

Feature

Dietary sources, current intakes, and nutritional role of omega-3 docosapentaenoic acid

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Summary

Fish oils and long-chain omega-3 fatty acids are well recognized for their critical role in human diets. Docosapentaenoic acid (DPA, 22 : 5n-3) has always been a part of healthy nutrition, since infants obtain almost as much DPA as DHA from human milk. Fish oil supplements and ingredients, oily fish, and grass-fed beef can serve as the primary DPA sources for the general population. Although the DPA levels in fish oils are substantially lower than those of EPA and DHA, concentrated DPA products are now becoming commercially available, and DPA-based drugs are under development.

Epidemiological studies show that similar to eicosapentaenoic (EPA, 20 : 5n-3) and docosahexaenoic (DHA, 22 : 6n-3) acids, DPA is linked to various improvements in human health, perhaps owing to its structural similarity to the other two molecules. Studies in mammals, platelets, and cell cultures have demonstrated that DPA reduces platelet aggregation, and improves lipid metabolism, endothelial cell migration, and resolution of chronic inflammation. Further, other in vivo and in vitro studies have shown that DPA can improve neural health. A human supplementation trial with 99.8% pure DPA suggested that it serves as a storage depot for EPA and DHA in the human body. Future randomized controlled human trials with purified DPA will help clarify its effects on human health. They may confirm the available evidence pointing to its nutritional and biological functions, unique or overlapping with those of EPA and DHA.

Introduction

Long-chain (LC) omega-3 fatty acids (or omega-3s) contribute to various aspects of human wellbeing, from heart and vascular health to brain development and lifelong brain function. Indeed, these fatty acids participate in diverse processes including cell membrane structure, eicosanoid metabolism, gene transcription, and resolution of inflammation [1, 2]. Through these and other functions, LC omega-3s can improve heart rate variability, lower heart rate and blood pressure, improve endothelial function, decrease platelet aggregation, and lower blood triglyceride levels [1].

Because of their evident health benefits, LC omega-3s continue to be some of the most-researched nutrients. Many studies on LC omega-3s have been conducted using fish oils, as marine organisms are a major source of these nutrients. Although fish oils contain more than 40 fatty acids, the health benefits of fish oil intake have been attributed primarily to eicosapentaenoic (EPA, 20 : 5n-3) and docosahexaenoic (DHA, 22 : 6n-3) acids, the two most abundant omega-3s in fish oil. A subset of studies on LC omega-3s has used concentrated EPA or DHA (which are commercially available), or the combination. The third most prevalent LC omega-3 in fish oil, docosapentaenoic acid (DPA, 22 : 5n-3), is gaining traction among both scientists ([3], ISSFAL, 2014. <http://www.issfal.org/2014/satellites/dpa>) and consumers as an important contributor to the beneficial effects of fish oil intake. Most fish oils contain less than 2% DPA by weight, roughly one-third to one-fifth of the EPA or DHA content. However, the levels of DPA in human milk are higher than those of EPA and comparable to those of DHA [4], implicating it as potentially important in human development.

Further, DPA shares structural similarities with EPA and DHA. As an “elongated version of EPA”, DPA has two extra carbons in

the chain and the same number of double bonds as EPA. Biochemically it is a direct elongation product of EPA. The similarity of DPA to EPA and DHA may explain some of its overlapping biological functions with these better-studied fatty acids.

Worldwide, it is estimated that 28 million life-years are lost annually from ill health, disability, or early death due to inadequate omega-3 intake (IHME, 2013 <http://ihmeuw.org/27t0>). In the United States (US), for instance, LC omega-3 deficiency is ranked among the top-ten preventable causes of all-cause death [5]. Many people consume insufficient LC omega-3s [6], mostly due to poor dietary habits or lack of access to the nutrients.

