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DHA Selectively Protects SAMP-8-Associated Cognitive Deficits Through Inhibition of JNK

S. Vela[1] · Neira Sainz[2] · María J. Moreno-Aliaga[2,3,4,5] · M. Solas[1,5] · María J. Ramirez[1,5]

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Abstract

A potential role of marine n-3 polyunsaturated fatty acids (ω-3 PUFAs) has been suggested in memory, learning, and cognitive processes. Therefore, ω-3 PUFAs might be a promising treatment option, albeit controversial, for Alzheimer's disease (AD). Among the different mechanisms that have been proposed as responsible for the beneficial effects of ω-3 PUFAs, inhibition of JNK stands as a particularly interesting candidate. In the present work, it has been studied whether the administration of two different PUFAs (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) and a DHA-derived specialized pro-resolving lipid mediator (MaR1) is able to reverse cognitive deficits in the senescence-accelerated mouse prone 8 (SAMP8) mouse model of sporadic AD. The novel object recognition test (NORT) test showed that recognition memory was significantly impaired in SAMP8 mice, as shown by a significantly decreased discrimination index that was reversed by MaR1 and DHA. In the retention phase of the Morris water maze (MWM) task, SAMP8 mice showed memory deficit that only DHA treatment was able to reverse. pJNK levels were significantly increased in the hippocampus of SAMP8 mice compared to SAMR1 mice, and only DHA treatment was able to significantly reverse these increased pJNK levels. Similar results were found when measuring c-Jun, the main JNK substrate. Consequently to the increases in tau phosphorylation after increased pJNK, it was checked that tau phosphorylation (PHF-1) was increased in SAMP mice, and this effect was reversed after DHA treatment. Altogether, DHA could represent a new approach for the treatment of AD through JNK inhibition.

Keywords N-3 polyunsaturated fatty acids (ω-3 PUFAs) · Cognitive deficit · Alzheimer's disease · Tau · JNK inhibitors

Introduction

Alzheimer's disease (AD), the most common cause of dementia in the elderly, is a progressive, degenerative, and irreversible neurological disorder that causes deterioration of memory, judgment, and reasoning in the elderly. Neuropathologically, AD is characterized by a cascade of pathological events, including the formation of amyloid plaques (made up of aggregated forms of amyloid β peptide, Aβ), neurofibrillary tangles (composed of aggregated, hyperphosphorylated tau), synapse loss, brain hypometabolism, neuroinflammation, and brain atrophy [1]. It is essential to propose new strategies or therapeutic approaches for the disease, as there is no effective treatment for the disease [2].

Marine n-3 polyunsaturated fatty acids (ω-3 PUFAs) have been widely recognized to exert favorable anti-inflammatory actions on inflammatory-related diseases such as cardiovascular diseases, atherosclerosis, asthma, obesity, or metabolic syndrome [3–5]. In fact, due to its implication in neurogenesis [6], synaptogenesis, neuronal differentiation [7], and neurite outgrowth [8], a potential role of ω-3 PUFAs in memory, learning, and cognitive processes has been suggested [9]. Therefore, ω-3 PUFAs might be a promising treatment option, albeit controversial, for dementia, particularly AD [10]. Among ω-3 PUFAs, eicosapentaenoic acid (EPA, ω-3, 20:5) and docosahexaenoic acid (DHA, ω-3, 22:6) have been extensively studied. Approximately 60% of PUFAs in neuronal membranes consist of DHA, thus representing the most

✉ María J. Ramirez
mariaja@unav.es

[1] Department of Pharmacology and Toxicology, University of Navarra, Pamplona, Spain

[2] Centre for Nutrition Research, University of Navarra, Pamplona, Spain

[3] Department of Nutrition, Food Science and Physiology, University of Navarra, Pamplona, Spain

[4] CIBERobn, Physiopathology of Obesity and Nutrition, Institute of Health Carlos III (ISCIII), Madrid, Spain

[5] IdiSNA, Navarra Institute for Health Research, Pamplona, Spain

common ω-3 PUFAs in the human brain. Despite its critical role in brain function, human's capacity to synthesize DHA de novo is limited and its consumption through the diet is important. Moreover, normal aging and neurodegenerative diseases are characterized by a cognitive decline in correlation with a deficiency in DHA abundance both in blood and in brain [11, 12] and high dietary and plasma DHA levels are associated with decreased dementia risk and AD [13, 14].

