Review

Specialized Pro-Resolving Mediators from Omega-3 Fatty Acids Improve Amyloid-β Phagocytosis and Regulate Inflammation in Patients with Minor Cognitive Impairment

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Abstract. In this review we discuss the immunopathology of Alzheimer’s disease (AD) and recent advances in the prevention of minor cognitive impairment (MCI) by nutritional supplementation with omega-3 fatty acids. Defective phagocytosis of amyloid-β (Aβ) and abnormal inflammatory activation of peripheral blood mononuclear cells (PBMCs) are the two key immune pathologies of MCI and AD patients. The phagocytosis of Aβ by PBMCs of MCI and AD patients is universally defective and the inflammatory gene transcription is heterogeneously deregulated in comparison to normal subjects. Recent studies have discovered a cornucopia of beneficial anti-inflammatory and pro-resolving effects of the specialized proresolving mediators (SPMs) resolvins, protectins, maresins, and their metabolic precursors. Resolvin D1 and other mediators switch macrophages from an inflammatory to a tissue protective/pro-resolving phenotype and increase phagocytosis of Aβ. In a recent study of AD and MCI patients, nutritional supplementation by omega-3 fatty acids individually increased resolvin D1, improved Aβ phagocytosis, and regulated inflammatory genes toward a physiological state, but only in MCI patients. Our studies are beginning to dissect positive factors (adherence to Mediterranean diet with omega-3 and exercise) and negative factors (high fat diet, infections, cancer, and surgeries) in each patient. The in vitro and in vivo effects of omega-3 fatty acids and SPMs suggest that defective phagocytosis and chronic inflammation are related to defective production and/or defective signaling by SPMs in immune cells.

Keywords: Amyloid-β, fatty acids, inflammation, mild cognitive impairment, omega-3

INTRODUCTION

Phagocytosis of amyloid-β (Aβ) and inflammation are the two faces of innate immunity underlying much of the Alzheimer’s disease (AD) immunopathology and are an excellent target for AD prevention. Curcuminoids, vitamin D3, and omega-3 fatty acids are popular preventive supplements that have been shown to enhance phagocytosis and tame inflammation [1]. Here we review the pathology of the innate immune system in AD patients and the advances in the prevention of mild cognitive impairment (MCI) by the lipidic mediators termed specialized proresolving mediators (SPMs) that are derived from omega-3 fatty acids [2].
The strategy we employed in our in vitro studies is based on investigating the clearance of A\(\beta_1-42\) by immune and endothelial cells in the brain tissues of AD patients and using omega-3 fatty acids and SPMs as agonists in macrophages. The in vivo aim of this approach is to rectify the defective clearance of A\(\beta_1-42\) by the monocyte/macrophages of AD patients using supplementation with omega-3 fatty acids and increasing SPMs [3–5]. Omega-3 fatty acids are an important component of the Mediterranean diet, which is high in fish and olive oil, low in meat, and moderate in dairy products [6]. Omega-3 fatty acids are precursors of anti-inflammatory and pro-resolving mediators that improve the immune clearance of A\(\beta_1-42\) (see below “Role of SPMs in dementia and Alzheimer’s disease”).

**AMYLOID-\(\beta_1-42\) NEUROTOXICITY**

Neuronal damage in the AD brain is related to accumulation of A\(\beta_1-42\) and phospho-tau [7] as well as the inflammation induced by these proteins. Apolipoprotein E e4 allele genotype is a risk factor for accumulation of A\(\beta_1-42\) in the brain related to increased amyloidogenic \(\beta\)- and \(\gamma\)-cleavage of amyloid-\(\beta\) protein precursor (A\(\beta_{PP}\)), and loss of sitocin T1, and reduced clearance across the blood-brain barrier. The products of \(\beta\)- and \(\gamma\)-cleavage of A\(\beta_{PP}\) are the peptides sA\(\beta_{PP}\), A\(\beta_1-42\), icasp, and C31, which cause neurite retraction and cell death [8]. The mechanisms of A\(\beta_1-42\) neurotoxicity [9] involve inflammatory activation, prion-like toxicity, and production of neurofibrillary tangles. Upstream of A\(\beta_1-42\), neurotoxicity is attributed to prostaglandins, and additionally to F2-isoprostanes produced by free radical-catalyzed peroxidation of arachidonic acid [10]. In addition, possible culprits in neural damage, especially in APOE e4 carriers, are the products of oxidative stress, 4-hydroxy-2-nonenal, which is generated by peroxidation of the \(\omega-6\) polyunsaturated fatty acid (PUFA) arachidonic acid, and 4-hydroxy-2-hexenal, which is produced by peroxidation of the \(\omega-3\) PUFAs docosahexaenoic acid (DHA) [11].

