Esterification of Docosahexaenoic Acid in Brain Diseases

Subjects: Biochemistry & Molecular Biology

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Docosahexaenoic acid-containing lysophosphatidylcholine (DHA-LysoPC) is presented as the main transporter of DHA from blood plasma to the brain. This is related to the major facilitator superfamily domain-containing protein 2A (Mfsd2a) symporter expression in the blood–brain barrier that recognizes the various lyso-phospholipids that have choline in their polar head. In order to stabilize the DHA moiety at the *sn*-2 position of LysoPC, the *sn*-1 position was esterified by the shortest acetyl chain, creating the structural phospholipid 1-acetyl,2-docosahexaenoyl-glycerophosphocholine (AceDoPC). This small structure modification allows the maintaining of the preferential brain uptake of DHA over non-esterified DHA. Additional properties were found for AceDoPC, such as antioxidant properties, especially due to the aspirin-like acetyl moiety, as well as the capacity to generate acetylcholine in response to the phospholipase D cleavage of the polar head. Esterification of DHA within DHA-LysoPC or AceDoPC could elicit more potent neuroprotective effects against neurological diseases.

Keywords: docosahexaenoic acid ; phospholipids ; lysophospholipids ; blood-brain-barrier

1. Introduction

Lipids are major constituents of living cells, as they are important structural components of cell membranes. Polyunsaturated fatty acids (PUFAs) are long-chain fatty acids (18 carbons or more) that contain two or more double bonds. Depending on the location of the last double bond, PUFAs are classified into families such as omega-3 (last double bond on the third carbon starting from the methyl group) and omega-6 (last double bond on the sixth carbon from the methyl group). Contrary to fatty acids that can be synthesized in the human body, some of them cannot be produced de novo and must be incorporated through diet [1]. The latter are called essential fatty acids, and they include omega-6 family precursor linoleic acid (18:2*n*-6) and omega-3 family precursor α-linolenic acid (LNA, 18:3*n*-3). By a cascade of alternating desaturase and elongase enzymatic reactions, which are common to both families, longer PUFAs are biosynthesized from their respective precursors [2]. PUFAs are mainly found esterified within glycerophospholipids present in cell membranes at the *sn*-1 and *sn*-2 positions. Glycerophospholipids are grouped by the structure of their polar head group on the *sn*-3 position. Their amphiphilic nature (one hydrophilic head group and two hydrophobic fatty acids) confers fluidity and selective permeability to the membranes they constitute [3][4]. They are also precursors for signaling metabolites, including eicosanoids, growth hormones, and regulators, and they participate in important physiological processes, such as anti-inflammatory or pro-inflammatory responses [5][6][7][8].

There is a specific enrichment of essential fatty acids in human tissues, notably in the retina, brain, and heart. Contrary to arachidonic acid (ArA, 20:4*n*-6), which is the major PUFA of human tissues, docosahexaenoic acid (DHA, 22:6*n*-3) is the most prominent fatty acid in the brain, where it is considered functionally essential [9][10]. DHA concentration is especially high in neurons where it facilitates development and synaptic functions [11], with a special interest in human brain evolution [12]. A proper balance between omega-6 and omega-3 supplementation during pregnancy and infancy is required for correct neural development [13][14][15]. Along with aging, a decrease in long-chain PUFA levels in the brain has been observed, especially for DHA levels [16][17][18]. These deficiencies are correlated to a cognitive decline in normal aging but might be even more detrimental in pathological aging. In Alzheimer's disease, decreases in PUFAs, particularly in essential fatty acids such as DHA, have been observed [19][20][21]. These results hint at a possible correlation between neurodegenerative diseases and cerebral DHA deficiency.