ω-3 PUFAs serve as precursors of other molecules involved in resolution of inflammation, such as maresin 1 (MaR1) [15]. Interestingly, decreased levels of MaR1 have been observed in the hippocampus and entorhinal cortex of AD cases [16] and MaR1 effects have been described related to AD pathology, i.e., MaR1 induces Aβ phagocytosis [16].

The present work aims to perform a comparative study on the ability of two different ω-3 PUFAs, EPA, and DHA and a DHA-derived specialized pro-resolving lipid mediator (MaR1) to reverse the cognitive impairment showed by the senescence-accelerated mouse prone 8 (SAMP8), an experimental model of sporadic AD. SAMP8 strain is a spontaneous animal model of accelerated aging that harbors the behavioral and histopathological signatures of AD, namely, cognitive alterations, neuron and dendrite spine loss, gliosis and cholinergic deficits in the forebrain, β-amyloid deposits resembling senile plaques, and aberrant hyperphosphorylation of tau (for review, see [17]). SAMP8 mice are nowadays considered a robust model for exploring the etiopathogenesis of sporadic AD and a plausible experimental model for developing treatments [17].

Cognitive deficits in the SAMP8 mouse have been associated to JNK pathway activation [18, 19]. JNK is a kinase that has been involved in the development of neurodegenerative processes due to its implication in stress-triggered response [20], neuronal apoptosis [21], caspase activation [22], or gene modulation [20] or its involvement in the maturing process of neurofibrillary tangles in AD [23]. Moreover, different biological markers of neurodegeneration have proved to directly activate the JNK-c-Jun cascade such as cytokines, reactive oxygen intermediates, or Aβ peptide [24, 25]. Therefore, JNK has been proposed a promising target in the field of neurodegenerative disorders [26]. ω-3 PUFAs, or at least DHA, have been suggested to act as natural JNK inhibitors [27], although this point has not been completely demonstrated. Therefore, it is plausible to hypothesize that ω-3 PUFAs could exert their purported beneficial effects on AD through JNK inhibition.

Material and Methods

Animals and Treatments

Animals were housed in a temperature- (21 ± 1 °C) and humidity- (55 ± 1%) controlled room on a 12 h light/dark cycle. Experimental procedures were conducted in accordance with the European and Spanish regulations (2003/65/EC; 1201/2005) for the care and use of laboratory animals and approved by the Ethical Committee of University of Navarra (068-11).

ω-3 PUFAs (DHA, EPA) and MaR1 were administered to 9-month-old SAMP8 mice. The experimental groups were as follows: SAMR1 saline ($n = 10$), SAMP8 saline ($n = 8$), SAMP8 MaR1 ($n = 8$), SAMP8 DHA ($n = 8$), and SAMP8 EPA ($n = 8$). Mice were treated by oral gavage with 200 mg/kg of DHA, 200 mg/kg of EPA, and 25 μg/kg of MaR1 for 20 days. Highly purified DHA (80%) and EPA (90%) as ethylester were kindly provided by Solutex (Spain). MaR1 was purchased from Cayman Chemical (Michigan, USA).

The behavioral tests were conducted before daily gavage administration of different treatments (Fig. 1). Behavioral experiments were conducted between 09:00 h and 13:00 h. Observers were blind to the genotype. All behavioral tests were carried out in the same cohort of animals.

