Docosapentaenoic acid (22:5n-3): A review of its biological effects

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\begin{abstract}
This article summarizes the current knowledge available on metabolism and the biological effects of n-3 docosapentaenoic acid (DPA). n-3 DPA has not been extensively studied because of the limited availability of the pure compound. n-3 DPA is an elongated metabolite of EPA and is an intermediary product between EPA and DHA. The literature on n-3 DPA is limited, however the available data suggests it has beneficial health effects. In vitro n-3 DPA is retro-converted back to EPA, however it does not appear to be readily metabolised to DHA. In vivo studies have shown limited conversion of n-3 DPA to DHA, mainly in liver, but in addition retro-conversion to EPA is evident in a number of tissues. n-3 DPA can be metabolised by lipoxigenase, in platelets, to form 11-hydroxy-7,9,13,16,19- and 14-hydroxy-7,10,12,16,19-DPA. It has also been reported that n-3 DPA is effective (more so than EPA and DHA) in inhibition of aggregation in platelets obtained from rabbit blood. In addition, there is evidence that n-3 DPA possesses 10-fold greater endothelial cell migration ability than EPA, which is important in wound-healing processes. An in vivo study has reported that n-3 DPA reduces the fatty acid synthase and malic enzyme activity levels in n-3 DPA-supplemented mice and these effects were stronger than the EPA-supplemented mice. Another recent in vivo study has reported that n-3 DPA may have a role in attenuating age-related decrease in spatial learning and long-term potentiation. However, more research remains to be done to further investigate the biological effects of this n-3 VLCPUFA.
\end{abstract}

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Abbreviations: AA, arachidonic acid; ACC, Acetyl CoA Carboxylase; ALA, alpha linolenic acid; BAE, bovine aortic endothelial cells; CHREBP, carbohydrate response element binding protein; COX, cyclooxygenase; CPT-1, carnitine palmitoyl transferase-1; DHA, docosahexaenoic acid; 17S-H(p) DPA, 17S-hydro(peroxy) docosapentaenoic acid; DPA, docosapentaenoic acid; EC, endothelial cells; EPA, essential fatty acid; EPA, eicosapentaenoic acid; FASα, fatty acid synthase; HETE, 12-hydroxy-5,8,10,14-eicosatetraenoic acid; HNF-α, hepatic nuclear factor-α; HTT, 5,8,10-heptadecatrienonic acid; LA, linoleic acid; LOX, lipoxigenase; L-PK, liver pyruvate kinase; LT, leukotriene; LXR, liver X receptor; OHDPA, hydroxydocosapentaenoic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, prostaglandin; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element binding protein; TAG, triacylglycerol; TNF-α, tumor necrosis factor-α; TX, thromboxane; VEGF, vascular endothelial growth factor; VLCPUFA, very long chain polyunsaturated fatty acids.

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1. Introduction

The realisation that brain grey matter from many different mammals was rich in n-3 long chain polyunsaturated fatty acids (n-3 VLCPUFA), especially DHA was a stimulus for much research on the biological role(s) of n-3 VLCPUFA [1, 2]. Since then many studies have been conducted to investigate the beneficial effects of n-3 VLCPUFA in neural function, reducing risk of cardiovascular events, diabetes mellitus, inhibiting growth of tumor cells, modulating gene expression, anti-inflammatory activity and lipid lowering potential [3–8]. Most of these studies have been conducted on fish oils which typically contain all the three n-3 VLCPUFA, namely eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) (Fig. 1). Many studies have addressed the unique actions of EPA and DHA individually, because these two fatty acids have been available in purified form. What has emerged from this research is that there are both unique as well as overlapping actions. For example DHA has unique actions in promoting normal functioning of brain, while both EPA and DHA have overlapping actions in lowering blood lipid levels. Because pure n-3 DPA has not been readily available or at an affordable price, the role(s) of n-3 DPA have not been systematically examined. To date few studies have been conducted using pure or enriched n-3 DPA, yet the data available points to beneficial effects of n-3 DPA. The aim of this review is to summarize this current knowledge on the biological effects of n-3 DPA.