**AMYLOID-\(\beta_1-42\) CLEARANCE IN MODEL SYSTEMS**

Enhancement of A\(\beta_1-42\) clearance from the brain has a high priority in therapeutic research. A\(\beta_1-42\) clearance across the blood-brain barrier and choroid plexus in rodent model systems is reduced by APOE e4 due to redirection of A\(\beta_1-42\) from the low-density lipoprotein receptor-related protein 1 to the very low-density lipoprotein receptor [12–14]. A defect of systemic A\(\beta_1-42\) elimination by liver and kidney pathologies promotes A\(\beta_1-42\) accumulation [15]. Bexarotene stimulation of the peroxisome proliferator–activated receptor gamma (PPAR\(\gamma\)) and liver X receptor, in coordination with the retinoid X receptor, in the A\(\beta_{PP}\)/PS1 model increased memory and A\(\beta_1-42\) clearance and degradation [16].

**IMMUNE CLEARANCE IN HUMAN BRAIN AND RECEPTORS FOR A\(\beta_1-42\) ON IMMUNE CELLS**

In patients with sporadic AD, A\(\beta_1-42\) accumulation is related to decreased clearance, but not to increased production [25]. One cogent reason for decreased A\(\beta_1-42\) clearance is the reduction of immune clearance by AD macrophages, which display reduced phagocytosis and degradation in comparison to normal macrophages [3]. Although soluble A\(\beta_1-42\) is transported across the brain endothelia, A\(\beta_1-42\) aggregates in the brain and its clearance then depends upon degradation and transport by immune cells. In animal models, A\(\beta_1-42\) phagocytosis and degradation are attributed to brain microglia recruited from the bone marrow and the blood by chemokines, such as CCL2 [26]. In the AD brain, macrophage-like cells are observed on immunohistochemical examination to traverse from the microvessels into the neuropil, as documented in HIV-1 encephalitis [27, 28] and the AD brain [3]. Macrophages are also believed to phagocytize and degrade extracellular tau [29].
Both microglia and macrophages belong to the innate immune system and have similar receptors for Aβ1-42: (a) the scavenger receptors including class A (SCARA-1 and MARCO), class B (SCARB-1 and CD36), and other (CD68), (b) the receptor for advanced glycation end product (RAGE) called CD163; (c) the G-protein coupled receptors (GPCRs) lipoxin A4/formyl peptide receptor 2 (ALX/FPR2) and chemokine-like receptor 1 (CMKLR1); and (d) the toll-like receptors (TLRs) [30, 31]. In addition, the studies of non-steroidal anti-inflammatory drugs targeting prostaglandins have spurred interest in the modulation of prostanoid receptors [32]. Recently an increased risk of AD was found to be related to heterozygous variants in the triggering receptor expressed on myeloid cells 2 protein (TREM2) [33]. TREM2 is expressed on alternatively activated M2 macrophages and attenuates macrophage activation [34].

GPCRs are the most interesting from the omega-3 therapeutic viewpoint as the ALX/FPR2 antagonist blocked Aβ1-42-induced IL-1β in monocytes [35] and ALX/FPR2 antibody blocked enhancement of Aβ1-42 phagocytosis by resolvin D1 [36]. CMKLR1 is a receptor for another lipid mediator resolvin E1 [37]. Thus GPCR signaling may be crucial for the balance between inflammation and phagocytosis. The roles of Aβ receptors are summarized in an excellent review of animal studies [38]: a) CD14 functions in the recognition and binding of Aβ for its internalization and clearance from the brain parenchyma [39]; b) RAGE has a role in the induction of inflammatory cascade; c) TREM has a role in clearance of Aβ; and d) complement and Fc receptors, ALX/FPR2, CD36, and TLRs are important in both inflammation and phagocytosis. The multiplicity and heterogeneity of these receptors reduces therapeutic potential of the receptor blockade. The use of endogenous SPMs discussed below may provide a physiological approach to optimize the balance between effective phagocytosis and moderate inflammation.

