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Omega-3 fatty acids in neurodegenerative diseases: Focus on mitochondria

Gunter P. Eckert*, Uta Lipka, Walter E. Muller

Department of Pharmacology, Biocenter, Campus Riedberg, Goethe-University, Frankfurt, Biocentre Geb. N260, R.1.09, Max-von-Laue Str. 9, D-60438 Frankfurt, Germany

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ABSTRACT

Mitochondrial dysfunction represents a common early pathological event in brain aging and in neurodegenerative diseases, e.g., in Alzheimer's (AD), Parkinson's (PD), and Huntington's disease (HD), as well as in ischemic stroke. *In vivo* and *ex vivo* experiments using animal models of aging and AD, PD, and HD mainly showed improvement of mitochondrial function after treatment with polyunsaturated fatty acids (PUFA) such as docosahexaenoic acid (DHA). Thereby, PUFA are particular beneficial in animals treated with mitochondria targeting toxins. However, DHA showed adverse effects in a transgenic PD mouse model and it is not clear if a diet high or low in PUFA might provide neuroprotective effects in PD. Post-treatment with PUFA revealed conflicting results in ischemic animal models, but intravenous administered DHA provided neuroprotective efficacy after acute occlusion of the middle cerebral artery. In summary, the majority of preclinical data indicate beneficial effects of n-3 PUFA in neurodegenerative diseases, whereas most controlled clinical trials did not meet the expectations. Because of the high half-life of DHA in the human brain clinical studies may have to be initiated much earlier and have to last much longer to be more efficacious.

1. Introduction

After adipose tissue, the brain is the organ richest in lipids [1]. Thirty-five percent of brain lipids are long-chain polyunsaturated fatty acids (lc-PUFA). Lc-PUFA cannot be synthesized de novo, but can be formed from its precursors linoleic acid (LA) and α-linolenic acid (ALA) that belong to the omega-6 (n-6) and omega-3 (n-3) family, respectively. N-6 and n-3 PUFA are not inter-convertible, although they compete for the same enzyme system [2]. As components of phospholipids arachidonic acid (n-6; AA) and docosahexaenoic acid (n-3; DHA) are the most abundant lc-PUFA in the brain [2].

Although, *in vitro* experiments indicated that cerebral endothelium cells and astrocytes but not neurons avidly elongate and desaturate precursors of lc-PUFA, the extent of lc-PUFA biosynthesis in the brain is very low [3]. Thus, the majority of lc-PUFA originates from synthesis by the liver [4–6]. Accordingly, it was reported that dietary n-3 PUFA deprivation for 15 weeks up-regulates elongase and desaturase gene expression and subsequently enhances the conversion of ALA to DHA in the liver of rats, but not in the brain [7,8]. Administration of ALA increased the abundance of DHA in brain homogenates isolated from guinea pigs, rats, and mice [6,9–14]. Significantly higher DHA and oleic acid levels were detected in brains of mice that have been exposed to diets enriched in monounsaturated fatty acids

Abbreviations: 6-OHDA, 6-hydroxydopamine; AA, Arachidonic; AD, Alzheimer's disease; ALA, α-linolenic acid; ApoE4, Apolipoprotein E4 allele; APP, Amyloid precursor protein; ATP, Adenosine triphosphate; Aβ, Beta-amyloid peptide; CAG, Cytosine–adenine–guanine; DHA, Docosahexaenoic acid; DHA-OOH, DHA hydroperoxides; EPA, Eicosapentaenoic acid; FABP, Fatty acid-binding proteins; HD, Huntington's disease; HNF-4α, Hepatocyte nuclear factor 4; IL-6, Interleukin-6; LA, Linoleic acid; lc-PUFA, Long-chain PUFA; LD, Levodopa; LPS, Lipopolysaccharide; LXR, Liver X receptor; MMP, Mitochondrial membrane potential; MUFA, Monounsaturated fatty acids; n-3, omega-3; n6, omega-6; NPD1, Neuroprotectin D1; OXPHOS, Mitochondrial oxidative phosphorylation system; PD, Parkinson's disease; PFSO, Perilla frutescens seed oil; PPAR, Peroxisome proliferator activating receptor; ROS, Reactive oxygen species; RXR, Retinoid receptor; SNPC, Substantia nigra pars compacta; UCPs, Uncoupling proteins