While many government agencies worldwide offer guidelines for DHA and EPA intake, few currently recommend the intake of DPA; indeed, only Australia and New Zealand offer specific guidelines for DPA intake along with EPA and DHA (NHMRC, 2005. <https://www.nrv.gov.au/nutrients/fats-total-fat-fatty-acids>). However, DPA-enriched fish oils are now becoming commercially available as dietary supplements (Swanson, 2014. <http://www.swansonvitamins.com/health-library/products/omegaactiv-super-dpa-fish-oil.html>), and DPA-based drugs for hypertriglyceridemia (Matinas BioPharma. http://content.stockpr.com/_news/matinasbiopharma/2014-10-20_Matinas_BioPharma_Submits_Investigational_New_Drug_84.pdf), inflammatory conditions, and cancer are currently under development (SFC, 2014. Available from: <http://www.scfpharma.com/products/>). This paper reviews the dietary sources of DPA and its biological functions.

Biosynthesis

LC Omega-3s in human diets derive primarily from seafood, fish oil supplements, and foods fortified with fish oils. The shorter-

chain omega-3s, like α -linolenic acid (ALA), are predominantly sourced from plants. The conversion of ALA to LC omega-3s is minimal to absent. In healthy young women, up to 21% of dietary ALA is converted to EPA, while only 6% is converted to DPA and 9% to DHA [7]. In young healthy men, only about 8% of ALA is converted to EPA and DPA, and none is converted to DHA [8]. The conversion is reduced by roughly 40% when diets are high in pro-inflammatory omega-6 fatty acids, which are overly abundant in Western diets [9]. Omega-6s compete with omega-3s for enzymes in biosynthetic pathways in the human body [10]. In addition, genetic variations in desaturation and elongation genes can result in even more reduced conversion of shorter-chain omega-3s into EPA, DPA, and DHA [11]. Dietary habits and other lifestyle factors can also affect the biosynthesis of DPA. For example, a feline study showed that alcohol consumption reduced levels of DPA in the plasma and the liver [12]. Thus, an adequate supply of DPA, as well as EPA and DHA, may be best achieved through direct consumption [7, 8].

Biological functions of DPA

Epidemiological trials have demonstrated that higher levels of DPA in human blood are positively correlated with lower blood triglycerides, cholesterol, inflammation, and overall risk of coronary heart diseases and acute myocardial infarction [13–18]. For example, in a large epidemiological investigation of older adults, higher circulating levels of DPA were associated with lower total mortality, including death from coronary heart disease [19]. In a case-controlled study, which involved 73 patients with acute myocardial infarction and 84 matched controls, serum DPA levels were significantly higher in healthy individuals than in the affected group [17]. Further, a study in Australian men showed that the levels of DPA in blood platelets showed a strong negative correlation with mean platelet volume, a risk factor for acute myocardial infarction [20]. In the Edinburgh Artery Study, a cross-sectional survey of more than 1,500 people, DPA was the only LC omega-3 that reduced the likelihood of developing atherosclerosis, suggesting that it may have a protective effect [21]. A study in Australian men indicated that blood levels of DPA are influenced by diet, and its consumption has been positively linked to less carotid atherosclerosis [22]. Although these studies do not imply causation, they highlight the link between DPA and better cardiovascular health.

Causal *in vitro* studies showed that purified DPA, when applied to platelets or cell lines, reduced platelet aggregation [23], stimulated endothelial cell migration [24], and reduced inflammation [25]. In fact, it was reported that DPA treatment inhibited platelet aggregation more efficiently than EPA or DHA [26], which indicates that DPA may reduce the formation of blood clots more efficiently than the other two well-known LC omega-3s. Similarly, a study using human blood samples showed that DPA was equally effective to EPA and DHA in inhibiting platelet aggregation in female subjects [23]. Further, a recent *in vitro* study showed that application of LC omega-3s, including DPA, suppressed the synthesis of triglycerides and cholesterol in liver cells [27], which may explain data from epidemiological trials that linked DPA to better health outcomes.

Importantly, the structure of fatty acids affects the absorption rate of omega-3s into the body. One study showed that DPA was incorporated into cell phospholipids faster than EPA, and the rate is similar to that of DHA [28]. During the exposure of liver cells to DPA or DHA, the content of these fatty acids increased gradually at a similar rate and plateaued at 16% after 8 hours of supplementa-

tion [28]. In contrast, EPA content reached the saturation point at 12% [28].

