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Neurobiology of Disease

Omega-3 Fatty Acid Docosahexaenoic Acid Increases SorLA/LR11, a Sorting Protein with Reduced Expression in Sporadic Alzheimer's Disease (AD): Relevance to AD Prevention

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Environmental and genetic factors, notably ApoE4, contribute to the etiology of late-onset Alzheimer's disease (LOAD). Reduced mRNA and protein for an apolipoprotein E (ApoE) receptor family member, SorLA (LR11) has been found in LOAD but not early-onset AD, suggesting that LR11 loss is not secondary to pathology. LR11 is a neuronal sorting protein that reduces amyloid precursor protein (APP) trafficking to secretases that generate β -amyloid (A β). Genetic polymorphisms that reduce LR11 expression are associated with increased AD risk.

However these polymorphisms account for only a fraction of cases with LR11 deficits, suggesting involvement of environmental factors. Because lipoprotein receptors are typically lipid-regulated, we postulated that LR11 is regulated by docosahexaenoic acid (DHA), an essential ω -3 fatty acid

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related to reduced AD risk and reduced A β accumulation. In this study, we report that DHA significantly increases LR11 in multiple systems, including primary rat neurons, aged non-Tg mice and an aged DHA-depleted APPsw AD mouse model. DHA also increased LR11 in a human neuronal line. *In vivo* elevation of LR11 was also observed with dietary fish oil in young rats with insulin resistance, a model for type II diabetes, another AD risk factor. These data argue that DHA induction of LR11 does not require DHA-depleting diets and is not age dependent. Because reduced LR11 is known to increase A β production and may be a significant genetic cause of LOAD, our results indicate that DHA increases in SorLA/LR11 levels may play an important role in preventing LOAD.

Key words: SorLA; LR11; Alzheimer; docosahexaenoic acid; diet; omega-3 fatty acid; amyloid

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