Omega-3 Polyunsaturated Fatty Acids and Oxylipins in Neuroinflammation and Management of Alzheimer Disease[1,2]

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ABSTRACT

Alzheimer disease (AD) is becoming one of the most prevalent neurodegenerative conditions worldwide. Although the disease progression is becoming better understood, current medical interventions can only ameliorate some of the symptoms but cannot slow disease progression. Neuroinflammation plays an important role in the advancement of this disorder, and n–3 (ω-3) polyunsaturated fatty acids (PUFAs) are involved in both the reduction in and resolution of inflammation. These effects may be mediated by the anti-inflammatory and proresolving effects of bioactive lipid mediators (oxylipins) derived from n–3 PUFAs [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] in fish oil. Although interventions have generally used fish oil containing both EPA and DHA, several studies that used either EPA or DHA alone or specific oxylipins derived from these fatty acids indicate that they have distinct effects. Both DHA and EPA can reduce neuroinflammation and cognitive decline, but EPA positively influences mood disorders, whereas DHA maintains normal brain structure. Fewer studies with a plant-derived n–3 PUFA, α-linolenic acid, suggest that other n–3 PUFAs and their oxylipins also may positively affect AD. Further research identifying the unique anti-inflammatory and proresolving properties of oxylipins from individual n–3 PUFAs will enable the discovery of novel disease-management strategies in AD. *Adv Nutr* 2016;7:905–16.

Keywords: Alzheimer disease, neuroinflammation, polyunsaturated fatty acids, oxylipins, resolution of inflammation, omega-3 fatty acids, class switching

Introduction

Alzheimer disease (AD)[3] is the most common neurodegenerative disorder and constitutes ~60–80% of all dementia (1–3). Age is the most common predictor, with 1 in 5 people aged >80 y and 1 in 3 people >90 y having AD (4, 5). With the life expectancy of the global population increasing, the prevalence of AD is set to escalate. From 1980 to 2010, when the life expectancy increased by ~6 y for the US population, the age-adjusted death rates for AD increased 55-fold (6). Globally, 35.6 million people are living with dementia and this number is expected to reach 115.4 million by 2050 (7). An effective cure for the disease has yet to be discovered, and so lifestyle and nutritional factors are crucial in managing the disease. This review article aims to examine the role of n–3 PUFAs and PUFA-derived oxylipins in reducing neuroinflammation associated with AD.

Pathology of AD

AD is a disorder that has both familial and sporadic forms. Familial AD (FAD) has an onset <65 y of age and is found in <1% of the total cases (2). It is caused by autosomal dominant mutations in the amyloid precursor protein (*APP*) gene, the presenilin 1 (*PS1*) gene, and the presenilin 2 (*PS2*) gene (8). In the sporadic form of AD, the apolipoprotein E (*ApoE*) ε4 allele has the strongest association with the risk of developing AD (9). Homozygotes of the *ApoE* ε4 allele have 15 times more risk of developing AD than a noncarrier

of this allele (10), and each copy of the allele lowers the age at onset by 10 y (9).

Despite the large amount of research in AD over the past 3 decades, the exact disease-related alterations in the AD brain and the order in which they occur remain to be understood (2). Like many other chronic diseases, AD develops due to multiple factors rather than a single cause, including several changes in the brain that begin up to 20 y before any symptoms appear (2). Current understanding of the pathology indicates that AD is characterized by progressive loss of synapses and neurons (8). As AD progresses, the capacity of synapses to transfer information starts to diminish, the number of synapses decreases, and subsequently death of the neurons occurs (2). Progressive dysfunction of the synapses and neurons is usually preceded by molecular events involving the accumulation of oligomeric assemblies of misfolded proteins. Among these molecular lesions identified in AD, amyloid plaques and neurofibrillary tangles (NFTs) are the most defining ones (11, 12). Amyloid plaques are formed in the extraneuronal space from aggregates of toxic amyloid β (Aβ), and NFTs are formed inside neurons by hyperphosphorylated tau protein.

