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Deuterated polyunsaturated fatty acids reduce brain lipid peroxidation and hippocampal amyloid β-peptide levels, without discernable behavioral effects in an APP/PS1 mutant transgenic mouse model of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) involves progressive deposition of amyloid β-peptide (Aβ), synapse loss, and neuronal death, which occur in brain regions critical for learning and memory. Considerable evidence suggests that lipid peroxidation contributes to synaptic dysfunction and neuronal degeneration, both upstream and downstream of Aβ pathology. Recent findings suggest that lipid peroxidation can be inhibited by replacement of polyunsaturated fatty acids (PUFA) with isotope-reinforced (deuterated) PUFA (D-PUFA), and that D-PUFA can protect neurons in experimental models of Parkinson's disease. Here, we determined whether dietary D-PUFA would ameliorate Aβ pathology and/or cognitive deficits in a mouse model of AD (amyloid precursor protein/presenilin 1 double mutant transgenic mice). The D-PUFA diet did not ameliorate spatial learning and memory deficits in the AD mice. Compared to mice fed an hydrogenated-PUFA control diet, those fed D-PUFA for 5 months exhibited high levels of incorporation of deuterium into arachidonic acid and docosahexaenoic acid, and reduced concentrations of lipid peroxidation products (F2 isoprostanes and neuroprostanes), in the brain tissues. Concentrations of Aβ40 and Aβ38 in the hippocampus were significantly lower, with a trend to reduced concentrations of Aβ42, in mice fed D-PUFA compared to those fed hydrogenated-PUFA. We conclude that a D-PUFA diet reduces the brain tissue concentrations of both arachidonic acid and docosahexaenoic acid oxidation products, as well as the concentration of Aβs.

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1. Introduction

Alzheimer's disease (AD), the most common neurodegenerative disorder of aging, is characterized by progressive cognitive impairment resulting from degeneration of synapses and neurons that is most pronounced in the hippocampus, entorhinal cortex and functionally connected regions of the parietal, temporal, and frontal lobes (Leal and Yassa, 2013). The neurodegenerative process is associated with extracellular accumulation of aggregated forms of amyloid β-peptide (Aβ) and intraneuronal accumulation of hyperphosphorylated forms of the microtubule-associated protein Tau (Raskin et al., 2015). Aβ is generated by cleavages of the β-amyloid precursor protein (APP) by β- and γ-secretases. Mutations in APP and in presenilin 1 (PS1; the catalytic subunit of the γ-secretase enzyme complex) are responsible for rare cases of early-onset dominantly inherited AD. These mutations result in increased production of an aggregation-prone neurotoxic 42 amino acid form of Aβ, strongly suggesting that Aβ pathology is a pivotal event in the disease process (Bertram et al., 2010). The factors that result in Aβ accumulation and neuronal degeneration in the more common late-onset cases of AD are unclear but are presumably related to mechanisms of aging because aging is the major risk factor for AD. Studies of experimental cell culture and animal models of AD have

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shown that aggregating forms of Aβ can cause synaptic dysfunction and neuronal degeneration (Mattson, 2004). Evidence suggests that the cellular and molecular mechanisms by which Aβ damages neurons involves oxidative stress and disruption of cellular Ca^{2+} homeostasis, which results in neuronal network hyperexcitability and excitotoxicity (Bezprozvanny and Mattson, 2008; Mattson et al., 1992).

The brain is susceptible to oxidative stress due to the high metabolic rate of neurons and consequent elevated production of reactive oxygen species (ROS) (Camandola and Mattson, 2017). In addition, the brain contains high levels of polyunsaturated fatty acids (PUFA), arachidonic acid (ARA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), which are enzymatically produced from the diet-derived fatty acids linoleic acid (18:2, n-6) and linolenic acid (18:3, n-3), which are prone to attack by ROS, resulting in the nonenzymatic autocatalytic chain reaction of lipid peroxidation (LPO) (Porter et al., 1995). This insidious process requires just one initiating event to get the reaction chain started (Fig. 1), leading to extensive oxidative damage of membrane PUFAs, and the generation of multiple classes of LPO products including F2, F3, and F4 isoprostanes, which are generated from ARA, EPA, and DHA, respectively (Milne et al., 2007, 2011; Montine et al., 2004). A particularly sinister group of PUFA decomposition products are the highly reactive cytotoxic carbonyls 4-hydroxynonenal (HNE) and 4-hydroxyhexenal (HHE), which are highly toxic compounds that irreversibly cross-link various proteins (Negre-Salvayre et al., 2008). During aging, brain cells accumulate oxidatively damaged proteins, lipid membrane components, and DNA, and these oxidative modifications are greatly amplified in vulnerable brain regions of AD patients (Butterfield and Boyd-Kimball, 2004; Markesbery and Lovell, 2007; Mattson, 2009; Sultana et al., 2006). Membrane-associated oxidative stress/LPO plays a pivotal role in the synaptic dysfunction and neuronal degeneration of AD, both upstream and downstream of Aβ (Gwon et al., 2012; Hensley et al., 1994; Mark et al., 1997a,b; Mattson, 2004; McManus et al., 2011). Considerable evidence implicates LPO in AD pathogenesis including: the accumulation of isoprostanes, neuroprostanes, and proteins covalently modified by HNE in afflicted brain regions and cerebrospinal fluid of AD patients (Bradley et al., 2010; Lovell et al., 1997; Montine et al., 2004; Williams et al., 2006); LPO and HNE accumulation occurs in neurons exposed to neurotoxic Aβ species (Mark et al., 1997a,b); and HNE impairs neuronal Ca^{2+} homeostasis and energy metabolism, rendering neurons vulnerable to excitotoxicity and apoptosis (Bruce-Keller et al., 1998; Keller et al., 1997a,b; Kruman et al., 1997; Mark et al., 1997a). In addition, data suggest that lifestyle factors that increase AD risk (overweight and a