Open Field

Locomotor activity was measured for 30 min in an open field (35 × 35 cm, 45 cm height) made of black wood, using a video-tracking system (EthoVision 11.5, Noldus Information Technology B.V., Netherlands), in a softly illuminated room. Total path velocity (cm/s) was analyzed.

Morris Water Maze

The Morris water maze (MWM), a hippocampus-dependent learning task, was used to test spatial memory and to evaluate the working and reference memory functions. The water maze

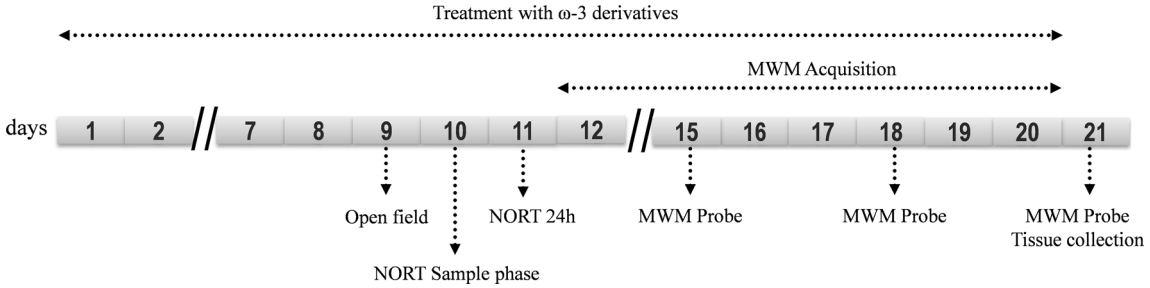

Fig. 1 Schematic representation of the experimental design. MWM, Morris water maze; NORT, novel object recognition test

is a circular pool (diameter of 145 cm) filled with water (21–22 °C) and virtually divided into four equal quadrants identified as northeast, northwest, southeast, and southwest. To test learning capacity, hidden-platform training was conducted with the platform placed in the northeast quadrant 1 cm below the water surface over 9 consecutive days (4 trials/day). Several large visual cues were placed in the room to guide the mice to the hidden platform. Each trial was finished when the mouse reached the platform (escape latency) or after 60 s, whichever came first. Mice failing to reach the platform were guided onto it. After each trial, mice remained on the platform for 15 s. To test memory, probe trials were performed at the 4th, 7th, and last days of the test (10th day). In the probe trials, the platform was removed from the pool and mice were allowed to swim for 60 s. The percentage of time spent in the target quadrant was recorded. All trials were monitored by a video camera set above the center of the pool and connected to a video tracking system (EthoVision 11.5; Noldus Information Technology B.V., Wageningen, Netherlands).

Novel Object Recognition Test

The open field consisted of a square divided into four sections (35 cm × 35 cm × 45 cm each) with black walls. On the previous day to the experiment, animals were familiarized with the square for 30 min. During the first trial (sample phase), two identical objects were placed inside the cubicle, and the mice were allowed to explore for 5 min. During the second task, which took place 24 h later, one object was replaced by another and the exploration time was recorded for 5 min. Results were expressed as percentage of time spent exploring the new object with respect to the total exploration time (discrimination index). This behavioral test was carried out using a video-tracking system (EthoVision 11.5; Noldus Information Technology B.V., Wageningen, Netherlands).