A key protein involved in Aβ formation is APP, an integral membrane glycoprotein expressed in the brain that is involved in the regulation of synaptic function, neuronal activity, and brain cholesterol metabolism. APP can undergo sequential protein cleavage either through an α-pathway or a β-pathway (13). In the α-pathway, which is usually nonamyloidogenic, APP is cleaved first by α-secretase and then by γ-secretase. In the amyloidogenic β-pathway, APP is first cleaved by β-secretase [β-site APP cleaving enzyme 1 (BACE1)], releasing the soluble peptide APPβ into the extracellular matrix and leaving a 99–amino acid C-terminal fragment within the membrane. This fragment is further processed by γ-secretase to form Aβ40 or Aβ42 and APP intracellular C-terminal domain (AICD) (14). AICD is further stabilized by Fe65, an intranuclear adapter protein, and binds to transcription factor Tip60, initiating the transcription of the enzyme neprilysin involved in Aβ degradation, thus regulating Aβ concentrations (15). In AD, impaired APP and subsequent Aβ degradation result in increased deposition and reduced clearance of Aβ40 and Aβ42 peptides in the extracellular matrix, eventually leading to the oligomerization of Aβ and plaque formation (16). Although initially it was thought that Aβ deposition happens only in the extracellular space, new data from transgenic mice and human patients point to the possibility of intracellular accumulation and its involvement in AD pathology (17).

The cascade of events starting from the cleavage of APP and leading to neuronal loss is referred to as the "amyloid cascade" hypothesis (18). This hypothesis, proposed in 1992, posits that Aβ deposition, the primary pathologic episode in AD causing the establishment of senile amyloid plaques, leads to abnormalities in tau protein causing NFT (18). Tau is a microtubule-associated protein (MAP) involved in regulating microtubule dynamics and stability. In AD, hyperphosphorylation of tau protein dissociates it from the microtubule structure, resulting in aggregation of tau protein into filamentous NFTs (19). NFTs cause a physical barrier to intracellular communication. In addition, dissociation of tau protein results in the destabilization of microtubules. The disruption of intracellular communication and the destabilization of microtubules lead to neuronal death and dementia (20, 21).

In the inherited form of AD (FAD), impairment of APP metabolism is caused due to mutations in *APP, BACE1, PS1*, and *PS2*. Although these genetic causes have been identified in FAD, what causes the aggregation of Aβ in the sporadic form of AD has yet to be completely understood. Histopathologic hallmarks are indistinguishable between FAD and sporadic forms of AD. Genomewide association studies have identified potential roles of genes involved in endosomal vesicle recycling, cholesterol metabolism, and in the innate immune system (22, 23). However, most of the risk and pathology of sporadic AD have been accounted for by the *ApoE* ε4 allele (24). ApoE is a 299–amino acid glycoprotein involved in the transport of lipids, including cholesterol, through ApoE receptors on the surface of the cell. Although neurons usually synthesize ApoE only under stress, microglia, astrocytes, choroid plexus, and vascular smooth muscle cells in the brain constitutively express ApoE (25). Although ApoE mainly functions as a lipid transporter in the brain, it also regulates Aβ metabolism, aggregation, and deposition. Due to genetic polymorphisms, there exist 3 major isoforms, ApoE ε2, ApoE ε3, and ApoE ε4 (26), with differing amino acids at positions 112 and 158 (27). The exact mechanism by which the product from ε4 allele stimulates AD pathology is not completely understood. Several possibilities, such as ApoE ε4 interaction with tau protein, ApoE ε4–mediated enhancement of Aβ production and oligomerization, involvement of ApoE ε4 at the level of cholesterol metabolism, and interaction of ApoE ε4 with bacterial pathogens have been suggested but remain controversial (28).

Involvement of ApoE ε4 in the metabolism of Aβ is widely studied and probably the most accepted of the above possibilities due to the observation that ApoE is co-deposited with Aβ in amyloid plaques (29). One argument is that because Aβ can interact with both the lipid-binding site and the receptor-binding site within ApoE, and because the Aβ-binding site on ApoE overlaps with the lipid-binding region, Aβ might compete with lipids for ApoE binding (30). The transport of lipids to neurons by ApoE is essential for synaptic maintenance and repair (31). Thus, the disruption of lipid binding in AD by Aβ and Aβ oligomers may compromise synaptic integrity and function. In addition, ApoE ε3 and ApoE ε2 have higher affinity for HDLs, whereas ApoE ε4 has high affinity for LDLs and VLDLs (32). The specific ApoE isoform and its lipidation status seem to dictate the nature of interaction between Aβ and ApoE. For example, ApoE ε4/Aβ complexes are far less stable than ApoE ε3/Aβ and ApoE ε2/Aβ complexes (33). This renders ApoE ε4 less efficient than ApoE ε3 or ApoE ε2 in clearing Aβ (34), resulting in increased concentrations of Aβ oligomers in an isoform-dependent manner (ApoE ε4 > ApoE ε3 > ApoE ε2) (35).

