CHAPTER 13

Health Benefits of n-3 Polyunsaturated Fatty Acids: Eicosapentaenoic Acid and Docosahexaenoic Acid

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Abstract

Marine-based fish and fish oil are the most popular and well-known sources of n-3 polyunsaturated fatty acids (PUFAs), namely, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These n-3 PUFAs are known to have variety of health benefits against cardiovascular diseases (CVDs) including well-established hypotriglyceridemic and anti-inflammatory effects. Also, various studies indicate promising antihypertensive, anticancer, antioxidant, antidepression, antiaging, and antiarthritis effects. Moreover, recent studies also indicate anti-inflammatory and insulin-sensitizing effects of these

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Advances in Food and Nutrition Research, Volume 65
ISSN 1043-4526, DOI: 10.1016/B978-0-12-416003-3.00013-5

fatty acids in metabolic disorders. Classically, n-3 PUFAs mediate some of these effects by antagonizing n-6 PUFA (arachidonic acid)-induced proinflammatory prostaglandin E_2 (PGE_2) formation. Another well-known mechanism by which n-3 PUFAs impart their anti-inflammatory effects is via reduction of nuclear factor-κB activation. This transcription factor is a potent inducer of proinflammatory cytokine production, including interleukin 6 and tumor necrosis factor-α, both of which are decreased by EPA and DHA. Other evidence also demonstrates that n-3 PUFAs repress lipogenesis and increase resolvins and protectin generation, ultimately leading to reduced inflammation. Finally, beneficial effects of EPA and DHA in insulin resistance include their ability to increase secretion of adiponectin, an anti-inflammatory adipokine. In summary, n-3 PUFAs have multiple health benefits mediated at least in part by their anti-inflammatory actions; thus their consumption, especially from dietary sources, should be encouraged.

I. SOURCES AND INTAKES OF EICOSAPENTAENOIC ACID AND DOCOSAHEXAENOIC ACID

Marine fish is the well-known source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA ($C_{20}H_{30}O_2$; 20:5n-3) and DHA ($C_{22}H_{34}O_2$; 22:6n-3) are long-chain ω-3/n-3 polyunsaturated fatty acids (PUFAs). Technically, EPA is a nonessential n-3 fatty acid as the human body can convert essential n-3 alpha-linolenic acid (ALA) into EPA and DHA. However, in humans, this conversion is not efficient enough to meet the EPA and DHA demand to impart beneficial health effects; thus, it is expected to obtain these fatty acids from dietary sources. The n-3 PUFA levels consumed in the United States and many other countries in the world are very low compared to the recommended intake of n-6/n-3 PUFAs (11:1 (n6:n3) vs. 2.3:1; Davis and Kris-Etherton, 2003; Whelan and Rust, 2006). EPA and DHA are among the most studied bioactive compounds of marine origin. Fish oil being the major and well-known source of EPA and DHA, dietary fish such as anchovy, bluefish, herring, mackerel, mullet, sardines, salmon, sturgeon, tuna, and trout are popular sources of fish oil. Further, due to its recognized health benefits and recommendation by several health agencies, fish oil (primarily DHA and EPA) has become a very popular dietary supplement. Fish oil is commercially available as soft gel capsules. These preparations are often available with added vitamins, antioxidants, and various flavors. EPA and DHA are not only found in fish oil but also in marine algal species. However, they are considerably less concentrated in most of the algae, compared to some fish sources. Most of the identified n-3 PUFA-rich algae contain higher amount of DHA compared to EPA.

Fat is a key component in the human diet. Research shows that excessive consumption of saturated fat negatively impacts several biomarkers of health while monounsaturated and n-3 PUFAs are beneficial to human health. Moreover, research shows that unbalanced dietary ratios of n-6: n-3 may lead to various health complications as well as disease progression while increased n-3 levels impart prevention and health promoting effects (Burghardt *et al.*, 2010; Goodstine *et al.*, 2003; Simopoulos, 2002; Wan *et al.*, 2010). The American Heart Association recommends eating fatty fish meals at least twice a week due to their promising health and especially cardiovascular benefits. Here, we review some of the health benefits of n-3 PUFAs, due in part to their anti-inflammatory effects in cancer, cardiovascular diseases (CVDs), obesity, and other metabolic disorders.

