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Review

Long-chain polyunsaturated fatty acids (LCPUFA) from genesis to senescence: The influence of LCPUFA on neural development, aging, and neurodegeneration

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ABSTRACT

Many clinical and animal studies demonstrate the importance of long-chain polyunsaturated fatty acids (LCPUFA) in neural development and neurodegeneration. This review will focus on involvement of LCPUFA from genesis to senescence. The LCPUFA docosahexaenoic acid and arachidonic acid are important components of neuronal membranes, while eicosapentaenoic acid, docosahexaenoic acid, and arachidonic acid also affect cardiovascular health and inflammation.

In neural development, LCPUFA deficiency can lead to severe disorders like schizophrenia and attention deficit hyperactivity disorder. Perinatal LCPUFA supplementation demonstrated beneficial effects in neural development in humans and rodents resulting in improved cognition and sensorimotor integration.

In normal aging, the effect of LCPUFA on prevention of cognitive impairment will be discussed. LCPUFA are important for neuronal membrane integrity and function, and also contribute in prevention of brain hypoperfusion. Cerebral perfusion can be compromised as result of obesity, cerebrovascular disease, hypertension, or diabetes mellitus type 2.

Last, we will focus on the role of LCPUFA in most common neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. These disorders are characterized by impaired cognition and connectivity and both clinical and animal supplementation studies have shown the potential of LCPUFA to decrease neurodegeneration and inflammation. This review shows that LCPUFA are essential throughout life.

Contents

Abbreviations: 5-LOX, 5-lipoxygenase; AD, Alzheimer's disease; ADAS-cog, cognitive subscale of the Alzheimer's disease assessment scale; ADHD, attention deficit hyperactivity disorder; ADP, adenosine diphosphate; ALA, α-linolenic acid; AMI, acute myocardial infarction; ARA, arachidonic acid; ATP, adenosine triphosphate; Aβ, β-amyloid; B12, vitamin B12; B6, vitamin B6; BBB, blood brain barrier; BDNF, brain-derived neurotrophic factor; BSID, Bayley Scales of Infant Development; cAMP, cyclic adenosine monophosphate; CDP-choline, cytidine diphosphate choline; CDR, clinical dementia rating; CIBIC-plus, clinician's interview-based impression of change scale which included caregiver-supplied information; CK, choline kinase; COX, cyclooxygenase; CPT, 1,2 diacylglycerol choline phosphotransferase; CREB, cAMP response element binding protein; CT, cytidine triphosphate-phosphocholine cytidyl transferase; CTP, cytidine triphosphate; DAG, diacylglycerol; DBS, deep brain stimulation; DHA, docosahexaenoic acid; DMII, diabetes mellitus type 2; EPA, eicosapentaenoic acid; FADS, fatty acid desaturase; GDNF, glial cell-derived neurotrophic factor; GLA, γ linolenic acid; I-DOPA, I-dihydroxyphenylalanine; IQ, intelligence quotient; LA, linoleic acid; LCPUFA, long-chain polyunsaturated fatty acids; LDL, low density lipoprotein; LT, leukotrienes; MCI, mild cognitive impairment; MDI, mental development index; MetS, metabolic syndrome; MMSE, mini-mental state examination; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; NPD1, neuroprotectin D1; NPI, neuropsychiatric inventory; p.p., post partum; PC, phosphatidylcholine; PD, Parkinson's disease; PDI, psychomotor development index; PE, phosphatidylethanolamine; PG, prostaglandins; PPAR, peroxisome proliferator-activated receptor; PS, phosphatidylserine; RAR, retinoic acid receptor; RBANS, repeatable battery for the assessment of neuropsychological status; rdbpc, randomized double blind placebo controlled; RXR, retinoid X receptor; SFA, saturated fatty acids; SNpc, substantia nigra pars compacta; Trk B, tyrosine kinase B; TX, thromboxanes; UTP, uridine triphosphate; VEP, visual evoked potential; VLDL, very low density lipoprotein.

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1. Introduction

Long-chain polyunsaturated fatty acids (LCPUFA) are lipids which are mainly derived from diet and important in maintaining human health. With the industrial revolution, the Western dietary intake has drastically changed from an omega-3 polyunsaturated fatty acids (n-3 PUFA) rich diet to an almost n-3 PUFA deficient diet accompanied by a sedentary lifestyle [1]. Regarding fatty acid content, Western dietary intake has shifted to an increase in omega-6 polyunsaturated fatty acids (n-6 PUFA), saturated fatty acids (SFA) and *trans* fatty acids, and a decrease in n-3 PUFA [1]. The current diets are also associated with large cultural differences in health. For example, the traditional Greenland Inuit diet was based on whale, seal, fish, and wildfowl, which was demonstrated to result in lower risk for ischemic heart disease [1–3]. The Mediterranean diet is not only based on fish, but also fruits, vegetables, and whole grain and it has been shown that it leads to a lower risk of cardiovascular disease and contributes to a healthy brain [4–10]. The common factor between these diets is that they are low in saturated fats and refined grains.