Mammalian model studies have provided an abundance of evidence attesting to the unique biological role of DPA. One study showed that DPA is less actively oxidized than oleic acid and EPA [29]. In other words, DPA is not readily burned as energy. Instead, it was conserved and deposited in various tissues or immediately participates in biological processes [29]. Other studies have shown that DPA improved lipid metabolism [30, 31] reduced tension of the blood vessel walls [30], inhibited chronic inflammation [30], and decreased aortic plaque build-up (ISSFAL, 2014).

Some mechanistic evidence also exists to demonstrate how DPA functions. Following EPA supplementation in macrophages, DPA inhibited the pro-inflammatory mediators derived from cyclooxygenase (COX) metabolism showing that EPA exerts anti-inflammatory effects indirectly through elongation to DPA [25]. DPA has therefore been suggested to play a major role in the inhibition of inflammation [25]. A recent and profound development in understanding DPA's role in the body came with the discovery of the structures and *in vivo* and *in vitro* synthesis of DPA-derived specialized pro-resolving mediators, which exhibited potent anti-inflammatory and tissue-protective properties [2, 32, 33].

DPA has also been linked to better mental health and cognitive function. Observational studies show that DPA levels in patients with depression and schizophrenia were lower than in healthy people [34, 35]. Additionally, low blood levels of DPA during pregnancy were linked to a higher prevalence of postpartum depression [36]. In rodent studies, supplementation with purified DPA increased the levels of DPA and DHA in the brain, and reduced depression symptoms as measured by behavioural tests [37]. Another study in mice suggested that DPA might help to improve outcomes of spinal cord injury [38]. In a separate study, DPA supplementation of aged rats improved brain function, as measured by long-term potentiation and performance in spatial learning tasks, and reduced age-related oxidative damage of the brain [39].

The first ever human supplementation trial with 99.8% pure DPA showed that its consumption significantly increased the levels of EPA, DPA, and DHA in blood plasma of the participants [40]. Additionally, it has been demonstrated that DPA was both retro-converted to EPA and further elongated to DHA [40]. The authors suggested that DPA may serve as a reservoir or pool for the EPA and DHA, which can be used by the body as needed [40]. These findings underscore the importance of DPA as a regular dietary component.

Food sources of DPA and current intakes

According to the US Department of Agriculture (USDA) National Nutrient Database for Standard Reference, seafood is the richest source of LC omega-3s, including DPA (USDA, 2014. <http://www.ars.usda.gov/ba/bhnrc/ndl>). Raw salmon provides up to 393 mg DPA per 100 g of edible portion (USDA, 2014). Atlantic mackerel and Florida pompano (which contains even more DPA than EPA) deliver over 200 mg of DPA per 100 g portion (USDA, 2014). Pacific herring, sablefish, whitefish, bluefin tuna, and rainbow trout deliver 100 to 200 mg of DPA per 100 g of edible portion (USDA, 2014).

Seal meat and blubber are particularly rich in DPA. For example, bearded seal oil contains 5.6% DPA, which is more than in any other marine oils (USDA, 2014). Bang et al. [41] estimated that Greenland Intuits, who were absolute carnivores before their exposure to Western civilization, consumed, on average, 400 g seal meat

per person per day. Based on the numbers provided in the report, it can be estimated that the population consumed anywhere between 1.7 to 4.0 grams DPA per day [41]. The authors suggested that the high intake of LC omega-3 fatty acids, including DPA, may explain the rarity of ischemic heart disease in this population [41]. However, as seal hunting remains highly controversial, seal meat and oils are not likely to contribute to DPA intake for most consumers.

Recently, the US Food and Drug Administration recommended that women who are pregnant, might become pregnant, or are breastfeeding should consume 8 to 12 ounces of fish per week (FDA, 2014. <http://www.fda.gov/food/foodborneillnesscontaminants/metals/ucm393070.htm>). The consumption of 12 ounces of salmon would provide up to 1,336 mg DPA per week (USDA, 2014).