**IMMUNE PATHOLOGIES IN AD PATIENTS**

Peripheral blood mononuclear cells (PBMCs) of AD patients display specific immune pathologies. Defective phagocytosis of Aβ1-42 by immune cells of AD patients was first noted with AD macrophages [40]. In subsequent studies, almost all AD patients have been found defective in Aβ1-42 phagocytosis in macrophages and monocytes, and deregulated with respect to inflammatory activation of PBMCs. The defect in phagocytosis was found to be specific for genuine Aβ1-42, as scrambled Aβ1-42 was not phagocytized, whereas E. coli was phagocytized by both normal and AD macrophages [41]. In a “tissue assay” with sections of the AD brain incubated with macrophages, strikingly different results were observed with normal macrophages phagocytizing and clearing Aβ1-42 compared to AD macrophages aggregating and becoming apoptotic after up loading Aβ1-42 in the AD brain tissue [3]. Fibrillar Aβ1-42 was cleared by normal macrophages but caused apoptosis of AD macrophages. These defects may explain the apoptosis of macrophages around blood microvessels and release of Aβ1-42 in the wall of congophilic brain vessels [42].

**ENHANCEMENT OF IMMUNE CLEARANCE OF Aβ1-42 IN THE AD BRAIN**

In the AD brain, Aβ plaques are cleared by macrophages, which appear distinct from ramified microglia [28]. According to a confocal microscopic study of the AD brain in a “tissue assay” (monocytes are co-incubated with the AD brain tissue slices), monocyte/macrophages intrude into neurons and upload Aβ [42]. Thus monocyte/macrophages, depending on their fitness, may upload and clear Aβ1-42 from both the plaques and neurons. Epidemiological studies of dementia in various populations have produced strong rationale for AD prevention using natural substances based on local customs [16, 17, 19]. Fortuitously, these substances have been shown to increase Aβ1-42 phagocytosis [1]. The nutrients believed to be related to better cognition according to population studies include omega-3 fatty acids, vitamin D3, curcumin, and other natural substances [1]. Using these substances in vitro, Aβ1-42 phagocytosis by monocytes and macrophages was modulated by vitamin D3, curcumin, and, in particular, by the omega-3 fatty acids DHA and eicosapentaenoic acid [36]. Administration of omega-3 fatty acids to patients with dementia in a randomized, double-blind, placebo-controlled clinical trial significantly slowed the decline of Mini-Mental State Examination (MMSE) scores in a subgroup of MCI patients with MMSE 22-27 points [43]. A recent study of supplementation by omega-3 fatty acids, antioxidants, and resveratrol in the drink Smartfish (Smartfish Inc., Oslo, Norway) showed that MCI patients on this supplement maintained their cognition with initial MMSE 25.9 and final MMSE 25.7 after 4–17 months [5].
OMEGA-3 FATTY ACID
ANTI-INFLAMMATORY AND PRO-RESOLVING MECHANISMS

The roles of prostaglandin E₂ in inflammation, thromboxanes in platelet aggregation and constriction of vascular smooth muscle, and leukotrienes in asthma were gleaned in the laboratory of Samuelson [44] in the 1960s and 1970s [44]. The anti-inflammatory and pro-resolving lipoxins derived from arachidonic acids were discovered in 1980s at Karolinska Institute, and the first resolvins in Serhan’s laboratory in 2000 [45]. The concept of active resolution of inflammation became apparent in inflammatory exudates when the lipid mediator class switched from pro-inflammatory prostaglandins and leukotrienes to anti-inflammatory and pro-resolving lipoxins [45, 46]. Therefore, this class switch process leads to a shift in the exudate lipid mediator profile from one that is pro-inflammatory during the initial pro-inflammatory response to an anti-inflammatory and pro-resolving with elevated SPMs [47].