Potential Therapeutic Agents

The currently approved drugs for AD do not address the progressive neurodegeneration in AD and have yielded only mild symptomatic improvements (36). Most of these drugs target pathways in the amyloid cascade, focusing on diminishing Aβ generation from APP, preventing formation and facilitating removal of toxic Aβ aggregates, or preventing hyperphosphorylation and aggregation of tau protein (37). Immunization approaches that use anti-Aβ antibodies, although successful at clearing Aβ and reducing plaque load, have failed to improve cognitive abilities (38–40) and in some cases have caused serious side effects such as greater brain atrophy and meningoencephalitis (38). Compounds that inhibit Aβ aggregation or destabilize Aβ oligomeric species have to pass through the challenge of the blood-brain barrier to be effective (37). Drugs targeting inhibition of β-secretase (41), inhibition or modulation of γ-secretase (42), or upregulation of α-secretase (43) also are being investigated. However, although these enzymes are primarily involved in APP metabolism, they also have other substrates that are physiologically important, which makes inhibition a less viable option (37). Another approach is to modulate tau phosphorylation and aggregation by inhibiting glycogen synthase kinase 3 (GSK3), but a phase III clinical trial that examined this found no improvements in cognition and functional status (44, 45).

Inflammation in AD

In all of the amyloid cascade alterations that occur in AD, inflammation plays a crucial role in the clinical progression (46). Numerous studies have reported the association of elevated markers of inflammation and the accumulation of activated microglia with the pathologic lesions of AD (47). The deposition of Aβ causes activation of microglia, recruitment of astrocytes, and sustained production of proinflammatory cytokines (48, 49). These cytokines in turn accelerate Aβ production and amyloid formation, thus initiating a cycle of inflammation and amyloidogenesis (46, 50). In addition, inflammatory processes in cerebral vasculature also accelerate the progression of AD (51). The expression of inflammatory adhesion molecules is elevated in the endothelial cells of the AD brain (52, 53). In comparison to age-matched controls, AD brain microvessels released higher concentrations of inflammatory factors such as NO, TNF-α, TGF-β, IL-1β and IL-6 (52, 54, 55). Release of these inflammatory mediators contributes to the vicious cycle of amyloidogenesis and the resulting increase in inflammation. Although the involvement of inflammation in the development of disease is well documented, the cause of this inflammation is not yet understood. Revealing the causes of inflammation is crucial in developing preventative measures. In the meantime, strategies that target the resolution of inflammation represent an additional approach to treating this disease.

n–3 PUFAs are one such potential modulator of neuroinflammation (56). Increases in inflammation accelerate amyloidogenesis (46, 50) and n–3 PUFAs reduce the amyloid load and tau hyperphosphorylation by reducing neuroinflammation (57, 58). n–3 PUFAs are PUFAs with a double bond at the third carbon atom from their methyl end (**Figure 1**). Two major types of n–3 PUFAs, DHA and EPA, are abundantly present in fish oil. A plant-derived source of n–3 PUFA is α-linolenic acid (ALA; 18:3n–3), which is present in flaxseed oil and other plant oils.

In vitro experiments in immortalized BV-2 microglial cells, the main immune cell mediators in the brain, showed that EPA and/or DHA administration decreases the expression of proinflammatory factors, such as inducible NO synthase (iNOS), cyclo-oxygenase (COX) 2, IL-1β, IL-6, TNF-α, and NF-κB, and downregulates the cell-surface expression of the protein CD14 and Toll-like receptor 4 receptors involved in initiating the inflammatory response (59–61). In other types of brain cells (glial cultures and c6 glioma cells), the administration of EPA attenuates the increase in expression of proinflammatory cytokines such as IL-1β and IL-6 and promotes expression of the anti-inflammatory cytokine IL-4 (62–64). In rats, the consumption of a diet containing EPA for 4 wk before LPS-induced hippocampal inflammation prevented the reduction in hippocampal protein concentrations of anti-inflammatory cytokines IL-4 and IL-10 (65) and mitigated an increased expression of proinflammatory IL-1β (66). In humans, epidemiologic and observational studies have established an association of higher concentrations of n–3 PUFAs as well as lower n–6 to n–3 PUFA ratios with lower proinflammatory cytokine production (67–69). In elderly patients with chronic heart failure, n–3 PUFA supplementation resulted in reductions in plasma concentrations of TNF, IL-6, and intercellular adhesion molecule 1 (ICAM-1) (70), suggesting that similar effects may be observed in the brain. Indeed, there is an emerging literature that suggests the potential beneficial effect of n–3 PUFAs on inflammation in AD and other types of neurological disorders.

