Isotope-Reinforced Polyunsaturated Lipids (D-PUFA) Mitigate Symptoms in Diverse Alzheimer’s Mouse Models


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Abstract

PUFAs linoleic (Lin; ω6), α-linolenic (Lnn,ω3) acids, ARA, EPA, DHA are essential nutrients (have to be supplied with diet), vital for neuronal, mitochondrial and other membranes. Autoxidation of PUFAs (lipid peroxidation (LPO)) is detrimental to cells and is linked to retinal and neurodegenerative diseases like PD and Alzheimer’s (AD). Antioxidants cannot stop the LPO, mainly because only low ratios of antioxidants can be present in lipid membranes (e.g. PUFAs/vit E=2000/1) [1]. LPO of PUFAs is initiated by abstraction of bis-allylic H atoms. Replacing those with deuteriums (D-PUFA) dramatically protects PUFAs from autoxidation, inhibiting the LPO [2,3].

We assessed the effects of D-PUFA drugs in two animal models of AD. APP/PS1 mice express mutant human APP and PS1 and exhibit robust Aβ plaque deposition, whereas aldehyde dehydrogenase 2 (ALDH2) KO mice are an oxidative stress-induced model of sporadic AD (via reactive carbonyls), exhibiting significant cognitive impairment. The two strains model different aspects of AD. We report that dosing animals with D-PUFA drugs strongly mitigates or even reverses various aspects of AD pathology in two AD models.

Chain Reaction of Lipid Peroxidation (LPO)

LPO generates multiple types of damage, from deteriorating membrane properties to various toxic and/or signaling compounds [1]. D-PUFAs [2], even at low concentrations [3], inhibit the LPO (Fig. 1). D-PUFAs inhibit LPO. A, D-PUFAs inhibit the rate-limiting step of ROS-driven abstraction off a bis-allylic site. B, ROS-driven H abstraction off a bis-allylic site generates stabilized free radicals (C), which quickly react with abundant O2 (D) forming lipid peroxyl (LOOH) which abstract H off the next PUFAs (turning themselves into lipid peroxides LOOH (E)), sustaining the chain (B). LOOH (E), which have greater volume compared to PUFAs, decompose through multiple pathways, into numerous species: isoprostanes, reactive carbonyls such as 4-HNE (a), 4-HNE (b), malonic dialdehyde (c), acrylaldehyde (d), oxalic aldehyde (e), methylglyoxal (f). The chain is eventually terminated by an antioxidant or homologous recombination. (G) and (H), D2-Lin and D2-Lnn esters used in this study

D-PUFA Containing Diet, Deuterium Incorporation

Diets were based on 12% fat AIN93M. The fat fraction included saturated monounsaturated fats and 10% PUFAs (1:1 ratio) of either H-Lin and H-Lnn (control), or D2-Lin and D2-Lnn (drug). Mice had ad libitum access to food and water. All mice were housed with a 12h light/dark cycle. Deuterium incorporation was monitored by nMRS, reaching D-PUFA incorporation levels necessary to inhibit the LPO [3].

APP/PS1 2TG Mice

55 male APP/PS1 or C57Bl6 mice were fed D-PUFA or H-PUFA diets for 5 months starting at 4-7 MO. No difference was observed between D- and H-cohorts in the behavioural tests. While in cortex various Aβ species were at the same level for D- and H-diets, there was a substantial decrease in hippocampus in the D-group (Fig. 2).

Conclusions

Animal models do not fully recapitulate human neurological conditions, only some features at best. Two AD mouse models were used to test the hypothesis that LPO-inhibiting D-PUFA drugs can alleviate/reverse various aspects of AD.

In APP/PS1 mice, while no behavioral/memory improvement was detected in D-PUFA cohort, a favorable decrease in Ap38, 40, 42 levels, and a smaller decline in the Ap42/Ap40 ratio were observed, as well as decreased LPO markers.

In ALDH2−/− mice, all memory related metrics were strongly improved, in addition to decreased LPO markers. It is hence likely that D-PUFA drugs’ striking amelioration of cognitive and biochemical deficits is the result of suppression of LPO and reactive carbonyl accumulation. D-PUFAs, currently in human trials for Friedreich ataxia, thus may be a promising new approach to treating Alzheimer’s disease.

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4) Radde R. et al. (2006) EMBO Rep. 9, 940-946