Western Blotting

Mice were sacrificed by decapitation between 09:00 and 12:00 h. Brains were removed and dissected on ice to obtain the hippocampus and stored at − 80 °C. Total tissue homogenates were obtained by homogenizing the hippocampus in ice-cold RIPA buffer (50 mM Tris-HCl pH = 7.4, 0.25% DOC, 1% Nonidet P-40, 150 mM NaCl, 1 mM EDTA, 1 mM PMSF, 1 μg/ml leupeptin, 1 μg/ml aprotinin, 1 mM Na_3VO_4, 1 mM NaF), centrifuged at 14000×g 4 °C for 20 min, and the supernatant was aliquoted and frozen at − 80 °C. Hippocampi of SAMP8 and SAMR1 mouse homogenates (30 μg of protein) were separated by electrophoresis on polyacrylamide gels (7.5%). Membranes were probed overnight at 4 °C. The primary antibodies used are described in Table 1. Secondary antibodies conjugated to IRDye 800CW or IRDye 680CW (LI-COR Biosciences, Lincoln, NE) were diluted to 1:5000 in TBS with 5% BSA. Bands were visualized using the Odyssey Infrared Imaging System (LI-COR Biosciences, Lincoln, NE). β-Actin (mouse monoclonal, 1:10000, Sigma-Aldrich) was used as an internal control.

Statistical Analysis

Data were analyzed by SPSS for Windows 15.0, and normality was checked by Shapiro–Wilk's test ($p < 0.05$). In the acquisition phase of the Morris water maze, overall treatment effects were examined by two-way repeated measures ANOVA (genotype × trial). Differences between trials within groups were analyzed using a factorial ANOVA with replicates. Data in the retention phase were analyzed with one-way ANOVA followed by Tukey's post hoc test. Neurochemical data were analyzed by one-way ANOVA. Correlation between variables was investigated by Pearson's or Spearman's correlation coefficients, depending upon the normality of variables.

Results

Effects on Cognitive Tests

Locomotor activity was measured as velocity in open field. No differences between groups were found (one-way

Table 1 List of primary antibodies used for western blot studies

Protein	Primary antibody dilution	Molecular weight	Company
pJNK (Thr183/Tyr185)	1:1000	46, 54 kDa	Cell Signaling Technology, MA, USA
JNK	1:1000	46, 54 kDa	Cell Signaling Technology, MA, USA
pc-jun (Ser73)	1:500	48 kDa	Cell Signaling Technology, MA, USA
pIRE1 (Ser724)	1:1000	110 kDa	Abcam, Cambridge, MA, USA
pTau AT8 (Ser202/Tyr205)	1:1000	79 kDa	Thermo Fisher Scientific, MA, USA
pTau PHF-1 (Ser396/Ser404)	1:1000	79 kDa	Donated by Peter Davies
Tau	1:1000	45 to 60 kDa	Sigma-Aldrich, St. Louis, MO, USA
β-Actin	1:10000	42 kDa	Sigma-Aldrich, St. Louis, MO, USA

ANOVA; $F_{(4,41)} = 1.963$; $p = 0.122$), indicating that purported behavioral performance differences between groups are not associated to locomotor activity alterations (Fig. 2a). This assumption is further supported by the fact that there was no difference between groups in the discrimination index in the sample trial in the novel object recognition test (NORT) (one-way ANOVA, $F_{(4,41)} = 2.006$; $p = 0.116$, Fig. 2b).

The NORT test showed that recognition memory was significantly impaired in SAMP8 mice, as shown by a significantly decreased discrimination index (one-way ANOVA; $F_{(4,41)} = 5.472$, $p < 0.01$; Tukey's $p < 0.05$ vs. SAMR1 saline), which was reversed by MaR1 and DHA (Fig. 2b).

In the acquisition phase of the test (Fig. 2c), significant differences between strains were found (repeated measurements ANOVA; $F_{(4,37)} = 22.20$; $p < 0.001$) and SAMP8 mice showed higher escape latency compared to SAMR1 mice, indicating a cognitive impairment. None of the treatments reversed this cognitive impairment. In the retention phase, no significant differences were found among groups in the first probe trial (day 3 of the MWM task) (one-way ANOVA; $F_{(4,41)} = 0.219$; $p = 0.926$). However, in the second probe trial (one-way ANOVA, $F_{(4,41)} = 5.150$, $p < 0.01$) and in the last probe trial (one-way ANOVA, $F_{(4,41)} = 6.146$, $p < 0.001$), the SAMP8 saline group showed memory deficit that only DHA treatment was able to reverse (Fig. 2d).

