory pathways in a way that could be beneficial for TBI patients: platelet aggregation and thromboxane B_2 synthesis were reduced within 60 minutes of infusion (Elmadfa et al., 1993). In a different study, the ratio of n-3 to n-6 fatty acids in monocyte membranes likewise increased, monocyte synthesis of interleukin-1 and TNF decreased, and monocyte adhesion/transendothelial migration decreased within 48 hours after initiation of infusion (Mayer et al., 2003).

Animal Studies

In a 2010 study using an impact acceleration head injury model, 40 adult male Sprague-Dawley rats were assigned to four groups (n = 10 per group), of which two groups received dietary supplementation of n-3 fatty acids (EPA:DHA = 2:1) at a dosage of 10 or 40 mg/kg/ day, starting on postinjury day one (Mills et al., 2010). The authors found that, compared to injured rats on the control diet, n-3 fatty acids significantly reduced the number of beta-amyloid precursor protein-positive (injured) axons at 30 days postinjury, achieving levels similar to those in uninjured animals.

CONCLUSIONS AND RECOMMENDATIONS

The n-3 fatty acid status of the active-duty military population is unknown. A survey by Lieberman et al. (2010) sought to determine the current usage of dietary supplements in U.S. Army soldiers on active duty. Fish oil was grouped in an "other" category that included supplements such as melatonin, caffeine, coenzyme Q10, and lycopene. The authors reported that 11 percent of military personnel in combat-arms positions and 23 percent of those in Special Forces were taking "other" supplements. Data on the EPA and DHA concentrations measured in frozen serum (some archived for up to several years) from military personnel suggest that the levels are lower than in the civilian population (Lewis et al., 2011). There were a number of methodological differences, however, in the comparison civilian studies, such as measurement of fresh (not frozen) serum samples, expression of DHA as a percentage of fatty acids in serum phospholipids (rather than total fatty acids), or measurement of DHA levels in red blood cell membranes (rather than serum). Differences in DHA concentra tions between military and civilian populations might thus be attributable to methodological issues. In order to definitively determine if such differences exist, it will be necessary to conduct a prospective study in which samples from both populations are collected, stored, processed, and assayed in a uniform manner. By better determining the n-3 fatty acid status of military personnel, these data will also provide a basis for recommending increases in intake of n-3 fatty acid should future research findings indicate a role in resilience to TBI.

It is well documented that fish-oil supplementation will decrease inflammation. The influences of n-3 fatty acids on prostaglandin, leukotriene, cytokine, and ROS were described earlier in this chapter, and extensive reviews are available (Calder, 2006; Massaro et al., 2008). When taken orally, the effects of n-3 fatty acids are not evident for days to weeks because of their slow incorporation into cellular membranes. Initiation of oral administration after TBI therefore may not be of immediate benefit (although when evaluated 30 days after injury, the 2010 animal study by Mills and colleagues showed reductions in neuronal toxicity). On the other hand, evidence from human subjects indicates that intravenous administration of n-3 fatty acids can have more immediate effects. This is especially relevant to military operational settings, where the feasibility of a feeding tube or oral administration is greatly reduced immediately following injury. Overall, continuous administration—whether enteral, parenteral, or intravenous—is considered to be most effective in the early phase of severe TBI.

RECOMMENDATION 13-1. DoD should conduct animal studies that examine the effectiveness of preinjury and postinjury oral administration of current commercial preparations of purified n-3 fatty acids on TBI outcomes.

RECOMMENDATION 13-2. Based on the evidence that fish oil decreases inflammation within hours of continuous administration, human clinical trials that investigate fish oil or purified n-3 fatty acids as a treatment of TBI are recommended. For acute cases of TBI, it should be noted that there are intravenous fish oil formulations available in Europe, but these are not approved by the Food and Drug Administration. Continuous enteral feeding with a feeding formula containing fish oil should provide equivalent effects for this purpose in the early phase of severe TBI when enteral access becomes available.

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