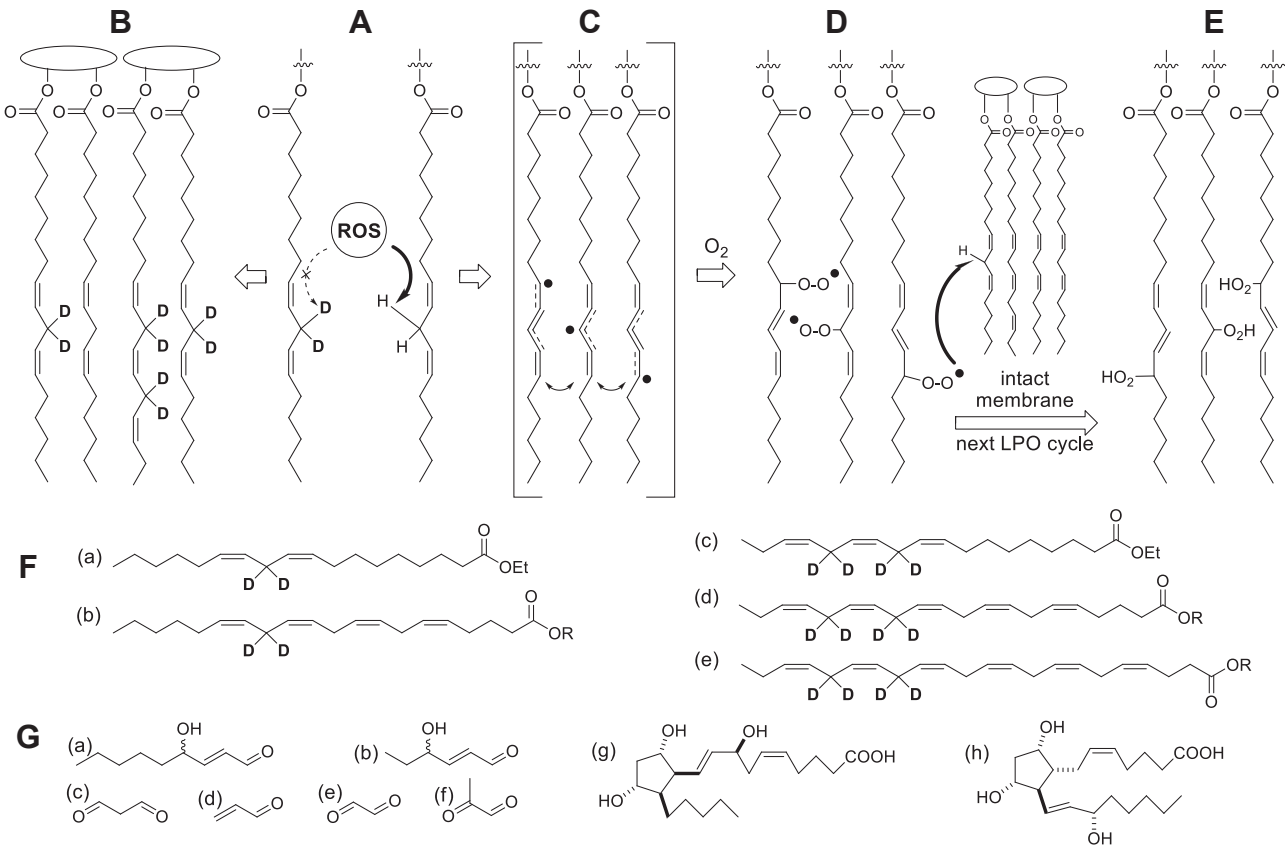

Fig. 1. Protective effect of D-PUFAs on lipid peroxidation (LPO). (A) D-PUFAs inhibit the rate-limiting step of reactive oxygen species (ROS)-driven abstraction off a bis-allylic site. (B–E) Lipid bilayer made mostly of D-PUFAs is impervious to LPO. ROS-driven hydrogen abstraction off a bis-allylic site (A) generates resonance-stabilized free radicals (C), which quickly react with abundant molecular oxygen to form lipid peroxyl radicals (D). These newly formed ROS species (L-OO·) abstract hydrogen off a neighboring PUFA molecule (turning themselves into lipid peroxides [LOOH]) (E), thus sustaining the chain reaction of LPO. The chain is eventually terminated by a chain-terminating antioxidant or homologous recombination (not shown). (F) 11,11-D_2-Lin, (a) an omega-6 D-linoleic acid used in this study, is enzymatically converted into 13,13- D2-arachidonic acid (b). 11,11,14,14-D4-Lnn (c), an omega-3 D-linolenic acid used in this study, is enzymatically converted into 13,13,16,16-D4-EPA (d) and 15,15,18,18-D4-DHA (e). (G) lipid peroxides (E), which have greater volume compared to nonoxidized lipids, further decompose through multiple pathways, into numerous species such as reactive carbonyls, for instance 4-HNE (a), 4-HHE (b), malonic dialdehyde (c), acrylic aldehyde (d), oxalic aldehyde (e), methylglyoxal (f), etc. Other classes of products include arachidonic acid-derived isoprostanes (g; $iPF_{2\alpha}$-IV or 8-F_2-IsoP is one of 64 different isomers) as well as $PGF_{2\alpha}$ (h), a prostaglandin that can be produced both enzymatically and nonenzymatically. Abbreviations: D-PUFA, deuterated polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; HNE, hydroxynonenal; HHE, hydroxyhexenal.