2. Synthesis and metabolism of n-3 DPA

Alpha-linolenic acid (ALA) (n-3), one of the two essential fatty acids (EFA), can be metabolized in vivo by desaturation and elongation enzymes to form a series of highly unsaturated n-3 VLCPUFA. The major products of this pathway are EPA, DPA and DHA [9]. n-3 DPA is formed by chain elongation of EPA which is believed to be mediated by the enzymes fatty acid elongase-2 (FAE-2) and FAE-5 [10, 11]. The conversion of n-3 DPA to DHA was initially believed to be the result of the activity of Δ4 desaturase, converting 7,10,13,16,19–22:5 (DPA) to 4,7,10,13,16,19–22:6 (DHA). But later studies reported that DPA was first elongated to 24:5n-3 which was then desaturated, by the activity of Δ6 desaturase, to form 24:6n-3 [12]. 24:6n-3 is translocated from the endoplasmic reticulum to the peroxisome where this 24 carbon fatty acid is then chain-shortened to 22:6n-3 (DHA) by β-oxidation. However, in some marine algae like Pavlova lutheri and Thraustochytrium sp., the Δ4 desaturase cDNA has been sequenced and isolated [13, 14]. It has been shown that introduction of this Δ4 desaturase into Saccharomyces cerevisiae and Brassica juncea results in production of DHA in vegetative tissues [13].

ALA supplementation studies conducted in 1960s, in rats, showed the increase in the tissue proportions (liver and heart) of ALA, EPA, DPA and DHA. These were long-term studies, conducted for a duration of 80–100 days, and involved refeeding rats which had initially been made EFA deficient. The results showed that after supplementation with ALA there were increases in ALA, EPA, n-3 DPA and DHA as the dietary ALA level was increased [15–17]. However, most human supplementation studies have led to the belief that the major products of ALA metabolism are EPA and n-3 DPA and that the capacity of humans to convert ALA to DHA is limited [18–20]; tracer studies report that females have greater capacity for synthesis of DHA than males [19, 20]. A recent review has summarized the data from various ALA supplementation studies conducted in human adults and concluded that ALA supplementation generally leads to an increase in plasma EPA and n-3 DPA levels but has little or no effect on DHA levels [21]. In animals, ALA has been shown to be more prone to deposition in adipose tissue, β-oxidation or excretion via skin rather than metabolism to DHA [22]. An alternative reason for limited synthesis of DHA from ALA is the competit-
tion between 24:5n-3 and ALA for the δ6 desaturase enzyme (Fig. 1) [23]. In other words, when there is a high ALA level, the ALA itself (or indeed LA) could inhibit metabolism of 24:5n-3 to 24:6n-3, thus limiting the availability of the precursor to form DHA.

In case of n-3 DPA, endothelial cells supplemented with DPA show a substantial increase in EPA in the cells, but there is little evidence of DHA formation. Similarly when these cells were supplemented with EPA, there was a significant increase in n-3 DPA, but not DHA [24,25]. However, media from n-3 DPA-incubated cells contained small amounts of DHA suggesting that n-3 DPA was converted to DHA and then released into the media [24]. In primary rat hepatocytes, it was observed that 14c-EPA was elongated to n-3 DPA linearly over a 24 h period; in turn, the n-3 DPA was elongated to 24:5n-3, however no DHA was detected in these primary hepatocytes. The conversion of n-3 DPA to EPA is referred to as retro-conversion. The process of retro-conversion was first described in 1970 [26] for DHA, and subsequent work in human fibroblasts indicated the retro-conversion of both DHA and n-3 DPA was likely to involve the peroxisomal acyl-CoA oxidase and one cycle of β-oxidation (Fig. 1) [27,28]. It has been demonstrated using fibroblasts, that cells deficient in this enzyme cannot perform the chain-shortening of n-3 DPA to EPA [27].