Role of Dietary n–3 PUFAs

It is estimated that primary intervention of known environmental risk factors in AD could prevent up to 20% of predicted new cases by 2025 (71, 72). In fact, the discordant occurrence of AD in monozygotic twins and differences in onset of up to 15 y in such patients show the role of modifiable environmental factors in disease progression (73–75). In particular, the potential role of n–3 PUFAs in modulating
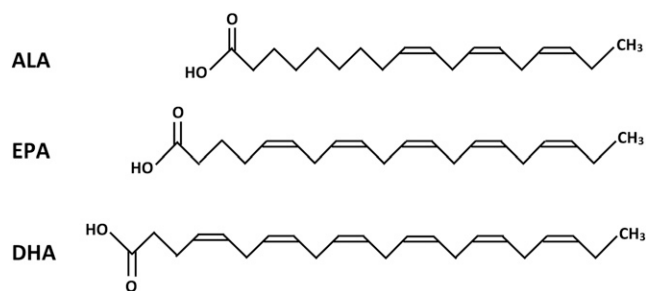
FIGURE 1 Structure of ALA, EPA, and DHA. ALA, α-linolenic acid.

the risk of cognitive impairment has gained special attention due to the fact that observational studies reported a lower incidence of AD in populations who consume a high amount of fish (76–78). DHA, a predominant n–3 PUFA in fish oil, is a key component of membrane phospholipids in the brain (79); and oxidative products of PUFAs act as cellular mediators and may be involved in improving neuronal health, neurogenesis, and neuronal function through several mechanisms, resulting in the reduction in and resolution of inflammation. Interest in n–3 PUFAs for the treatment of AD is evidenced by guidelines from the 2013 International Conference on Nutrition and the Brain that included guidelines on modifications in dietary fat intake (80) and a recent letter from 109 scientists in 36 countries that urged the health ministers of the G8 countries to promote clinical trials for the prevention of AD, including those with n–3 FAs (72).

These expert recommendations with regard to n–3 PUFAs and AD come from the positive effects of n–3 FAs in cognition as elucidated by a large body of evidence from observational studies, randomized controlled trials, and animal studies (78, 81–91). For example, a cross-sectional population-based study in 1613 subjects reported that, with an increase of 137 mg n–3 PUFAs/d, the risk of cognitive decline was reduced by 19% (OR: 0.81; 95% CI: 0.66–1.00) (85). A recent meta-analysis by Wu et al. (92) indicated that a higher intake of fish was associated with a lower risk of AD. In a systematic review, Otaegui-Arrazola et al. (86) analyzed fish intake and the incidence of AD from population-based longitudinal observational studies. They identified and summarized 8 studies, of which 7 showed that, in the general population, the consumption of fish ≥1 time/wk significantly reduced AD risk and was associated with slower cognitive decline rates and better cognitive function. A recent retrospective cohort study in patients with mild cognitive impairment (MCI) and AD showed improvements in cognition and less atrophy with the long-term (6–48 mo) use of fish-oil supplements in *ApoE ε4* participants (93). In addition, lower plasma and erythrocyte membrane n–3 PUFAs are linked to poorer cognition (94). Note also that some of the benefits observed with fish consumption might be derived from other ingredients in fish, such as vitamin D (95), because vitamin D deficiency has been linked to an increased risk of dementia and AD (96).

Results from interventional studies with fish-oil supplementation in humans have been inconclusive. A study in participants with subjective memory complaints showed improvements in some cognitive functions with 6 wk of 37.5 mg EPA+DHA supplementation/d combined with phosphatidylserine (97). In a randomized, double-blind, placebo-controlled study, improvements in cognitive performance were reported with 1.8 g n–3 PUFA supplementation/d for 24 wk in patients with MCI but not in patients with AD (98). The OmegAD study also found similar results in which benefits of n–3 PUFAs (1.7 g DHA and 0.6 g EPA/d for 6 mo) were observed in very mild AD but not in advanced AD (99). This suggests that n–3 PUFA supplementation might not be beneficial in advanced stages of disease in which substantial neuronal loss has occurred. However,

benefits in the earlier stages of disease suggest a potential role of n–3 PUFAs on primary prevention of AD.

Collectively, these results support the role of n–3 PUFAs in preventing and ameliorating AD-related symptoms. DHA and EPA, the major n–3 PUFAs in fish oil, are postulated to be the beneficial elements. However, the n–3 PUFA supplements used in the studies were usually a mixture of EPA and DHA (mainly fish oil), and individual effects of n–3 PUFAs are not well studied. The exact composition of the FAs tested in fish-oil preparations vary greatly depending on the source of the fish and method of preparation (100), and experiments evaluating the individual effects of EPA and DHA are rare due to the difficulty and higher cost associated with purifying EPA and DHA. However, understanding the specific roles of each of the major n–3 PUFAs will facilitate therapeutic interventions and possibly enhance the generation of structural analogs as treatment options. A longitudinal population-based study showed that the top quartile of plasma DHA concentrations was associated with a lower risk of developing all-cause dementia and AD than were the other 3 quartiles (101); furthermore, cholesteryl-ester DHA concentrations were low in both serum and brains of patients with AD (102). Improvements in some cognitive functions were reported in patients with subjective memory complaints with DHA supplementation (103). Another study in patients with AD and patients with MCI reported significant improvements in immediate memory and attention score with 240 mg DHA supplementation/d in MCI but not in advanced AD (104). No improvements were found in patients with advanced AD with DHA supplementation in one study (105), or with EPA supplementation in another (106).