The molecular basis of the omega-3 actions in the central nervous system was discovered in Serhan’s [48] and Bazan’s laboratories [49]. These researchers observed the production of 10R,12S-docosatriene called neuroprotectin D1 (NPD1), 10R,17S-dihydroxy-4Z,7Z,11E,13E,15Z,19Z-docosahexaenoic acid in oxidative stress-challenged human retinal pigment epithelial cells [50] and the rat brain undergoing ischemia-reperfusion [49]. Interestingly, IL-1ß enhances the production of NPD1 which in turn inhibits IL-1ß-stimulated production of COX-2 and caspase-3 activation [51], suggesting that during inflammation the SPMs production is tightly regulated to achieve optimal phagocytosis and neuroprotection.

STIMULATION OF INFLAMMATION BY PROSTAGLANDINS AND LEUKOTRIENES AND TERMINATION OF ACUTE INFLAMMATION BY SPECIALIZED PRO-RESOLVING MEDIATORS

Inflammation is induced by the pro-inflammatory leukotrienes LTB₄ (potent leukocyte chemotactant), LTC₄, LTD₄, LTE₄ (vascular leakage, smooth muscle contraction), and the prostaglandins E₂ and D₂ (PGD₂ and PGE₂), and cytokines that stimulate vascular leakage and promote neutrophil diapedesis in the early phase of inflammation. LTB₄ stimulates inflammation by binding to the G-protein coupled receptors (GPCRs) BLT₁ and BLT₂ that are present in the membranes of the relevant cell types and triggers the expression of chemokines and cytokines (IL-6 and IL-8). After the early phase, PGE₂ and PGD₂ switch production of lipid mediators to SPMs via the upregulation of the key biosynthetic enzyme 15-lipoxygenase (15-LO) type 1 in leukocytes [52]. This promotes the conversion of (a) arachidonic acid to lipoxin A₄ (LXA₄) and LXB₄, and (b) the omega-3 PUFA DHA to the D-series resolvins and protectins/neuroprotectins [52]. The mediators are produced in humans by 15-LO and 5-lipoxygenase that convert the PUFA substrate via subsequent lipoxigenation reactions [52]. For recent detailed reviews on the biosynthetic pathways, interested readers are directed to the reviews [53, 54]. Specific members of these new families of mediators from the DHA metabolome are named D-series resolvins (Resolvin D1 to D6), protectins (including protectin D1-neuroprotectin D1), and maresins (MaR1 and MaR2) [53].

Resolution of inflammation involves limiting of neutrophil recruitment, promotion of nonphlogistic recruitment, and activation of monocytes, and non-phlogistic phagocytosis and lymphatic clearance of apoptotic neutrophils by macrophages [55]. Alternatively, chronic inflammation can result from excessive and/or unresolved inflammatory responses. Resolution of inflammation is mediated by SPMs, each with a specialized function. LXA₄ inhibits leukocyte trafficking in vivo by activating the lipoxin A₄ receptor (denoted BLT). Resolvin E1 directly activates CMKLR1/ERK1 on mononuclear cells and dendritic cells and acts as a competitive antagonist at the leukotriene B₄ receptor (denoted BLT). Resolvin D1 binds to ALX/FPR2 and another G-protein coupled receptor called GPR 32, and inhibits neutrophil migration and promotes their phagocytosis by macrophages [56]. Aspirin-triggered resolvin D1 (AT-ResD1) inhibits the release of IL-6 and protects the brain after surgical injury from neuroinflammation, synaptic dysfunction, and cognitive decline [57]. DHA is also converted by macrophages via 14-lipoxygenation to the Maresins (macrophage mediators in resolving inflammation). The first member of this family identified was Maresin 1 (MaR1; 7R,14S-dihydroxy-docosa-4Z,8E,10E,12Z,16E,19Z-hexaenoic acid). These mediators potentiate stimulate macrophage phagocytosis of apoptotic cells in a stereospecific manner. They also regulate both inflammation and chemotherapy induced pain by inhibiting TRPV1 currents in neurons and limits neutrophil recruitment [58]. Recently, a novel family of macrophage-derived pro-resolving
mediators coined Maresins Conjugates in Tissue Regeneration (MCTR) was identified. These novel resolution agonists carry potent organ-protective, tissue-regenerative, and pro-resolving actions [59]. The production of proresolving mediators is evolutionarily conserved being identified in a number of species from planaria, to mice, baboons and humans [60, 61]. Whereas in planaria RvE1, MaR1, MCTR1 and MCTR2 accelerate tissue regeneration, in mice and humans, this process is regulated by select macrophage subtypes [62].

