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Full-length Article

Fish oil feeding attenuates neuroinflammatory gene expression without concomitant changes in brain eicosanoids and docosanoids in a mouse model of Alzheimer's disease

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ABSTRACT

Background: Neuroinflammation is a recognized hallmark of Alzheimer's disease, along with accumulation of amyloid-β plaques, neurofibrillary tangles and synaptic loss. n-3 polyunsaturated fatty acids (PUFA) and molecules derived from them, including eicosapentaenoic acid-derived eicosanoids and docosahexaenoic acid-derived docosanoids, are known to have both anti-inflammatory and pro-resolving properties, while human observational data links consumption of these fatty acids to a decreased risk of Alzheimer's disease. Few studies have examined the neuroinflammation-modulating effects of n-3 PUFA feeding in an Alzheimer's disease-related model, and none have investigated whether these effects are mediated by changes in brain eicosanoids and docosanoids. Here, we use both a fat-1 transgenic mouse and a fish oil feeding model to study the impact of increasing tissue n-3 PUFA on neuroinflammation and the production of pro-inflammatory and pro-resolving lipid mediators.

Methods: Fat-1 mice, transgenic animals that can convert n-6 to n-3 PUFA, and their wildtype littermates were fed diets containing either fish oil (high n-3 PUFA) or safflower oil (negligible n-3 PUFA) from weaning to 12 weeks. Animals then underwent intracerebroventricular infusion of either amyloid-β 1-40 or a control peptide. Hippocampi were collected from non-surgery and surgery animals 10 days after infusion. Microarray was used to measure enrichment of inflammation-associated gene categories and expression of genes involved in the synthesis of lipid mediators. Results were validated by real-time PCR in a separate cohort of animals. Lipid mediators were measured via liquid chromatography tandem mass spectrometry.

Results: Fat-1 and wildtype mice fed fish oil had higher total hippocampal DHA than wildtype mice fed the safflower oil diet. The safflower-fed mice, but not the fat-1 or fish oil-fed mice, had significantly increased expression in gene ontology categories associated with inflammation in response to amyloid-β infusion. These effects were independent of changes in the expression of genes involved in the synthesis of eicosanoids or docosanoids in any group. Gene expression was replicated upon validation in the wildtype safflower and fish oil-fed, but not the fat-1 mice. Protectin, maresin and D and E series resolvins were not detected in any sample. There were no major differences in levels of other eicosanoids or docosanoids between any of the groups in response to amyloid-β infusion.

Conclusions: Fish oil feeding decreases neuroinflammatory gene expression in response to amyloid-β. Neither amyloid-β infusion or increasing brain DHA affects the brain concentrations of specialized pro-resolving mediators in this model, or the concentrations of most other eicosanoids and docosanoids.

Abbreviations: AD, Alzheimer's disease; ARA, arachidonic acid; CD, cluster of differentiation; $iPLA_2$, calcium independent phospholipase A_2; $cPLA_2$, cytosolic phospholipase A_2; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDHA, hydroxy DHA; HETE, hydroxyeicosatetraenoic acid; icv, intracerebroventricular; IL, interleukin; LO, lipoxygenase; LC/MS/MS, liquid chromatography tandem mass spectrometry; Fcgr2b, low affinity immunoglobulin gamma Fc region; MHC, major histocompatibility complex; PD1, protection D1; PUFA, polyunsaturated fatty acids; PG, prostaglandin; TREM, triggering receptor expressed on myeloid cell; TSPO, translocator protein; TLR, toll-like receptor; WTFO, wildtype mice fed fish oil; WTSO, wildtype mice fed safflower oil.

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1. Introduction

Neuroinflammation is recognized as a hallmark of Alzheimer's disease (AD). Neuroinflammatory markers, such as glial cells, cytokines or complement, are elevated in animal models of AD (Ma et al., 2011; Souza et al., 2013; Hopperton et al., 2016) and in human subjects (Vanzani et al., 2005; Flanders et al., 1995; Griffin et al., 1989; Lue et al., 1996) post-mortem. Elevations in microglia have also been reported in patients with AD *in vivo* (for review see (Knezevic and Mizrahi, 2017). The neuroinflammatory hypothesis of AD suggests that aberrant activation of immune cells in the brain contributes to neuronal loss and dysfunction (Griffin, 2006). This is supported by studies showing that patients with AD have greater concentrations of microglia and astrocytes in the brain than cognitively intact controls with similar levels of AD pathology (Perez-Nievas et al., 2013). In addition, in animal models of AD, neuroinflammation appears to precede plaque deposition (Wright et al., 2013), and treatments that decrease inflammation seem to decrease AD pathology (Vom Berg et al., 2012; Craft et al., 2004; Tweedie et al., 2012). Polymorphisms in a variety of inflammation-associated genes have been implicated as risk factors for AD, which also supports this hypothesis, including cluster of differentiation (CD) 33 (Bradshaw et al., 2013), triggering receptor expressed on myeloid cell (TREM) 2 (Guerreiro et al., 2013), interleukin (IL)-6 (Chen et al., 2012), IL-1 (Nicoll et al., 2000) and toll-like receptor (TLR) 4 (Chen et al., 2012).

