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Review

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

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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 lipoxygenase, in platelets, to form ll-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.

Contents

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; EFA, essential fatty acid; EPA, eicosapentaenoic acid; FASn, fatty acid synthase; HETE, 12-hydroxy-5,8,10,14-eicosatetraenoic acid; HNF-α, hepatic nuclear factor-α; HTT, 5,8,10-heptadecatrienoic acid; LA, linoleic acid; LOX, lipoxygenase; 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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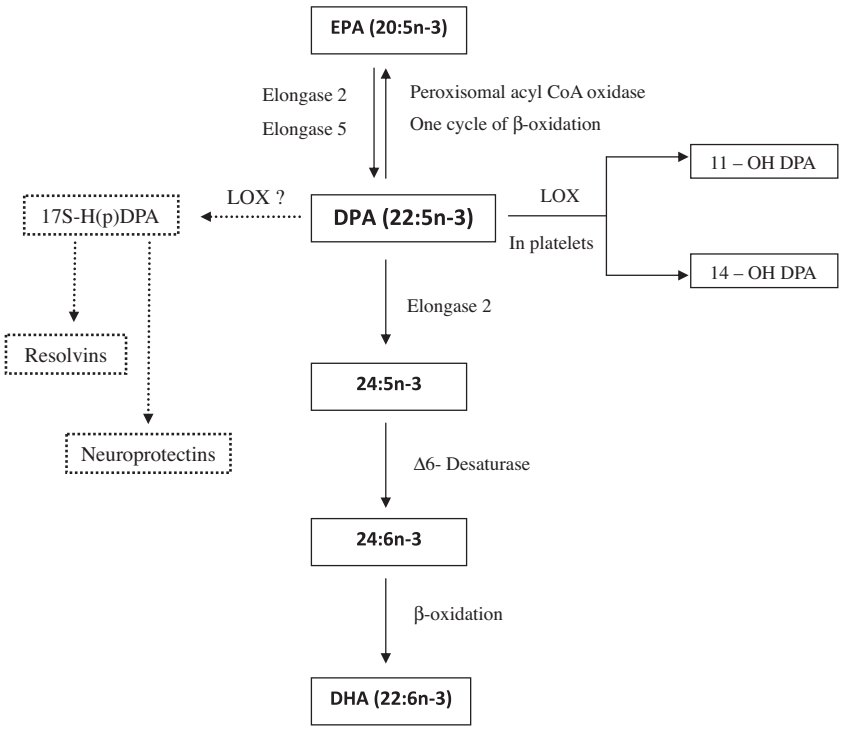

Fig. 1. Metabolites of n-3 DPA. DPA forms two hydroxy acids (11- and 14-OH DPA) via an indomethacin-insensitive pathway. DPA can be retro-converted into EPA in cells and animals and is likely to involve the peroxisomal acyl-coA oxidase and one cycle of β-oxidation. Since n-3 DPA is known to be metabolized by LOX enzymes, it is speculated that n-3 DPA might also act as a precursor for production of DPA-related D-series of resolvins or neuroprotectins. (Abbreviations: EPA – eicosapentaenoic acid; DPA – docosapentaenoic acid; DHA – docosahexenoic acid; LOX – lipooxygenase; OH DPA – hydroxy docosapentaenoic acid; 17S-H(p)DPA – 17S hydro (peroxy) docosapentaenoic acid.)

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 competi-