Long-duration studies in human subjects are complex and therefore few. Animal models of AD, on the other hand, provide an opportunity to test long-term interventions aimed at primary prevention starting at an early age. Most studies with supplementation of n–3 PUFAs in animal models of AD have had positive results. Hooijmans et al. (107), examining animal studies reported up to April 2011, conducted a systematic review and meta-analysis of the effects of long-term n–3 PUFAs on AD. The study assessed 4 outcome measures (cognition, Aβ deposition, neuronal loss in the hippocampus, and cortical FA concentrations) from 15 animal studies that used supplementation for ≥10% of the animal's life span. Three of these 15 studies used a mixed source of n–3 PUFAs, and other studies used DHA as the supplement. Analysis of the pooled data from the studies showed a substantial reduction in Aβ deposition with n–3 PUFA supplementation, as well as significant improvements in cognition and a striking reduction in hippocampal neuronal loss or neurodegeneration.

A PubMed search for publications between April 2011 and November 2015, which adopted the keywords and filters used by Hooijmans et al. in the review discussed above, retrieved 8 more animal studies that included n–3 PUFA supplementation in animal models of AD (Table 1) (108–115). All 8 of these studies showed improvements in cognitive and neuronal variables with n–3 PUFA supplementation. Three of these 8 studies used a mixed source of EPA and DHA. In

aged mice, 2-mo EPA + DHA treatment increased these long-chain n–3 PUFAs in the brain and restored spatial memory deficits (113). Markers of neuroinflammation were also reduced significantly in the hippocampus of these aged mice. In the study by Kariv-Inbal et al. (114), a fish-oil diet mitigated the worsened neuronal markers and behavioral performance in ApoE ε4 mice. Oral administration of 300 mg EPA and DHA $\cdot$ kg^{-1} $\cdot$ d^{-1} to Aβ-infused rats for 12 wk before infusion resulted in a significantly lower number of reference and working memory errors, increased EPA and DHA concentrations and decreased arachidonic acid (AA; an n–6 PUFA, 20:4n–6) in the corticohippocampal region, and lower oxidative stress in the cerebral cortex and hippocampus (115).

The remaining 5 animal studies used DHA supplementation alone. Hosono et al. (109) supplemented Tg2576 mice with DHA for 4 mo and reported a reduction in memory impairment. In another transgenic APP/PS1 rat model of AD, DHA supplementation reduced hippocampal Aβ plaque density and prefibrillar Aβ oligomers and improved cognition (108). Torres et al. (110) administered a 2-hydroxy derivative of DHA (OH-DHA) orally to a double transgenic PS1/APP mouse model of AD for 4 mo at a dose of 15 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}. OH-DHA supplementation significantly downregulated Aβ concentrations (without affecting APP transgene expression) and normalized tau hyperphosphorylation. Fiol-deRoque et al. (112) reported significant improvements in memory recovery in the radial arm maze test in the above-mentioned mice. In another experiment with tau knockout mice, Ma et al. (111) reported that 5 mo of DHA supplementation improved microtubule stability by restoring phosphorylated and total GSK3β and mitigating hyperactivation of the tau C-Jun N-terminal kinases. These improvements in tau hyperphosphorylation also resulted in partial correction of hippocampal synaptic deficits.

Differential Effects of Individual n–3 PUFAs on AD

As indicated, although EPA and DHA are both neuroactive n–3 PUFAs, their effects on neuroinflammation and AD might be different from each other (see Table 2). EPA has a prominent effect on mood disorder–related symptoms. In studies in patients with depressive disorder, EPA administration significantly improved markers of depression (121, 122), and a meta-analysis of randomized controlled trials showed a greater antidepressant effect of EPA than DHA (123). Another clinical trial that compared EPA and DHA as monotherapy for major depressive disorder found no beneficial effect with either EPA or DHA (124). In addition, although both EPA and DHA have anti-inflammatory effects, EPA appears to be more effective than DHA. A study that investigated differential effects of purified EPA and DHA on stimulated peripheral blood mononuclear cells from patients with AD showed that EPA was more effective than DHA in reversing the proinflammatory profile of the AD patients' cells (125). Stronger anti-inflammatory effects of EPA were reported in several other models as well (126, 127). In neuronal tissue, EPA acts as an anti-inflammatory agent by blocking the effects of IL-1 (128, 129), which is associated with age-related impairment in neuronal function (130). A study in older subjects discovered that higher plasma EPA, but not DHA, was associated with lower gray matter atrophy of the right hippocampal and parahippocampal area (131).