Animal studies report lower neuroinflammation with interventions aimed at increasing brain docosahexaenoic or eicosapentaenoic acids (DHA and EPA), such as diets containing fish oil or purified n-3 polyunsaturated fatty acids (PUFA) (for review, see (Trepanier et al., 2016). DHA and EPA are precursors to a family of molecules including resolvins, protectin and maresins, collectively referred to as specialized pro-resolving lipid mediators (Fig. 1A and B, for review, see (Serhan, 2014)). These molecules decrease the magnitude and duration of inflammation in various models in the periphery, and in the brain in models of stroke (Bazan et al., 2012); Parkinson's disease (Tian et al., 2015), surgery-induced cognitive decline (Terrando et al., 2013) and traumatic brain injury (Harrison et al., 2015). Levels of brain protectin D1 (PD1) decrease with disease progression in the 3×Tg mouse

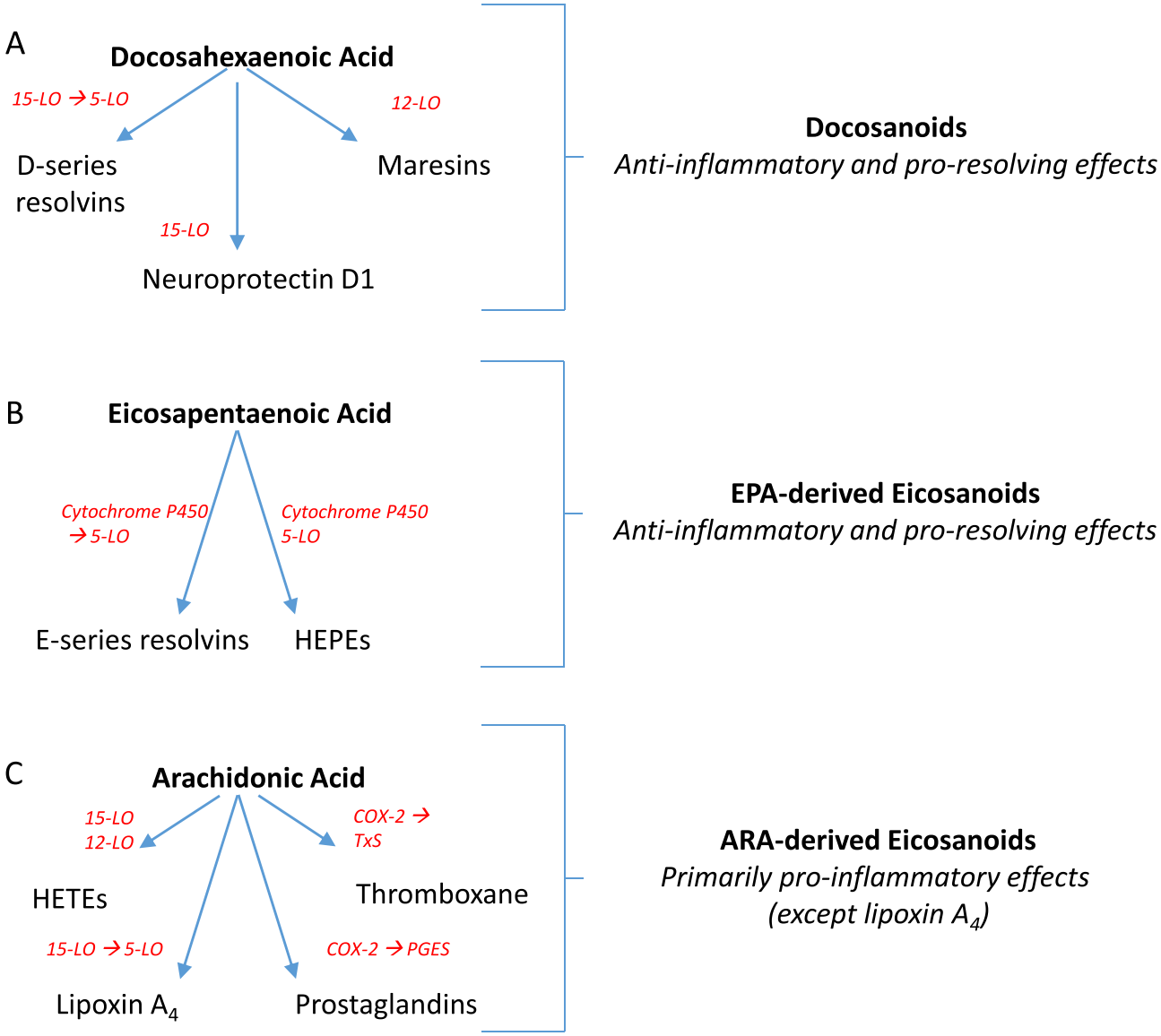

Fig. 1. Bioactive lipid mediators derived from DHA, EPA and ARA. A) Docosahexaenoic acid-derived docosanoids, B) Eicosapentaenoic acid-derived eicosanoids, C) Arachidonic acid-derived eicosanoids. Major synthetic enzymes are provided in italics. Cyclooxygenase-2 (COX-2), Hydroxyeicosatetraenoic acids (HETE), Lipoxygenase (LO), Prostaglandin E synthase (PGES), Thromboxane synthase (TxS).