Over the years, the importance of LCPUFA in neural development, aging, and neurodegeneration has been shown in both clinical and animal studies [11–18]. Supplementation with LCPUFA has shown to be beneficial in the development of both children and (young) rodents. Several animal studies and studies in children revealed an improvement in cognition and motor skills after LCPUFA supplementation [18–20]. On the other hand, LCPUFA deficiency can lead to neurodevelopmental disorders such as schizophrenia, ADHD, or mood disorders [21–25]. LCPUFA have also been shown to be advantageous in neurodegenerative disorders. For example, dietary LCPUFA supplementation showed an attenuation of cognitive impairment and decreased anxiety in both human and animal studies [26–28].

In this review, we will focus on the involvement of LCPUFA from genesis to senescence. We will cover the stages of neural development, normal aging, and neurodegeneration. In all these stages, the role of LCPUFA in the brain will be discussed with emphasis on synaptic plasticity, neurogenesis, cognition, and vascular health.

We searched the PubMed database for original articles published in English from 1995 until August 31, 2013. The main search topics concerned LCPUFA, influence of LCPUFA in neural development of preterm and full term infants, influence of LCPUFA in disorders such as autism, attention deficit hyperactivity disorder (ADHD), mild cognitive impairment (MCI), cerebrovascular disease, Alzheimer's disease (AD), and Parkinson's disease (PD). The search strategy was based on the following search terms: LCPUFA, neural development, cognition, autism, ADHD, healthy aging, MCI, cerebrovascular disease, AD, PD, filter: clinical trials. Moreover, to identify potentially relevant new papers we filtered our total list of relevant papers by hand. Based on the title and abstract, we selected the studies. If these two components were not sufficient for selection, we evaluated the total publication.

2. LCPUFA in neural development

During the embryonic phase in humans (until 7 weeks) the structure of the brain is defined, while growth during the fetal phase (start at 8 weeks) is characterized by functional development [29,30]. At birth, the brain is fully developed but only 25% of its definitive volume; postnatally, the brain expands by an increase in glial cells, outgrowth of axons and dendrites, and myelination of nerve fibers. This human brain growth spurt starts prenatally in the third trimester of pregnancy [31]. At this time, the infant brain starts accumulating docosahexaenoic acid (DHA, 22:6n-3) *in utero* and this continues up to the first 24 months of neonatal brain growth, although the postnatal DHA accumulation occurs at a slower rate [31,32]. In this period, neural development is most dependent on an adequate supply of LCPUFA.

LCPUFA are essential nutrients in the development and functioning of brain and visual system [12,17,33]. The most abundant LCPUFA in the brain are DHA which is mainly derived from fish, and arachidonic acid (ARA, 20:4n-6) from animal sources like meat and eggs. Linoleic acid (LA, 18:2n-6) is the precursor molecule of ARA which is derived from LA by desaturation and elongation of the carbon chain. DHA is derived from α-linolenic acid (ALA, 18:3n-3), forming eicosapentaenoic acid (EPA, 20:5n-3) in the process. The placental fatty acid composition is dependent on the supply from maternal plasma fatty acids. After birth, breast-fed infants are subsequently supplied with n-3 and n-6 fatty acids from breast milk, which support the rapid growth and development of the infant brain [17,34–36]. The most important LCPUFA responsible for the growth of the brain are DHA and ARA. Aside from inflammation and cardiovascular health, LCPUFA are important building blocks of neuronal membranes. The lipid bilayer of neuronal membranes consists of phospholipids, with DHA, ARA, and EPA as their main components. Three compounds are important for the membrane formation as shown in the Kennedy cycle (Fig. 1): a uridine source, a fatty acids source, and a choline source [37,38]. Other phospholipids are also synthesized via the Kennedy cycle and incorporate LCPUFA, such as phosphatidylethanolamine (PE) that uses ethanolamine instead of choline [39]. Phosphatidylserine (PS) exchanges a serine molecule for choline in phosphatidylcholine (PC) or ethanolamine in PE [39].

Humans, like all mammals, can synthesize saturated and monounsaturated fatty acids, but they are not able to synthesize the n-3 fatty acid ALA and the n-6 fatty acid LA due to lack of the conversion enzyme n-3-desaturase, making ALA and LA essential fatty acids [40]. Humans are able to convert EPA to DHA, and ARA to all-cis-4,7,10,13,16-docosapentaenoic acid (osbond acid), but the conversion rate by the responsible delta-5- and delta-6-desaturase is very slow [41,42]. These n-3 and n-6 PUFA are obtained by dietary intake or endogenous conversion of the parent precursors. LA and ALA require the same conversion enzymes, which means that there is competitive inhibition between these 2 substrates. Especially delta-6-desaturase favors the conversion of n-3 fatty acids to that of n-6 fatty acids [40,43]. Despite the preference for conversion of n-3 PUFA, a high LA intake may shift the balance towards conversion of n-6 PUFA and can interfere with the desaturation and elongation of ALA [44]. This imbalance can also lead to inhibition of the conversion of ALA to DHA, by slowing down the conversion rate of ALA into EPA and of EPA into DHA by delta-6-desaturase. The fatty acid desaturase (FADS) 1 and FADS2 genes are responsible for the expression of the conversion enzymes delta 5 desaturase and delta 6 desaturase making them a rate limiting factor in the LCPUFA conversion [41,42,45]. Thus, polymorphisms