**ROLE OF MACROPHAGES IN RESOLUTION OF INFLAMMATION**

Macrophages are key players in various host protective processes ranging from protection against pathogen infections to clearance of cellular debris and tissue repair and regeneration, with different macrophage subsets being associated with the propagation or resolution of inflammation [63, 64]. Classically M1 macrophages are regarded as pro-inflammatory, whereas macrophages displaying the M2 phenotype are anti-inflammatory/pro-resolving. Recent evidence demonstrates that macrophage phenotypes in vivo display intermediate characteristics to these extreme descriptions giving rise to more physiologically relevant phenotypes, such as those described by Stables and colleagues [65] and Schif-Zuck and colleagues [66]. A number of studies have now investigated the actions of pro-resolving mediators on regulating the macrophage phenotype switch. Resolvin D1 promotes the adipose macrophage phenotype switch toward an M2-like phenotype in a mouse model of diet induced obesity [67], and in obese-diabetic mice in hepatic macrophages during a model of insulin resistance and nonalcoholic steatohepatitis [68]. Resolvin D1 decreases the expression of anti-coactivator-associated arginine methyltransferase 1 (CARM1), as well as downstream genes including colony-stimulating factor 3, intercellular adhesion molecule 1, and monocyte inflammatory protein 2 in resolution phase peritoneal macrophages. This ability to switch macrophages from an inflammatory to a tissue protective/pro-resolving phenotype was also found with other pro-resolving mediators, including the maresin conjugates in tissue regeneration (MCTR1 and MCTR2) [59], maresin 1, as well as the maresin biosynthetic intermediate 13S, 14S-epoxy-MaR (13S,14S-epoxy-17R/S-HDHA, and 14R/S-HDHA, but not other SPMs, showing a significant increase in RvE1, 18R/S-HEPE, 17R/S-HDHA, and 14R/S-HDHA, but not other SPMs, after short-term omega-3 supplementation [76, 77]. In another study, plasma concentrations of all SPMs were increased after a single administration of omega-3 fatty acids are popular supplements taken by many people for prevention of health problems including dementia. Studies in healthy volunteers showed a significant increase in RvE1, 18R/S-HEPE, 17R/S-HDHA, and 14R/S-HDHA, but not other SPMs, after short-term omega-3 supplementation [76, 77].

**HETEROGENEITY OF INFLAMMATION IN AD PATIENTS**

It is important to realize that the results of therapeutic trials will not be uniform due to the heterogeneity of MCI patients. In our study of AD patients, we distinguished two subgroups: Type I (non-inflammatory) and Type II (inflammatory), but even in the inflammatory group, the upregulated cytokines and chemokines and the responses to anti-inflammatory therapy by omega-3 differed between patients (see next paragraph). Another example of the heterogeneity is found in the study of β-secretase inhibitors, which failed to achieve overall significance but observed an effect in an MCI subgroup [70]. Thus anti-inflammatory and other therapeutic approaches in MCI and AD patients need to be personalized.

**ROLE OF SPMs IN DEMENTIA AND ALZHEIMER’S DISEASE**

SPMs are investigated in AD on the basis of their anti-apoptotic effects, down regulation of inflammation in neural cells, shift to non-amyloidogenic processing of AβPP, and activation of PPAR signaling. A protective role of the neuroprotectin D1 (NPD1) in the AD brain has been suspected due to its decreased level and a decreased expression of phospholipase A2 and 15-LOX type 1 in the hippocampal cornu ammonis region 1 [71]. Furthermore, in a mouse model of surgery-induced cognitive decline, aspirin-triggered resolin D1 prevented surgery-induced neuronal dysfunction by modulating astrocyte activity and synaptic plasticity in the hippocampus, thus ameliorating cognitive loss [57]. Surgery and anesthesia have also been implicated in the progression of AD pathology, suggesting a possible role for inflammation and oxidative stress damage in modulating Aβ accumulation and tau phosphorylation [72, 73]. However, not all anesthetic agents have been shown to exacerbate AD pathology [74]; some may exert even neuroprotective actions, including jumpstarting endogenous resolution and providing anti-inflammatory actions [75].
capsule and aspirin [60] We have evaluated immuno-
supportive and pro- and anti-inflammatory effects of
nutritional supplementation in MCI patients by the
Smartfish drink (Smartfish, Oslo, Norway) containing
omega-3, natural anti-oxidants, resveratrol and vita-
min D3. After a 4- to 17-month supplementation,
the phagocytosis of Aβ by monocytes was signifi-
cantly increased and the pro-resolving mediator RvD1
increased in the macrophages of 80% of the MCI
patients [5].