Involvement of JNK Activation on the Effects of DHA

pJNK levels were significantly increased in the hippocampus of SAMP8 mice compared to SAMR1 mice, and only DHA treatment was able to significantly reverse the increased pJNK levels (one-way ANOVA, $F_{(4,41)} = 5.501$, $p < 0.01$; Tukey's $p < 0.05$; Fig. 3a). Interestingly, there was a significant and negative correlation between pJNK levels and cognitive decline, i.e., the reduction of pJNK levels in SAMP8 hippocampus and improvement in cognitive function in 24-h interval NORT (Spearman's rho = − 0.601, $p < 0.01$, $n = 40$) and last day of retention probe in MWM (Spearman's rho = − 0.560, $p < 0.01$, $n = 40$). Similar results were found when measuring c-Jun, the main JNK substrate, and DHA was the only treatment able to reverse the increase of p-c-Jun levels observed in SAMP8 strain of mice (one-way ANOVA, $F_{(4,41)} = 2.639$, $p < 0.05$; Tukey's $p < 0.05$; Fig. 3b).

The involvement of endoplasmic reticulum stress (ERS) in the mechanism by which DHA inhibits JNK has been checked by measuring pIRE1α. Significant increase of pIRE1α was observed in SAMP8 mice compared to the SAMR1 group which was not affected by any of the treatments (one-way ANOVA, $F_{(4,41)} = 5.917$, $p < 0.001$; Tukey's $p < 0.05$; Fig. 3c).

As activated JNK could lead to an increase in tau phosphorylation, the AT8 and PHF-1 antibodies were used to