* Corresponding author. Tel.: +49 69 798 29378; fax: +49 69 798 763 29378.
E-mail address: g.p.eckert@em.uni-frankfurt.de (G.P. Eckert).
URL: http://www.eckert-science.com (G.P. Eckert).

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(MUFA). Electrophysiolgogical recordings of brain slices isolated from those mice demonstrated that these changes are of functional significance: Shorter duration of action potentials, reduction in the duration of post-synaptic responses, and increased firing activity were recorded in neurons of the enthorinal cortex that play a critical role in learning and memory [15]. Although it is not clear if these experiments are transferable to the human situation, data show that the endogenous production of eicosapentaenoic acid (EPA) and DHA results in stable plasma concentrations of these fatty acids when animal foods are wholly excluded from human diet [16]. However, the mean intake of lc-PUFA mainly depends on fish consumption, which is often under the recommended daily intake [17].

Lc-PUFA are required for the normal development of the central nervous system, but especially DHA seems to be involved in neuropsychiatric disorders, such as depression or dementia [18]. Lc-PUFA deficiency can impair cerebral functions and alter the course of brain development, perturbs the composition of brain cell membranes of neurons, oligodendrocytes and astrocytes, as well as of myelin, synaptosomes and mitochondria [19].

Lc-PUFA and its oxidized metabolites, such as neuroprotectin D1 (NPD1) or synaptamides, are essential for physiological functions of the brain [20,21]. In the brain DHA mediates membrane-protein interactions [22], gene expression [23], neurogenesis [24–27] and learning [28–30]. Lc-PUFA supplementation also reverses stress-induced modifications on brain monoamine levels in mice [31] and protects against MK-801 induced neurotoxicity in the prefrontal cortex of rats [32]. DHA and the DHA derived metabolites promote cell survival via the induction of anti-apoptotic and neuroprotective gene expression [33,34]. Lc-PUFA promote mitochondrial biogenesis [35,36] and modulate expression of genes in the brain, associated with energy metabolism and adenosine triphosphate (ATP) production [24].

1.1. Mitochondria and lc-PUFA

Tissues with high rates of oxidative metabolism are rich in DHA, which may be explained by a critical role related to oxidative metabolism [37,38]. DHA from dietary sources is rapidly incorporated into mitochondrial membranes isolated from brains of mice [39]. High DHA levels in mitochondrial phospholipids of eukaryotic cells suggest that DHA-phospholipids are essential for the mitochondrial oxidative phosphorylation system (OXPHOS) [38]. The OXPHOS represents the final biochemical pathway involved in the production of energy in form of ATP. It is embedded in the lipid bilayer of the mitochondrial inner membrane and is composed of five multi-protein enzyme complexes (I–V) and two electron carriers. Electrons from carbon oxidations are transferred via NADH into the OXPHOS. The passage of electrons releases energy, which is largely stored in the form of a proton gradient across the inner mitochondrial membrane. This electrochemical proton gradient builds up the mitochondrial membrane potential (MMP) and is the driving force for complex V, to generate ATP [40]. The mitochondrial respiratory chain is highly dependent on oxygen and constantly generates low physiological levels of reactive oxygen species (ROS), which exaggerates in consequence of mitochondrial dysfunction [41].