The brain damage in AD has been ascribed to
inflammatory cytokines, in particular IL-1β, TNF-α, IL-
1β, and TGF-β [78]. However, the transcriptome of
AD patients’ PBMCs is either “inflammatory” (with
increased TLRs, IL-1, IL1R1, and chemokines) or
“non-inflammatory” (with opposite findings); how-
ever, both groups have increased IL1RN, ITGB2,
and NFκB [36]. Omega-3 nutritional supplementation
upregulated transcription of cytokines in “pro-
inflammatory” patients (but not to the “inflammatory
level) and downregulated transcription in “inflamma-
tory” patients [5, 36]. Omega-3 attenuated cognitive
decline in MCI patients with MMSE >27 in a placebo-
controlled study [43]. In our study, which was not
placebo-controlled, the mean MMSE score was 25.9
at baseline and 25.7 after supplementation [79]. How-
ever, there are caveats in the effects of omega-3
supplementation. Previous studies [80] showed that
omega-3 supplementation has less protective effect
gainst dementia in APOE ε4 carriers. In our study of
14 MCI patients, three had the APOE ε4 genotype.
In these patients, the improvement of Aβ1−42 phago-
cytosis on supplementation and the MMSE score were
not sustained in two patients. The Aβ1−42 phago-
cytosis was generally adversely affected by intercurrent
infections, surgeries, cancer, and lack of adherence
to the supplementation (even for a short time). Some
MCI patients did not produce RvD1 in macrophages
despite immune and cognitive improvements, indicat-
ing a defect in the biosynthetic pathway for this potent
pro-resolving mediator.

**BLOOD BIOMARKER TEST OF Aβ1−42 PHAGOCYTOSIS**

The benefits of omega-3 fatty acids are difficult to
analyze in small samples by psychological tests due to
the heterogeneity of their cognitive effects in individual
patients. However, Aβ1−42 phagocytosis and inflam-
matory activation are the key pathologies in AD and
MCI patients, which can be accurately measured by
flow cytometry and PCR. The flow cytometric test of
fluorescent Aβ1−42 phagocytosis by monocytes had the
following results: (a) Aβ1−42 uptake of <450 mean
fluorescence intensity (MFI) units in AD and most
MCI patients; (b) Aβ1−42 uptake of >450 MFI units in
cognitively-normal subjects; (c) Aβ1−42 uptake >1000
MFI Units in cognitively-highly active University pro-
fessors; (d) Aβ1−42 uptake in AD range in non-
inflammatory "non-inflammatory" patients (but not to the "inflammatory"
level) and down regulated transcription of cytokines in "non-
inflammatory" patients (with opposite findings); how-
ever, both groups have increased IL1RN, ITGB2,
and NFκB [36]. Omega-3 nutritional supplementation
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ing a defect in the biosynthetic pathway for this potent
pro-resolving mediator.

**FUTURE DIRECTIONS**

Omega-3–derived specialized pro-resolving medi-
ators have strong effects on acute inflammation in
vitro and in vivo and may attenuate chronic inflam-
mation in patients with neurodegenerative diseases.
Yet, large studies of omega-3 supplementation have
not produced a consensus about their beneficial cogni-
tive effects in MCI and AD patients. These difficulties
can be partially overcome by nutritional supplementa-
tion of individual patients while monitoring adherence
to daily therapy, Aβ1−42 phagocytosis, inflammation,
and lipid mediators. Nutritional supplementation is
compromised by lack of daily adherence, intercurrent
infections, surgeries, cancer, endocrine and metabolic
factors, and lack of a healthy and active lifestyle.

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