II. HEALTH BENEFITS OF N-3 PUFAS

Fish oil-derived n-3 PUFAs have been a healthy nutritional supplement for long time due to numerous health benefits including promising effects to improve cardiovascular health (Harris, 2007; Lu *et al.*, 2011), brain function, and overall health during pregnancy (Koletzko *et al.*, 2008). Also, fish oil-derived n-3 PUFAs are well known to prevent inflammation (Calder, 2008; Fetterman and Zdanowicz, 2009; Figueras *et al.*, 2011), aging (Dyall *et al.*, 2010), arthritis (Wall *et al.*, 2010), insulin resistance (Kalupahana *et al.*, 2010a), and depression and slows the progression of certain cancers (Astorg, 2004; Cabanes *et al.*, 2003; Leitzmann *et al.*, 2004; Fig. 13.1). Further, it has been shown that fish oil-derived n-3 PUFAs can prevent cardiac remodeling and dysfunction under pressure overload conditions in rats (Duda *et al.*, 2009) and atrial fibrillation associated with heart failure in a rabbit (Kitamura *et al.*, 2011). Also, EPA and DHA are known to induce breast cancer cell apoptosis and impart anticancer effects. Wu *et al.* (2005) showed that *in vivo* and *in vitro* treatment of n-3 PUFAs can inhibit the breast cancer growth through activation of a neutral sphingomyelinase-mediated pathway (Wu *et al.*, 2005). Moreover, it has been reported that an approach with fish oil nutritional intervention can improve the health in lung cancer patients (Murphy *et al.*, 2011). In a recent study, we reported that EPA significantly prevents and reverses insulin resistance in high-fat diet-induced obese mice via modulation of adipose tissue inflammation (Kalupahana *et al.*, 2010a). Moreover, it has been reported that supplementation of long-chain ω-3 PUFAs in elderly female patients reduces the occurrence of depressive symptoms, improves phospholipid fatty acid profile and health-related quality of life (Rondanelli *et al.*, 2011).

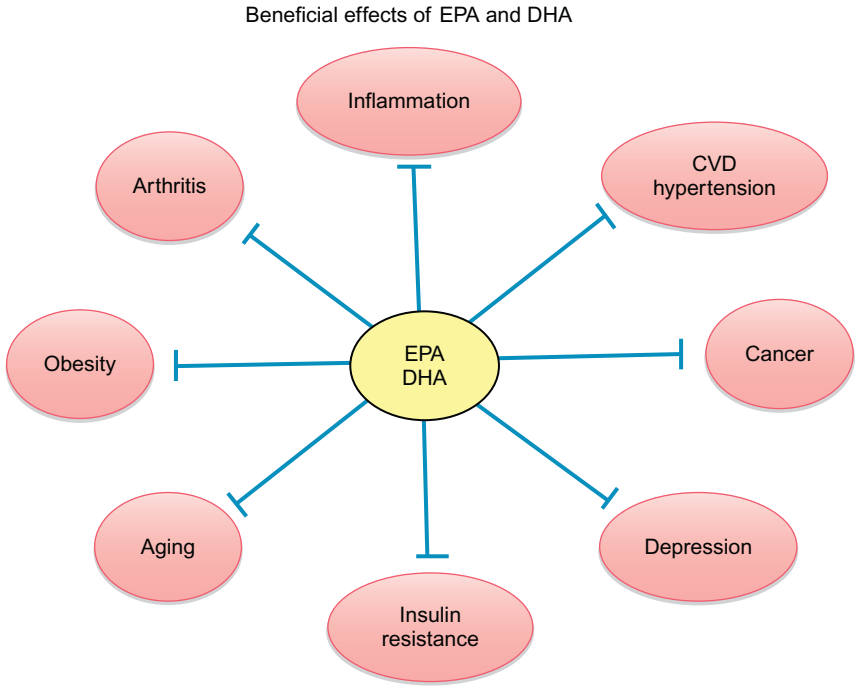

FIGURE 13.1 Beneficial effects of EPA and DHA. Scientifically validated beneficial effects of EPA and DHA as evident by epidemiological evidence as well as *in vivo* and *in vitro* studies. Blocked lines are to indicate the suppression effects. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CVD, cardiovascular disease.