EPA also has been shown to improve cognition. In AD, Hashimoto et al. (132) studied the effect of preadministration of EPA in cognition and learning with the use of rats infused with Aβ and reported a decrease in the number of reference memory errors and working memory errors. DHA appears to be effective in cognitive variables and in reducing AD-related structural abnormalities. In triple transgenic (3xTg)-AD mice, DHA improved cognition and reduced entorhinal cortex neuron dysfunction (133); and in female APPswe/PS1ΔE9 transgenic mice, a DHA diet reduced plaque load (134). In the APP/PS1 transgenic rat model of AD, DHA supplementation reduced hippocampal Aβ plaque density, increased soluble Aβ oligomer concentrations, and improved behavioral aspects (108). DHA-containing phosphatidylcholine treatment improved learning and memory abilities,

TABLE 1 Studies published after April 2011 that included n–3 PUFA supplementation in animal models of AD[1]

Study, year (ref)	AD model	Supplement	Duration	Dose	Outcome
Teng et al., 2015 (108)	Transgenic *APP/PS1* rats	DHA from algal sources	4 mo	0.6% (wt:wt) of the diet	Reduced Aβ plaque density Improved behavioral testing
Hosono et al., 2015 (109)	Tg2576 mice	DHA	4 mo	2.4 g/kg diet	Reduced Aβ(1–42)-to-Aβ(1–40) ratio
Torres et al., 2014 (110)	Transgenic 5xFAD mice	2-Hydroxy DHA	4 mo	15 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}	Reduction in Aβ accumulation Improved cognitive scores
Ma et al., 2014 (111)	Tau knockout mice	DHA alone or with α-lipoic acid	5 mo	0.6% DHA (or with 500 ppm α-lipoate)	Protected against hyperphosphorylation Lower hippocampal synaptic deficits Improved Morris water maze deficits
Fiol-deRoque et al., 2013 (112)	Transgenic 5xFAD mice	2-Hydroxy DHA	4 mo	15 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}	Improved radial arm maze test scores
Labrousse et al., 2012 (113)	Aged C57Bl6/J mice	EPA+DHA	2 mo	5.45 g EPA + 3.6 g DHA/kg diet	Reduced inflammatory markers Improved spatial memory deficits
Kariv-Inbal et al., 2012 (114)	*ApoE*-targeted replacement mice	Fish oil	4 mo	3.03 g fish oil/kg diet	Reduced hippocampal Aβ concentrations Improved behavioral performance
Hashimoto et al., 2011 (115)	Aβ-infused rats	Purified EPA+DHA	12 wk	300 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}	Improved reference and working memory

[1] Aβ, amyloid β; *APP*, amyloid precursor protein; ppm, parts per million; *PS1*, presenilin 1; ref, reference.

TABLE 2 Effect of EPA and DHA on markers of neuroinflammation[1]

PUFA; study, year (ref)	Effect
DHA	
Rey et al., 2016 (116)	Resolvin D1, a DHA oxylipin, decreased LPS-induced expression of TNF-α, IL-6, and IL-1β
Zhao et al., 2011 (117)	NPD$_1$, a DHA oxylipin, downregulated Aβ42-triggered expression of COX-2 and of B-94 (a TNF-α–inducible proinflammatory element)
Lu et al., 2010 (59)	Reduced expressions of TNF-α, IL-6, iNOS, and COX-2
Pan et al., 2009 (118)	Mitigated increases in IL-6
De Smedt-Peyrusse et al., 2008 (61)	Downregulated LPS-stimulated cell surface expression of CD14 and TLR4
	Lowered TNF-α protein expression, IL-1β protein expression, and activation of NF-κB
Kawashima et al., 2008 (62)	Attenuated IL-1β–induced IL-6 production
Lukiw et al., 2005 (119)	NPD$_1$, a DHA oxylipin, downregulated COX-2, TNF-α, and IL-1β expression
Marcheselli et al., 2003 (120)	NPD$_1$, a DHA oxylipin, downregulated NF-κB activation and *COX2* gene expression
EPA	
Rey et al., 2016 (116)	Resolvin E1, an EPA oxylipin, decreased LPS-induced expression of TNF-α, IL-6, and IL-1β
Lu et al., 2010 (59)	Inhibited iNOS and COX-2 expression and NO production
Kawashima et al., 2008 (62)	Inhibited IL-6 production, attenuated IL-1β–induced *IL6* gene expression
Moon et al., 2007 (60)	Inhibited PGE$_2$, IL-1β, IL-6, TNF-α, and release of NO
	Downregulated the production of COX-2, iNOS, and proinflammatory cytokines at mRNA and/or protein levels
	Suppressed NF-κB activation by blocking IκB degradation
Lynch et al., 2007 (63)	Elevated IL-4 and blocked LPS-induced increases in IL-1β
Minogue et al., 2007 (64)	Lowered LPS- and Aβ-induced increases in IL-1β protein
Kavanagh et al., 2004 (65)	Prevented LPS-induced reduction in anti-inflammatory IL-4 and IL-10