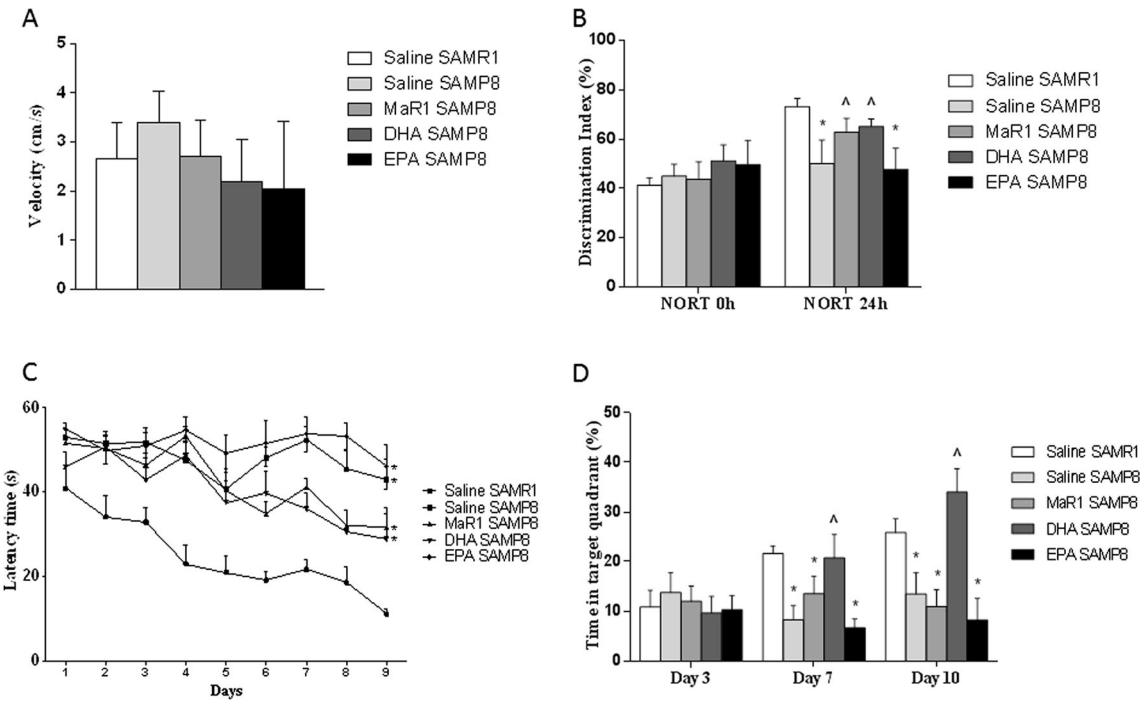

Fig. 2 Behavioral test. Differential effects of ω-3 PUFAs (DHA and EPA) and MaR1 (a DHA-derived SPM) on locomotor activity (**a**), novel object recognition test (NORT, **b**), and Morris water maze (acquisition phase, **c**, and retention phase, **d**). In **a**, average velocity in the open field. In **b**, sample phase and 24-h interval of NORT are represented. Data are presented as discrimination index (percentage of time exploring the new object/total exploration time). *vs. SAMR1 saline, ^vs. SAMP8 saline; Tukey's test, $p < 0.05$, one-way ANOVA. In **c**, *vs. SAMR1 saline; repeated measures two-way ANOVA; Dunnett test, $p < 0.05$. In **d**, *vs. SAMR1 saline, ^vs. SAMP8 saline; Tukey's test, $p < 0.05$; one-way ANOVA. DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; MaR1: maresin 1. Data are presented as mean ± SEM ($n = 8$ per group)