Two recent in vivo studies also provide evidence for retro-conversion of n-3 DPA into EPA. A study conducted in Sprague Dawley rats reported that n-3 DPA supplementation for 7 days (oral gavage of 50 mg/day of DPA as a free fatty acid) increased n-3 DPA concentrations in all tissues examined and EPA concentrations in liver, heart and skeletal muscle. However, the DHA concentration was increased only in liver [29]. Similarly a study conducted in C57BL/KsJ-db/db mice reported that after 4 weeks of supplementation with a synthetic triacylglycerol containing three n-3 DPA residues (tri-DPA), the proportion of EPA was increased in liver and kidney but there was no evidence of an increase in DHA in any of the tissues examined [30]. There is evidence of formation of DHA from n-3 DPA in the retina of miniature poodle dogs which received an intravitreal injection of 14c-DPA [31].

3. Isomers of DPA

There is another isomer of DPA which is an n-6 fatty acid. The n-6 DPA content is low in most mammalian tissues, except testes tissue [32,33]. In fish and fish oils, the n-3 isomer of DPA is substantially higher than the n-6 isomer [34]. An algal oil from Schizochytrium sp. which is rich in DHA, also contains about 15% n-6 DPA [35]. The physiological behaviour of n-3 and n-6 DPA differs profoundly despite only differing in the position of two double bonds in the acyl chain [36]. Deficiency of n-3 fatty acids in animals leads to a depletion of DHA and a compensatory rise in n-6 DPA level in most tissues, especially brain and retina [37,38]. Supplementation with n-6 DPA did not produce the benefits afforded by DHA for spatial task performance or in other words for brain function [39]. In retina, DHA is the major VLCPUFA in the rod outer segment (ROS) membrane phospholipids. In n-3 PUFAs deficiency studies, the n-6 DPA does not completely replace DHA in phosphatidylethanolamine (PE) and phosphatidylcholine (PC) species in the retina and the loss of this one double bond is enough to induce functional deficits in retinal signalling pathways [40]. Similarly, n-6 DPA could not fully support the protective role of DHA in cell survival and apoptosis in mouse neuroblastoma cells [41].

4. Biological effects of n-3 DPA

The n-3 VLCPUFA have been shown to have many beneficial biological effects. These include their role in cell membrane functions, eicosanoid production and regulation of gene expression. However, most of these studies have been conducted using either fish oil (mixture of n-3 VLCPUFA) or pure EPA and DHA. Although there are studies which suggest a positive association between dietary n-3 DPA and heart health [42,43], there are only a limited number of studies which have investigated the biological effects of pure n-3 DPA and most of these studies have been conducted using either endothelial cells or platelets (Table 1).

A recent study reported that aged rats fed either EPA or n-3 DPA for 56 days showed neuroprotective effects [44]. Both EPA and n-3 DPA attenuated the age-related increases in caspase 3 activity and microglial activation and the changes observed were associated with restoration of long-term potentiation and improved performance in spatial learning task. The authors reported that both n-3 DPA and EPA reduce the age-related oxidative changes in vivo.

4.1. Effect of n-3 DPA on eicosanoid production

Eicosanoids are the signalling molecules in the body that control many physiological systems. Eicosanoids include prostaglandins (PG), prostacyclins, thromboxanes (TX) leukotrienes (LT), lipoxins, hydroxyeicosatetraenoic acid and epoxyeicosatetraenoic acid [45]. Eicosanoid synthesis is induced in the body in different physiological and/or pathological conditions including inflammation and cancer. They are involved in modulating the intensity and duration of inflammation and immune response [46]. Arachidonic acid (AA), is the substrate for the production of eicosanoids, under the action of cyclooxygenase (COX) and lipooxygenase (LOX) enzymes. In platelets, AA is metabolised by COX to form TXA2, 5,8,10-heptadecatrienoic acid (HHT) and by LOX to 12-hydroxy-5,8,10-eicosatrienoic acid (12-HETE) [47]. In platelets, n-3 DPA is metabolized into 11- and 14-hydroxy docosapentaenoic acids via the LOX pathway [47]. When platelets were incubated with n-3 DPA, along with AA, this inhibited the COX enzyme thereby reducing the TXA2 and HHT production from AA. In turn, more AA was available for shunting to the LOX pathway resulting in increased production of 12-HETE.