[1] Aβ, amyloid β; COX, cyclooxygenase; IκB, inhibitor of κB; iNOS, inducible nitric oxide synthase; NPD$_1$, neuroprotectin D1; PGE$_2$, prostaglandin E$_2$; ref, reference; TLR4, Toll-like receptor 4.

reduced phosphorylated tau concentrations, and partially corrected neuronal morphology in an Aβ23–35-induced AD rat model (135). Interestingly, DHA supplementation for 18 mo in human patients did not reduce cognitive decline (105). In conclusion, although both EPA and DHA showed benefits in inflammation and cognition in AD, EPA appears to be beneficial in mood disorders and DHA beneficial in preserving the structural integrity of the brain. In addition, active metabolites of EPA and DHA (i.e., oxylipins; see below) are different, which might play a major role in their inflammation-related mechanisms in AD (136–138).

Although the effects of fish-oil–based n–3 PUFAs on AD have been tested in animal and human trials, plant-based n–3 PUFAs such as ALA have received less attention. In contrast to other tissues (139), however, cerebral and cerebellar neurons appear to more efficiently convert ALA to DHA (140–142), and this can result in improvements in reference memory tasks (143). In addition, ALA conversion to EPA is efficient (141, 144), which could be important if oxygenated EPA metabolites (oxylipins) are the specific mediators of neuroprotection in AD. Neuroprotective effects of ALA in other forms of neurological diseases have been shown. In a rat model of spinal cord ischemia, ALA caused significant protection by reducing the loss of motor neurons and preventing apoptotic neuronal cell death (145). Yamamoto et al. (146) reported increased learning ability with supplementation of ALA-rich oil in rats. In an in vivo model of cerebral global ischemia, intracerebroventricular administration of ALA 30 min before induction of ischemia almost completely inhibited neuronal loss (147). ALA supplementation in rats improved cerebrovascular flow, which plays a pivotal role in the pathology of AD (148, 149), possibly by the activation of the tandem of pore domains in a weak inwardly rectifying K+ channel-1 related K+ channel (TREK-1) potassium channel, which is an important vasodilatation mediator. Specifically in AD, a prospective study conducted in participants aged 65–94 y found that ALA intake was strongly protective among persons with the *ApoE* ε4 allele (78). Spinal cord injury is associated with excitotoxicity, inflammation, and oxidative stress (150); and supplementation of ALA to spinal cord ischemic rats after injury reduced neuronal loss and improved functional outcome (145). The administration of ALA after this type of injury in adult rats showed significant neuroprotection by reducing neuronal cell loss, oligodendrocyte loss, and neuronal apoptosis and improving functional outcome (151, 152). In a brain ischemia rat model, the administration of ALA inhibited microglia activation, attenuated cell apoptosis, and improved behavioral function recovery (153).

Role of Oxylipins Derived from n–3 PUFAs in Their Anti-Inflammatory Effects

PUFAs participate in the process of causing or resolving inflammation through a class of lipid-derived mediators called oxylipins. These bioactive lipids are oxygenated FA metabolites biosynthesized by COX, lipoxygenase (LOX), and cytochrome P450 (CYP) enzymes (154). Oxylipins derived from n–3 PUFAs can potentially modulate neuroinflammation in 2 ways; first, through their anti-inflammatory effects, and second, through their proresolving effects. Oxylipins formed from n–3 PUFAs are generally anti-inflammatory, whereas those produced from n–6 PUFAs are generally proinflammatory (155, 156). n–3 PUFA–derived oxylipins act as anti-inflammatory compounds by reducing the concentration of and competing with proinflammatory oxylipins produced from n–6 PUFAs (157, 158). Inflammation is normally terminated by resolution, an active process involving a number of biochemical steps (159). The resolution of inflammation is important to achieve homeostasis in the tissue, but this process appears to be dysregulated in AD (160).