Approximately 90% of cellular ROS can be traced back to mitochondria and are mainly originated from unpaired electrons as by-products of the oxidative phosphorylation. Detoxification of highly reactive superoxide anions by superoxide dismutase (SOD) – a mitochondrial matrix protein – results in hydrogen peroxide production, which in turn is reduced to water, catalyzed either by glutathione peroxidase or catalase [42]. Increased activity of the isoform SOD2 was detected in brains of rats feed with a EPA+DHA diet (500 mg/100 g diet) during post-natal development as response to ROS production within mitochondria [43]. Recent data demonstrated that SOD2 induced oxidative stress in an AD mouse model [44].

Proteins of the OXPHOS and PUFA in mitochondrial membranes are key targets of ROSs deleterious effects leading to membrane depolarization and subsequently impaired mitochondrial function [41,45]. In mitochondria obtained from rat brains, DHA was the most sensitive fatty acid for peroxidation [46]. Inhibition of the OXPHOS system not only increases ROS production but also inhibits the beta-oxidation and produces a secondary carnitine deficiency that impairs the mitochondrial pathway for synthesis of DHA-containing phospholipids [47].

Oxidative damage, either of OXPHOS proteins or of lc-PUFA in mitochondrial membranes results in loss of the MMP representing one early hallmark of apoptosis [48]. In consequence, the mitochondrial pathway of apoptosis is initiated by the assembly of the mitochondrial permeability transition pore (mPTP), which releases cytochrome *c* and apoptosis inducing factor (AIF) into the cytosol leading to activation of caspases and further down-stream cell death mechanisms [49]. Mitochondrial proteins of the Bcl-2 family are important regulators of the intrinsic apoptotic pathway. Anti-apoptotic Bcl-2 protein is mainly localized in the outer mitochondrial membrane and upon release it stabilizes the inner mitochondrial membrane against several injuries [50]. Blocking this protective effect of Bcl-2 with HA 14-1, a ligand of the Bcl-2 surface pocket, prevented Bcl-2 interaction with pro-apoptotic Bax and reduced the protective function of Bcl-2 [51]. Inhibition of Bcl-2 reduced the MMP, increased the respiration capacity, enhanced the generation of ROS, increased the release of cytochrome *c*, activates caspase-9 and -3, and decreased the synthesis of ATP [52–54].

Decreased Bcl-2 expression and increased expression of Bax have been associated with activation of c-Jun N-terminal kinase (JNK). Phosphorylation of Bcl-2 by JNK antagonizes its anti-apoptotic effect. Thus, JNK has multiple effects on mitochondrial function [55,56]. EPA showed neuroprotective actions on irradiation evoked apoptosis and lipopolysaccharide-induced dysfunction in rat hippocampus [57–59]. Daily oral reatment of rats with EPA (500 mg per rat) inhibited the irradiation induced increase in ROS production, JNK activation, cytochrome *c* release and caspase-3 activation [58]. Similar effects of EPA were observed after rats were challenged with lipopolysaccharides (LPS) [59]. Thus, the neuroprotective effect of EPA on mitochondrial function might be provoked by the inhibition of JNK activation via peroxisome proliferator activating receptor (PPAR)-α, which suppresses the JNK-c-Jun-pathway [60].

Nuclear receptors such as PPAR-α, HNF-4α, and LXRα mediate the nuclear effects of lc-PUFA [61,62]. Dietary DHA induces gene expression changes in encoding for transcription factors and regulators, fatty acid binding proteins and inflammatory proteins in brains of mice [63]. EPA increases mRNA expression of PPAR-α & -γ [64,65] and act as agonist on both nuclear receptors [66,67]. DHA represents a ligand of the retinoid X receptor (RXR) [68].

2. Mitochondrial dysfunction in brain—Impact of lc-PUFA

Increasing evidence suggests that mitochondrial dysfunction plays an important role in brain aging and the pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and ischemic stroke. Alterations of mitochondrial efficiency and function are mostly related to alterations in concentration and efficiency of the constituents of the respiratory complexes. The resulting mitochondrial dysfunction, especially in from of severe changes in MMP, is believed to be crucial for the onset and progression of neurodegenerative diseases.