DHA has many beneficial properties, especially for cerebral diseases such as Alzheimer's disease, that were covered in numerous reviews [22][23][24][25][26]. These include pro-neurogenic, anti-oxidative, anti-inflammatory, and anti-apoptotic properties. These potent neuroprotective effects might be partly due to the conversion of DHA into active secondary metabolites such as protectins, including protectin DX [27], resolvins, and maresins [28]. DHA can also be transformed into

N-Docosahexaenoylethanolamide, an endocannabinoid-like lipid mediator that has been named synaptamide due to its capacity to induce synaptogenesis, neurogenesis, and neurite outgrowth [29][30][31]. Due to its enrichment in double bonds, DHA can also provide fluidity to cell membranes [3][32][33]. As increasing its accretion into the brain through esterification into structured phospholipids improves cognitive functions in healthy brains [34], it might also heighten its neuroprotection against neuronal death.

2. DHA-Containing Phospholipid for the Treatment of Alzheimer's Disease

Amyloid beta (Aβ) induced neurotoxicity can lead to the elevation of oxidative stress in the brain. In an in vitro model of Aβ1-42 neurotoxicity, primary neurons treated with PC from eggs showed less neuronal death with a reduced lactate dehydrogenase release [35]. In a rat model injected with Aβ1-40, diets enriched with DHA-containing PC (DHA-PC) or PS (DHA-PS) could increase the antioxidative enzyme superoxide dismutase (SOD) level and could reduce lipid peroxidation, inflammatory, and apoptotic levels, alongside improving spatial learning cognitive functions [36]. An increase of glutathione peroxidase (GSH-Px) and SOD activities with the improvement of cognitive deficits have also been shown in Aβ25-35-induced Alzheimer's disease rat models treated for 30 days with DHA-PC [37]. In humans, a prospective follow-up study showed that subjects with baseline plasma DHA-PC levels in the upper quartile had 39% and 47% lower risks of developing Alzheimer disease and all-cause dementia, respectively, compared with participants with levels in the lower 3 quartiles [38].

In a study of senescence-accelerated prone 8 (SAMP8), mice were fed with a high-fat diet, as a model of Alzheimer's disease, or with a diet enriched with DHA-PC or DHA-PS, which both increased the activity of antioxidative enzymes GSH-Px and SOD while decreasing malondialdehyde, a marker of lipid peroxidation [39]. The mice also showed enhanced cognitive performances, improved neuroprotection through decreased neuroinflammation and apoptosis, and amelioration in Aβ pathology.

The observed improvement of brain health and cognitive functions in the pathology of Alzheimer's disease could be due not only to the neuroprotective effects of DHA (anti-inflammatory, anti-oxidative, and anti-apoptotic) but also to the beneficial transport of DHA through the BBB, increasing its bioavailability in neural cells. Another working hypothesis is that DHA can also prevent the accumulation of Aβ peptides [22][40][41][42] and the formation of fibrils [43][44][45], thus decreasing the apoptotic effects of oligomers. DHA is suggested to act on multiple pleiotropic mechanisms, leading to beneficial effects on the pathology of Alzheimer's disease [21][23]. An additional hypothesis is that the choline moiety in the polar head of PC is crucial for neuroprotection, as Ko M. et al. reported that PC but not PS was able to protect against Aβ-induced cell toxicity [35].

3. Potential Therapy to Other Neurological Diseases

Mice treated with 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) to mimic oxidative damage induced by the pathology of Parkinson's disease were fed with DHA- and eicosapentaenoic acid (EPA)-containing phospholipids, which were extracted from squid roe and contained mainly DHA-PC, DHA-containing PE (DHA-PE), and DHA-LysoPC [46]. Compared to the control group (only treated with MPTP), mice fed with DHA/EPA-PC had increased levels of antioxidative enzymes (GSH-Px and SOD) along with a reduction of motor impairments and a decrease of pro-apoptotic markers. Further study on the same model showed that a DHA-PC enriched diet could elevate activities of glutathione and SOD, alleviate the loss of dopaminergic neurons following MPTP treatment (notably through the reduction of pro-apoptotic markers), and dampen cognitive impairments in locomotor activity [47]. Parkinson's disease is mainly characterized by the abnormal aggregation of α-synuclein protein forming Lewy bodies, an imbalance in the levels of reactive oxygen species, and the loss of dopaminergic neurons. Omega-3 fatty acids, and particularly DHA, can interact with α-synuclein to prevent its detrimental oligomerization [48][49][50]. Another pathway of action of DHA is the modulation of dopamine-induced neurodegeneration [51][52] and the enhancement of anti-oxidative pathways [52].