Platelet aggregation is an early event in the development of thrombosis and is initiated by TXA2. The results from an ex vivo study conducted in rabbit platelets showed that EPA, n-3 DPA and DHA inhibited collagen- or AA-stimulated platelet aggregation dose-dependently, and that n-3 DPA was the most potent inhibitor [48]. These fatty acids also suppressed TXA2 formation by platelets which were exposed to collagen, thrombin or AA. In these experiments, n-3 DPA was the most potent inhibitor of COX-1 activity; n-3 DPA enhanced formation of 12-HETE in response to collagen or AA by intact platelets, while EPA and DHA had less of an effect. These results suggest that n-3 DPA possesses potent activity for interfering with the COX pathway and accelerating the LOX pathway, thus inhibiting platelet aggregation most effectively. In a human whole blood ex vivo study, n-3 DPA was equally effective as EPA and DHA in inhibiting platelet aggregation, in female subjects however, in male subjects only EPA inhibited platelet aggregation [49].

n-3 DPA has also been shown to reduce the prostacyclin production (by two fold) in endothelial cells (EC) compared with control cells when stimulated with endogenous AA-mobilizing agents such as bradykinin and calcium ionophore A23187. It was also reported that prostacyclin production in cells incubated with EPA was less inhibited than in cells incubated with n-3 DPA. Since the inhibition was approximately proportional to the amount of EPA in cells, regardless of n-3 DPA content in the cells, this study suggested that inhibition of prostacyclin by n-3 DPA was due to its retro-conversion into EPA [50].

EPA and DHA also act as precursors of novel pro-resolving and anti-inflammatory mediators. These mediators include resolvins of the E series from EPA, resolvins of the D-series or their aspirin...
DPA pretreatment (0.5 mg/ml) was achieved at a concentration of serum. Moreover, maximum stimulation of EC migration by n-3 DPA (0.01–1.0 mg/ml) resulted in a control of wound-healing response of blood vessels. Direct pre-treatment of ECs with n-3 DPA (22:5(n-3)) led to a one-tenth of that required for maximal stimulation by EPA treatment (5.0 mg/ml), indicating that n-3 DPA is a potent stimulator of EC migration. In EC, EPA was elongated to n-3 DPA and DHA treatment decreased the hepatic TG levels compared to the control while EPA was most effective in reducing platelet aggregation compared with n-3 DPA and DHA. However, when grouped by gender, in females all three n-3 VLCPUFA were effective. But in men EPA was more effective than n-3 DPA and DHA.

**4.2. Effect of n-3 DPA on endothelial cell (EC) migration**

EC migration and proliferation are important processes in the control of wound-healing response of blood vessels. Direct pre-treatment of ECs with n-3 DPA (0.01–1.0 mg/ml) resulted in a dose-dependent increase in migration in response to fetal bovine serum. Moreover, maximum stimulation of EC migration by n-3 DPA pretreatment (0.5 mg/ml) was achieved at a concentration of one-tenth of that required for maximal stimulation by EPA pretreatment (5.0 mg/ml), indicating that n-3 DPA is a potent stimulator of EC migration. In EC, EPA was elongated to n-3 DPA, with little DHA being formed[25]. These data suggest that the stimulatory effect of EPA on EC migration occurs via n-3 DPA, and that n-3 DPA may act as a powerful anti-atherogenic factor.