n-3 PUFAs are mostly known for their consistent hypotriglyceridemic effects (Harris, 1996, 1997). Moreover, diets rich in PUFAs are able to alter adipose tissue gene expression and metabolism. Hypotriglyceridemic effects of n-3 PUFA are believed to be primarily mediated via peroxisome proliferator activated receptor (PPARα)-dependent mechanisms (Buettner *et al.*, 2006), which may also account for the improved insulin resistance and reduction of hepatic steatosis in people consuming diets high in n-3 PUFA.

A. n-3 PUFAs and cardiovascular diseases

n-3 PUFAs reduce the risk of sudden cardiac death. For example, in the Physicians Health Study, individuals with the highest n-3 PUFA level in blood had a 90% reduction in sudden cardiac death compared to ones with the lowest n-3 PUFA levels (Albert *et al.*, 2002). These fatty acids also

reduce the total mortality and sudden death in patients following myocardial infarction (Marchioli *et al.*, 2002). These beneficial effects of n-3 PUFA in reducing sudden cardiac death are attributed to two main factors. First, n-3 PUFAs reduce cardiac arrhythmias (Raitt *et al.*, 2005), which are responsible for the majority of sudden cardiac deaths. Second, these fatty acids increase atherosclerotic plaque stability (Thies *et al.*, 2003), thereby preventing plaque rupture and subsequent coronary events.

n-3 PUFAs also reduce several risk factors for CVDs. These include reductions in plasma triglyceride levels as well as several inflammatory cytokine levels. Detailed anti-inflammatory mechanisms of n-3 PUFA are discussed below.

III. ANTI-INFLAMMATORY EFFECTS OF EPA AND DHA

One of the main anti-inflammatory mechanisms is that EPA acts as a competitive inhibitor for proinflammatory arachidonic acid (AA) on cyclooxygenase (COX), which produces proinflammatory eicosanoids (Fig. 13.2). When EPA is subjected to oxygenation by COX, the less-inflammatory prostaglandin E_3 (PGE_3) is generated while AA generates highly proinflammatory prostaglandin E_2 (PGE_2). As EPA is structurally similar to AA, EPA can also compete with AA to incorporate into the cell membrane phospholipids and become the preferential substrate for COX

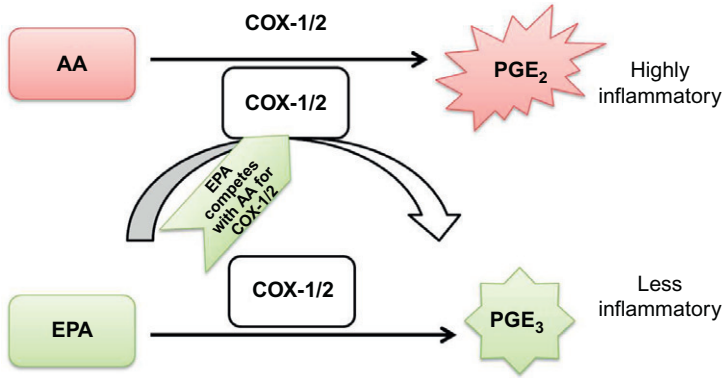

FIGURE 13.2 EPA competitively inhibits PGE_2 formation by COX-1 and COX-2. EPA competitively binds with COX-1 and COX-2 and produces less-inflammatory PGE_3 while suppressing AA binding which produces highly inflammatory PGE_2. AA, arachidonic acid; COX, cyclooxygenase; EPA, eicosapentaenoic acid; $PGE_{2/3}$, prostaglandin $E_{2/3}$. Calder (2009) was used as reference for the design.