In a model of dementia induced by short-term memory and learning impairment by treatment with scopolamine, mice fed with squid PC (enriched in DHA) performed better in a spatial-learning memory test and had increased antioxidative activity and a lower lipid peroxidation level compared to the control group [53]. Interestingly, elevated levels of acetylcholinesterase activity induced by scopolamine injection were reduced with squid PC treatment. In a following study by the same research group, it was shown that a DHA-deficient diet could lead to further damage due to scopolamine treatment through oxidative stress, apoptosis, inflammation, and delayed neurodevelopment [54], hinting at possible preventive therapy through a balanced omega-3 diet.

The potential use of DHA's beneficial properties on neuropsychiatric disorders is also currently under study [55]. Through its potency to reduce anti-inflammation and to promote neurogenesis, DHA was shown to reduce inflammatory markers in both in vitro and clinical studies [56]. The authors found correlations between higher levels of anti-inflammatory markers linked to DHA and lower levels of depressive symptoms. Similarly, in an in vivo study of forced swimming tests on rats, a decrease of inflammatory cytokines and an increase in serotonin levels were observed with omega-3 supplementation, suggesting anti-depressant effects of DHA [57]. Interestingly, dietary supplementation of DHA-containing phospholipids in a mice model of depression rescued depression-like behavior and inhibited neuroinflammation, suggesting increased effects on depression through DHA esterification in phospholipids [58].

4. AceDoPC as a Potential Antioxidant and Neurogenesis Inducer

In the case of AceDoPC initially, *sn2*-DHA-LysoPC was acetylated at the *sn*-1 position to prevent the migration of DHA from the *sn*-2 position as discussed above [59], but it appears that such an acetylation also confers some antioxidant activities to AceDoPC compared to non-esterified DHA. This was observed in an experimental stroke with a more significant lower size of post-stroke lesions and decreased oxidative stress after AceDoPC intravenous injection [60]. In an in vitro model of stroke on adult neural stem cells, strong antioxidant actions of AceDoPC could be seen on prostanoids and lipoxygenase product formation, with lipoxygenase products from ArA (leukotriene B4, $LTB_{4,}$ and 15-Hydroxyeicosatetraenoic acid, 15-HETE) being surprisingly more affected than prostanoids [61].

The inhibition of prostanoid formation could be explained by the inhibition of cyclooxygenases (COX), as shown in using purified COX-1 and COX-2 [62], suggesting an aspirin-like effect of the acetyl-containing AceDoPC. Beyond these effects on lipid metabolism, the treatment of AceDoPC by phospholipase D (PLD) leads to acetylcholine formation, likely by the combination of the acetyl group of the molecule with the released choline moiety due to PLD cleavage process [62]. AceDoPC also acts as an inhibitor of lipopolysaccharide-induced neuroinflammation, both in vitro and in vivo, with some specificities compared to DHA-PC [63].

In adult neural stem cells, nanomolar concentrations of AceDoPC increased neurogenesis by 2.5 fold (compared to the control) in the presence of AceDoPC, while 1.5 fold increase with non-esterified DHA was observed [61]. Enhanced neurogenesis by AceDoPC was even higher under pathological conditions (under hypoxia/ischemia-like conditions) while no effect was observed on gliogenesis. Another phospholipid that is structurally similar to AceDoPC but contains protectin DX, a metabolite of DHA, at the *sn*-2 position, was also produced [64]. This phospholipid, labeled AceDxPC, might enhance the beneficial effects of AceDoPC.

An additional interest of AceDoPC is due to the quick loss of its acetyl moiety [65] then releasing *sn*-2-DHA- LysoPC (with DHA at the *sn*-2 position), which is quickly isomerized into *sn*-1-DHA-LysoPC (with DHA at the *sn*-1 position) [66], a substrate for producing synaptamide [67].

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