*In vitro and ex vivo studies*

**1984** Careaga and Sprecher Human platelets Platelets metabolize 7,10,13,16,19-DPA (22:5(n-3)) into 11-hydroxy-7,9,13,16,19- and 14-hydroxy-7,10,12,16,19-DPA via an indomethacin-insensitive pathway. n-3 DPA inhibits the synthesis of both 5,8,10-heptadecatrienoic acid and thromboxane B2 from arachidonic acid

**1991** Rosenthal et al. Fibroblasts and retinoblasts Although fibroblasts desaturate [14C]22:5(n-3), the process appears to be slower than that of retinoblastoma cells

**1993** Christensen et al. Fibroblasts Peroxisomal acyl-CoA oxidase is responsible for the chain-shortening of DHA and n-3 DPA

**1995** Achar et al. Endothelial cells EPA, n-3 DPA and DHA are actively interconverted to each other in endothelial cells

**1996** Benistant et al. Endothelial cells Addition of n-3 DPA bound to albumin produced twofold less prostacyclin compared to control cells when stimulated with endogenous arachidonic acid-mobilizing agents.

**1996** Kanayasu-Toyoda et al. Endothelial cells The stimulative effect of EPA on EC migration occurs via n-3 DPA, and that n-3 DPA may act as a powerful anti-atherogenic factor

**2000** Akiba et al. Rabbit platelets (ex vivo) EPA, n-3 DPA and DHA inhibit collagen- or arachidonic acid-stimulated platelet aggregation dose-dependently among which n-3 DPA was the most potent inhibitor

**2001** Arita et al. Human promyelocytic leukemia cells n-3 VLCPUFA including n-3 DPA induce apoptosis of leukemia cells (HL-60), in part by direct action on the cells and by activation of the caspase cascade through cytochrome c release coupled with mitochondrial membrane depolarization

**2001** Williard et al. Rat brain astrocytes Astrocytes can synthesise and incorporate [3-14C]DHA into the cell PL from [3-14C]ALA and [3-14C]DPA and also release it into the media as free fatty acid [58]

**2003** Tsuji et al. Endothelial cells n-3 DPA suppressed tube-forming activity induced by vascular endothelial growth factor (VEGF) and n-3 DPA has a potent inhibitory effect on angiogenesis through the suppression of VEGFR-2 expression

**2003** Pawar and Jump Hepatocytes Metabolic labelling indicated that a significant fraction of [14C]EPA was elongated to n-3 DPA in hepatocytes. Cells treated with DPA or DHA led to a significant accumulation of EPA in the NEFA pool. EPA and DHA, but not n-3 DPA, are active ligands for PPARs.

**2005** Langelier et al. Neuroblastoma cells The incorporation of EPA, DPA, and DHA followed a dose–response saturating curve, whereas that of DHA was one-tenth of that required for maximal stimulation by EPA pretreatment (5.0 mg/ml), indicating that n-3 DPA is a potent stimulator of EC migration. In EC, EPA was elongated to n-3 DPA, while little DHA being formed[25]. These data suggest that the stimulatory effect of EPA on EC migration occurs via n-3 DPA, and that n-3 DPA may act as a powerful anti-atherogenic factor[25]. Another study conducted in bovine aortic endothelial (BAE) cells reported that the migration activity of these cells stimulated with vascular endothelial growth factor (VEGF) was suppressed by DPA pretreatment. The pretreatment of BAE cells with n-3 DPA also suppressed tube-forming activity induced by VEGF, which suggests its positive role in preventing angiogenesis. The effect of n-3 DPA was stronger than those of EPA and DHA. n-3 DPA treatment of BAE cells also caused the suppression of VEGF receptor-2 (VEGFR-2, the kinase insert domain-containing receptor) expression. These data indicate that n-3 DPA has a potent inhibitory effect on angiogenesis possibly through the suppression of VEGFR-2 expression [5].

**Table 1**

List of literature available on n-3 DPA.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Model</th>
<th>Findings</th>
</tr>
</thead>
</table>
| 1993 | Alvarez et al. | Miniature poodle dogs | Intravitreal injection of dogs with [14C]DPA (n-3) led to formation of [14C]-DHA in the rod outer segment lipids. There was no difference in % dpm of DHA generated in normal dogs and dogs affected with progressive rod-cone degeneration. There was also evidence of label in 24:5n-3 and 24:6n-3
| 2000 | Rissanen et al. | – | Men in the highest fifth of the proportion of serum DHA + n-3 DPA in all fatty acids had a 44% reduced risk of acute coronary events compared with men in the lowest fifth in a prospective population study.
| 2005 | Oda et al. | Serum levels (wt.%) of linolenic acid, EPA, n-3 DPA, and total n-3 VLCPUFA were significantly lower in patients with acute myocardial infarction than the control group in a case control study. |