activity. Oxygenation of AA by COX can be inhibited by n-3 PUFAs and PGE_3 is generated instead of PGE_2. Thus, n-3 PUFAs act like nonsteroidal anti-inflammatory drugs to decrease COX enzyme activities and subsequently decrease inflammation including in adipose tissue as indicated by our recent studies (Ferrucci *et al.*, 2006; Kalupahana *et al.*, 2010a; Wortman *et al.*, 2009). Indeed, treatment of EPA in the diet can decrease PGE_2 levels through competitive inhibition of AA (Lands *et al.*, 1973). Also, it has been shown that EPA and DHA can suppress the COX-2 activity in human umbilical vein endothelial cells (Lee *et al.*, 2009). Thus, PGE_2 levels can be manipulated by increasing consumption of EPA. COX, also known as prostaglandin H_2 synthase (PGH_2 synthase), has both COX and peroxidase activity. The COX complex is made up of COX-1 and COX-2 enzymes. COX-1 is constitutively expressed while the expression of COX-2 is inducible and highly regulated. Pharmacological inhibition of COX-2 with celecoxib decreases PGE_2 secretion in adipocytes, and subsequently, lipolysis can be also decreased (Wortman *et al.*, 2009). Therefore, when COX-associated biochemical reactions are intensively associated with EPA due to increased EPA levels and decreased proinflammatory AA levels, less harmful and significantly reduced inflammatory status can be expected. Thus, increased n-3 PUFA levels compared to n-6 PUFA can impart significant beneficial health effects against inflammation. Also, it has been recently suggested that increased n-3 PUFA levels in patients can improve the outcome of critically ill patients (Ott *et al.*, 2011).

IV. N-3 PUFAS AND METABOLIC DISORDERS

In both animals and humans, n-3 PUFA was shown to reduce inflammation and insulin resistance (Bierhaus *et al.*, 2004; Jones *et al.*, 2003, 2005). Both EPA and DHA are known to have anti-inflammatory activities that reduce the proinflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), IL-6, IL-8, resistin, plasminogen activator inhibitor 1, and monocyte chemotactic protein-1 (MCP-1) levels (Kalupahana *et al.*, 2010b). Obesity is associated with a chronic low-grade inflammation characterized by an increase in proinflammatory cytokines and adipokines. EPA and DHA are well known to beneficially alter several metabolic processes including carbohydrate and lipid metabolism. n-3 PUFAs increase β-oxidation of fatty acids and inhibit hepatic and adipose lipogenic gene transcription (Al-Hasani and Joost, 2005; Jones *et al.*, 1996; Sampath and Ntambi, 2004), thus shifting lipids from synthetic pathways to oxidative pathways. Further, dietary n-3 PUFAs act as ligand activators of PPARα, which induces the transcription of genes involved in β-oxidation (Neschen *et al.*, 2002). Lipid-metabolizing genes downregulated by PUFAs include the fatty acid

synthase, lipoprotein lipase, hormone-sensitive lipase, adipocyte lipid-binding protein (aP2), acetyl-CoA carboxylase, and the enzyme stearoyl-CoA desaturase-1 (Jones *et al.*, 1996; Sessler *et al.*, 1996).

Also, it was recently demonstrated that saturated fatty acids can activate Toll-like receptor 4 (TLR4) and TLR2 signaling in adipocytes leading to increased transcription of inflammatory markers via with nuclear factor-κB (NF-κB). NF-κB activation has been implicated in many inflammatory processes (Lira *et al.*, 2010). Some proinflammatory cytokines such as TNF-α and IL1 directly activate NF-κB. NF-κB activation has been reported to play a pivotal role in obesity, cancer, atherosclerosis, diabetes, arthritis, and other CVD, inflammatory, and immunological disorders (Bierhaus *et al.*, 2004; Jones *et al.*, 2003, 2005). It has been suggested that NF-κB may be an important therapeutic target for specific CVDs (Bierhaus *et al.*, 2004; Jones *et al.*, 2005; Ruan and Lodish, 2003). MCP-1, which plays a critical role in the development of CVD, is increased by activated NF-κB (Niu and Kolattukudy, 2009; Zhu *et al.*, 2008). Moreover, MCP-1 can induce adipogenesis, macrophage infiltration into adipose tissue, and insulin resistance (Kanda *et al.*, 2006; Younce *et al.*, 2009; Zhu *et al.*, 2008). Several studies have reported that NF-κB activation can be suppressed by fish oil and also identified that suppression of NF-κB activation has been strongly associated with mechanisms responsible for suppression of several disease conditions by fish oil (Encarnacion *et al.*, 2008, 2011; Lee *et al.*, 2009; Suzuki *et al.*, 2010; Zhao *et al.*, 2004). Further, Bellenger *et al.* (2011) showed that pancreatic n-3 fatty acid enrichment inhibits proinflammatory cytokines and NF-κB protein expression and increases IκBα protein expression in MLD-STZ-induced fat-1 transgenic mice.