Proresolving oxylipins produced from n–3 PUFAs are important mediators of this resolution phase of the inflammatory process (159). For example, resolvins, lipoxins, protectins, and maresins initiate pathways that signal the termination of an acute inflammatory phase (161). Understanding the role of specific oxylipins in neuroinflammation and its resolution may therefore shed light on how individual n–3 PUFAs mediate their beneficial effects in AD.

The most studied class of oxylipins is the eicosanoids produced from 20-carbon PUFAs, AA, and EPA. AA is the n–6 PUFA that is abundantly present on the membrane phospholipids of inflammatory cells (157) and generates proinflammatory oxylipins such as prostaglandin E (PGE) 2 and leukotriene B (LTB) 4. EPA exposure reduces the concentrations of AA oxylipins in inflammatory cells (157, 162, 163) in a dose-responsive manner (164). It can compete with AA for all 3 oxylipin pathways, resulting in the production of lower concentrations of AA-derived oxylipins and higher concentrations of EPA-derived oxylipins that are biologically less active (e.g., PGE_3, LTB_5) (165–167). In addition, EPA generates oxylipins such as E-series resolvins (RvEs) that mediate the resolution of inflammation (168, 169). For example, RvE1 (5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-eicosapentaenoic acid) competes with LTB_4 (158), prevents the infiltration of neutrophils into sites of inflammation (169), decreases pulmonary polymorphonuclear neutrophil accumulation, reduces proinflammatory gene expression (170), reduces proinflammatory cytokine production (171), and inhibits leukocyte recruitment (172). Other EPA oxylipins such as 18-hydroxy-eicosapentaenoic acid (18-HEPE) also impart anti-inflammatory effects (173).

DHA supplementation also reduces the production of AA-derived oxylipins. For example, glial cells in culture produce less thromboxane B_2 (TXB_2) and 6-keto-prostaglandin $F_{1\alpha}$ (6-k-$PGF_{1\alpha}$) and 12-hydroxy-eicosatetraenoic acid (12-HETE) when supplemented with DHA (174). In addition, many novel oxylipins derived from DHA via the LOX and CYP pathways have recently been identified, with many of these appearing to play a particular role in the resolution of inflammation. These include the D-series resolvins, protectins, and maresins (56, 169), which are elevated in the murine brain with DHA-rich fish-oil feeding (175). Reduced concentrations of DHA-derived neuroprotectin D_1 (NPD_1) have been reported in the AD brain (119, 160), and low concentrations of NPD_1 are inversely related to cellular markers of neuroinflammation (176). NPD_1 has been shown to be neuroprotective (119, 160, 177). In human neural progenitor cells stimulated with IL-1β, NPD_1 downregulates NF-κB activation and COX-2 expression (120). The infusion of NPD_1 in the mouse brain reduces infarct volume, leukocyte infiltration, NF-κB activation, and COX-2 expression with greater potency than does DHA itself (120). The infusion of the aspirin triggered epimer of NPD_1 (AT-NPD_1; 10,17R-dihydroxy-DHA) also reduces neuroinflammation similar to NPD_1 (178).

Although the body of literature for ALA is much smaller, it has been shown to reduce inflammation in various models (179, 180) and to provide neuroprotection (149). ALA also produces metabolically active oxylipins (181), and although much less is known about these, they may mediate its beneficial effects in AD. In older adults, 4 wk of ALA feeding normalized the proinflammatory oxylipin profile in blood (182), suggesting that it also could have effects on the brain. The ALA-derived oxylipin 13-hydroxy-octadecatrienoic acid (13-HOTrE) significantly suppressed IL-1β–induced expression of matrix metalloproteinase (MMP) 1, 3, and 9 proteins in chondrocytes, suggesting that it is an anti-inflammatory substance (183). This oxylipin also is associated with less glomerulomegaly, indicating that it may have an anti-inflammatory effect (184).

Conclusions

There is a pressing demand for more research in preventing, delaying, and diminishing the effects of AD (185). In this regard, n–3 PUFAs can help reduce and resolve inflammation, which plays a major role in the progression of AD. However, although the use of mixed sources of EPA and DHA in most studies prevents an understanding of the individual effects of these PUFAs, several studies do indicate that they may have distinct effects such as EPA's more prominent effects in mood disorders and DHA's ability to alleviate structural abnormalities. This may, in part, be due to their different effects on the oxylipin profiles they generate, and their effects on the reduction in and resolution of neuroinflammation. In addition, oxylipins synthesized from ALA also may have antineuroinflammatory effects. Future research delineating the unique anti-inflammatory and proresolving properties of oxylipins from individual n–3 PUFAs will help the development of novel disease management strategies in AD.

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