The major food sources of DPA in pregnant and lactating Canadian women were reported recently to be seafood (59%), poultry (14%), meat products (11%), and dairy (9%) (ISSFAL, 2014). About two-thirds of seafood-derived DPA intake in those women was attributed to salmon consumption (ISSFAL, 2014). In Australian children, EPA and DHA intakes were highly correlated with the consumption of fish and seafood products, while DPA intake was moderately correlated with the consumption of meat [42]. The main contributor to DPA intake in these children was meat, poultry, and game products (56%); fish and seafood (23%), cereal-based products and dishes (5.7%), milk products and dishes (5.6%), and egg products and dishes (3.6%) provided the remainder [42].

Among terrestrial sources, liver of New Zealand beef and lamb are the richest sources of DPA, containing approximately 140 mg DPA per 100 g of edible portion (USDA, 2014). Australian beef provides up to 80 mg DPA per 100 g of edible meat [43]. Levels of DPA in the United Kingdom food tables for lean trimmed meat are, on average, 20 mg per 100 g for beef, and 30 mg for lamb (FSA, 2002. <http://tna.europarchive.org/20110116113217/http://www.food.gov.uk/science/dietarysurveys/dietsurveys/>). US beef, on the other hand, contains negligible levels of DPA. Higher levels of DPA – and other omega-3s – in Australian red meat can be attributed to the predominant use of pasture-grazing production systems [43]. Relatively high levels of DPA in grass-fed beef may also support the theory of Miller et al., which suggested that DPA may serve as a reservoir of LC omega-3s in humans [40] and, perhaps, other mammals like cattle.

Despite the documented benefits of fish, not all individuals consume fish due to allergies or taste preferences. Highly refined dietary fish oil supplements offer the benefits of omega-3s for people who are averse to fish intake. In countries such as the US and Australia, where fish consumption is insufficient, fish oil supplements could become a significant dietary source of DPA. According to the USDA National Nutrient Database for Standard Reference, menhaden oil contains 4.9% DPA, which makes it the richest source of DPA among commercial fish oil supplements (USDA, 2014). Oils from salmon (3.0%; likely wild), sardine (2.0%), cod liver (0.9%), and herring (0.6%) also provide DPA (USDA, 2014). Some commercially-available concentrated DPA products currently contain approximately 10% DPA (Supply Side West, 2013. <http://omega3.supplysideinsights.com/articles/2013/04/omega-3-insights-awards-finalists-announced/>), which is comparable to the levels of EPA or DHA in many refined non-concentrated fish oils. As new fractionation technologies become more economically viable, higher concentrations of DPA will be available on a commercial scale in the near future.

Pharmaceuticals

At least two DPA-based drugs are currently under development. A monoglyceride form of DPA is currently being explored as an anti-cancer drug by a start-up biopharmaceutical company (SCF Pharma, 2015, www.scfpharma.com). In a rat model, administration of the compound resulted in the production of anti-inflammatory and pro-resolving mediators, and demonstrated potential for the treatment of pulmonary inflammatory conditions [44]. In a cell culture study, it completely inhibited the growth and proliferation of colon cancer cells [45]. This drug is currently at research and development stages.

Another emerging biopharmaceutical company is developing a DPA-based drug for treatment of severe hypertriglyceridemia (Matinas BioPharma, 2014). A study in rats conducted by the company demonstrated that the daily intake of 50 mg DPA/kg of body weight was at least as effective in reducing blood triglycerides as 400 mg EPA/kg (Matinas BioPharma, 2014).

Summary

The presence of DPA in human tissues and its relative abundance in human milk have long served as clues to its importance in human health, and it is increasingly recognized as an important part of our diet. Numerous observational trials have demonstrated a clear link between DPA intake and better health, while multiple *in vitro* and *in vivo* studies have shown direct effects of DPA on inflammation, lipid metabolism, and cognitive function. Moreover, the recent discovery of DPA-derived specialized pro-resolving mediators, and their structures and biological functions, opens a new chapter of DPA research. Well-designed and executed randomized controlled trials in humans would undoubtedly reinforce the totality of available data on DPA as a critical part of the human diet, along with EPA and DHA.

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