It has been shown that fish oil can not only suppress proinflammatory mediators but also can increase the anti-inflammatory ones such as adiponectin (Duda *et al.*, 2009; Kalupahana *et al.*, 2010b). Increased adiponectin levels can reduce inflammation and beneficially improve the metabolism. Specifically, the increased levels of adiponectin can significantly reduce the insulin resistance. Oster *et al.* (2010) showed that DHA increases cellular adiponectin mRNA and secreted adiponectin protein in 3T3-L1 adipocytes, possibly by a mechanism involving PPARγ. A recent dietary intervention study conducted on healthy Japanese female subjects by Kondo *et al.* (2010) showed that a fish-based diet intervention increased the serum adiponectin concentration in young, nonobese, healthy Japanese female subjects. Also, the same study indicated that the increment in serum ω-3 PUFA may regulate the serum adiponectin concentration (Kondo *et al.*, 2010).

Other reported mechanisms mediating PUFA effects in metabolic disorders include binding to GPCR-120 and generation of newly discovered resolvins and protectins (Ariel and Serhan, 2007; Schwab *et al.*, 2007). Stimulation of GPR120 with n-3 FAs causes broad anti-inflammatory

effects in monocytic RAW 264.7 cells and in primary intraperitoneal macrophages (Oh *et al.*, 2010). Further, it has been reported that inefficient biosynthesis of n-3-derived mediators of resolution of inflammation in muscle and adipose tissue contributes to the maintenance of chronic inflammation in obesity (White *et al.*, 2010). Hellmann *et al.* (2011) showed that resolving D1 can decrease adipose tissue macrophage accumulation and improves insulin sensitivity in obese-diabetic mice.

V. HEALTH CONCERNS

It is always a concern that heat, light, and oxygen can promote fish oil degradation which can produce harmful compounds such as peroxides. With the advances in food and pharmaceutical science, antioxidants are now incorporated into fish oil to prevent fish oil oxidation. Also, the effective storage and packaging methods have been developed to assure the quality. However, it is important to follow the storage guides provided with the products and simply avoid the exposure to heat, light, and oxygen. Also, extended cooking and deep frying can make fish oil unhealthy. Moreover, the quality and source of the fish oil is highly important. Some fish and fish oil may have unhealthy levels of heavy metals such as mercury and selenium. Some studies have reported that fish oil contaminated with mercury can increase CVD risk instead of expected CVD protection benefits while some studies indicate that there should be intensive investigations to confirm the harmful effects of mercury on CVD (Mozaffarian *et al.*, 2011; Virtanen *et al.*, 2005). Specially, when eating fish or taking fish oil supplements during pregnancy, it is always good to carefully select fish oil source for the safety of both the mother and the baby.

Taken together, n-3 PUFAs such as EPA and DHA are promising health promoting compounds and intake of dietary EPA and DHA can suppress the inflammation and inflammation-associated health complications. While there are several mechanisms suggested and detailed for the anti-inflammatory activities of EPA and DHA, here we have summarized a few important mechanisms such as competitive inhibition of AA-mediated PGE_2 formation, suppression of NF-κB activation, generation/production/secretion of anti-inflammatory mediators (adiponectin, resolving, and protectin), and anti-inflammatory activities mediated via GRP120. Also, EPA and DHA are known to beneficially alter the metabolic processes by reducing adiposity and increasing lipid oxidation, thus contributing antiobesity effects in general. Moreover, the reduction of excessive adiposity can directly reduce the low-grade chronic inflammation associated with obesity. Therefore, EPA and DHA can also be used in dietary interventions effectively to overcome obesity, inflammation, and many other disease conditions.

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