**Abbreviations:** EPA – eicosapentaenoic acid; n-3 DPA – docosapentaenoic acid; DHA – docosahexaenoic acid; LOX – lipoxygenase.
4.3. n-3 VLCPUFA regulate expression of several genes and enzymes

One of the roles of n-3 VLCPUFA in the body is in the regulation of gene expression. Although many genes and pathways have been reported to be regulated by n-3 VLCPUFA, it is the ability of these n-3 VLCPUFA to regulate genes involved in lipid oxidation and cellular inflammation that highlights a unique molecular activity (Fig. 2). A variety of mechanisms have been proposed to account for the impact on gene expression, demonstrated both acutely and chronically, following n-3 VLCPUFA exposure, including: alterations in membrane composition and associated lipid signalling, eicosanoid production, oxidant stress, nuclear receptor activation or covalent modification of specific transcription factors [52]. The discovery of Gottlicher et al. of nuclear receptors capable of binding fatty acids to modulate gene expression established a direct role for fatty acids at nuclear level [53]. The main receptors that interact with n-3 VLCPUFA to regulate gene expression are peroxisome proliferator receptors (PPAR), liver X receptor (LXR) and hepatic nuclear factor-4α (HNF-4α) [52]. In addition, n-3 VLCPUFA also regulate gene expression by interacting with the transcription factors including: sterol regulatory element binding protein (SREBP) and carbohydrate response element binding protein (ChREBP) [54]. The important lipogenic genes down-regulated by n-3 VLCPUFA are SREBP-1c, acetyl CoA carboxylase (ACC-2), fatty acid synthase (FASN) and ChREBP. SREBP-1c is a hepatic gene transcription factor that plays an important role in controlling transcription of genes involved in fatty acid synthesis, especially in liver [55]. Few studies have looked at the effect of pure n-3 DPA on genes involved in fat oxidation and fat synthesis. In hepatocytes, n-3 DPA has been shown to induce PPARα, but EPA and DHA had a stronger and more consistent effects [56]. A recent study reported that n-3 DPA reduced the expression of lipogenic genes in vivo. Supplementation of mice with pure n-3 DPA (in TAG form) for 4 weeks significantly reduced the hepatic enzyme activity of FAS and malic enzyme (ME) in the cytosolic fraction. In this study, the mice fed with n-3 DPA also showed a reduction in hepatic TAG levels [30]. The n-3 DPA fed to these animals was a synthetic tri-DPA which is not present naturally in the diet.

n-3 DPA has also been reported to have a positive role in reducing the expression of inflammatory genes. Inflammation is an immune response to injury. However, inflammation in walls of blood vessels is thought to play a role in the development of atherosclerotic plaques and thus lead to cardiovascular disease. Tumor necrosis factor (TNF-α) is a prototypic pro-inflammatory cytokine and a mediator of systemic inflammation and immune responses. Supplementation of L929 murine fibrosarcoma cells with EPA, n-3 DPA and DHA was shown to reduce TNF-induced necrotic cell death; in contrast, preincubation with oleic acid, linoleic acid or 20:3n-3 did not affect TNF-induced necrosis. The order of effectiveness was DHA > n-3 DPA ≥ EPA [57].

4.4. Conclusions and future perspective

These data suggest that n-3 DPA may possess some beneficial and perhaps unique properties, however, more extensive research is required to investigate the biological effects of pure n-3 DPA in vitro and in vivo as there are still questions that remain unanswered. For example is n-3 DPA an effective precursor of DHA in brain?; is it a significant a reservoir of EPA in the body?; is n-3 DPA conserved from β-oxidation relative to other n-3 polyunsaturated fatty acids?; does n-3 DPA have any unique/specific biological properties?

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