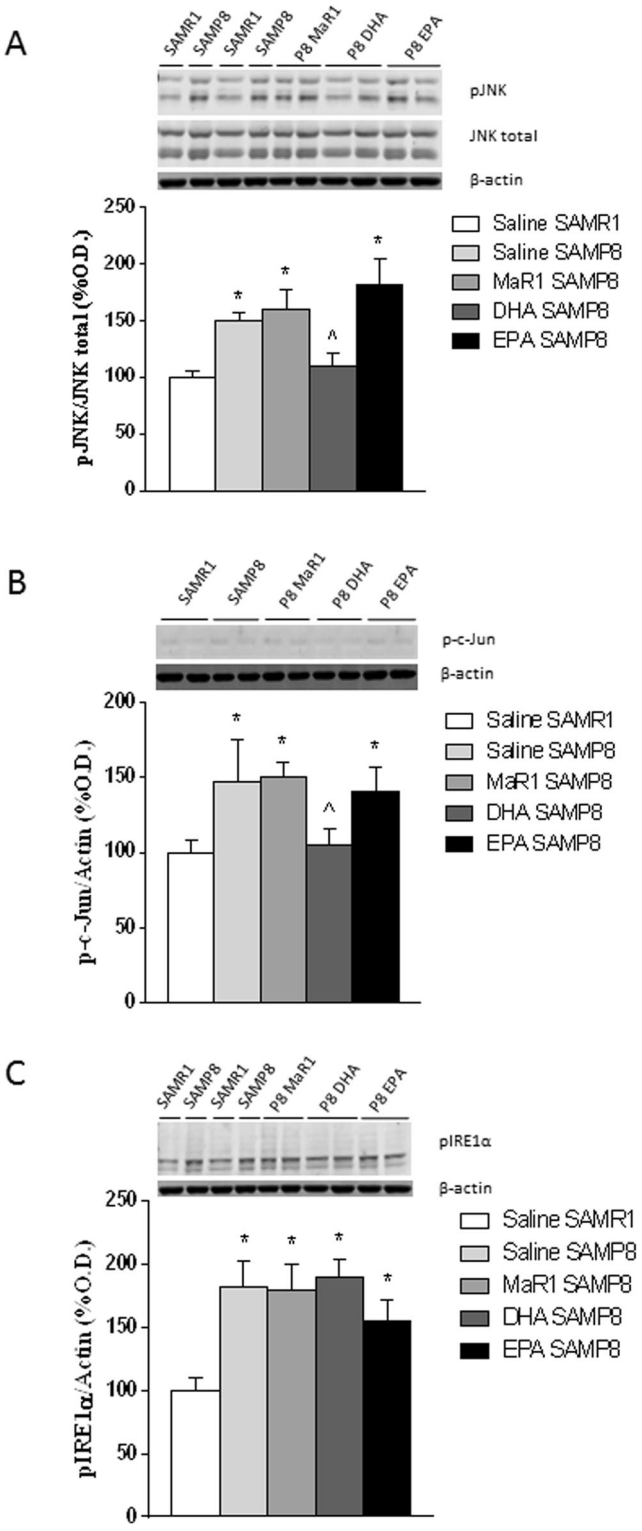

Fig. 3 Biochemical analysis. Differential effects of ω-3 PUFAs (DHA and EPA) and MaR1 (a DHA-derived SPM) on JNK immunoblotting (**a**), activated c-Jun immunoblotting (**b**), and activated IRE1α immunoblotting (**c**). A representative picture of western blot is shown. Results are expressed as % optical density (O.D.) of correspondent controls (SAMR1 mice) and normalized to total levels of protein. *vs. SAMR1 saline, ^vs. SAMP8 saline; one-way ANOVA, Tukey $p < 0.05$

measure pTau. A significant increase in AT8 levels was observed in SAMP8 animals when compared to control SAMR1 strain. However, this effect was not reversed either by DHA treatment nor by any other treatment (one-way ANOVA, $F_{(4,41)} = 3.131$, $p < 0.05$; Tukey's $p < 0.05$; Fig. 4a). On the other hand, PHF-1 expression was significantly increased in SAMP8 mice, and this effect was completely reversed by DHA treatment (one-way ANOVA, $F_{(4,41)} = 5.168$, $p < 0.01$; Tukey's $p < 0.05$; Fig. 4b).

Discussion

The beneficial effects of DHA have been demonstrated in AD experimental models, but the therapeutic effect in clinical trials is controversial [28, 29]. Indeed, a study performed by Quinn et al. [30] in which DHA was compared with placebo did not slow the rate of cognitive and functional decline in individuals with mild to moderate AD. However, because part of the rationale for the trial was epidemiological evidence that DHA use before disease onset modifies the risk of AD, it remains possible that an intervention with DHA might be more effective if initiated earlier in the course of the disease in patients who do not have overt dementia. Although the analysis in that study of the subpopulation of participants with baseline Mini Mental State Examination (MMSE) scores of greater than 20 failed to provide support for this hypothesis, other studies have reported post hoc analyses showing positive omega-3 fatty acid treatment effects in less impaired individuals, with MMSE scores of 27 through 30 [31]. However, clinical trials of ω-3 fatty acids in healthy elderly individuals have failed to show cognitive benefits within 6 months (Mental Health in Elderly Maintained with Omega-3 [MEMO] study, $n = 302$) [32] to 2 years (Older People and n-3 Long-Chain Polyunsaturated Fatty Acids [OPAL] study, $n = 867$) [33] of treatment. Because these healthy elderly individuals do not experience significant cognitive decline in this time frame, the absence of a cognitive effect does not exclude the possibility of a neuroprotective effect of DHA in individuals at risk of decline. Individuals intermediate between healthy aging and dementia, such as those with mild cognitive impairment, which might derive benefit from DHA supplementation, although further study will be necessary to test this hypothesis.

Moreover, given increasing evidence that neurolipids play important signal modulatory and structural roles in the brain, the mail goal of our study was to investigate the functions and mechanism of these bioactive lipids. In this line, data obtained in this work is important to understand that cognitive improvement is induced only when these compounds are able to inhibit pJNK, suggesting the beneficial effects that could offer any drug targeting JNK for the treatment of AD.

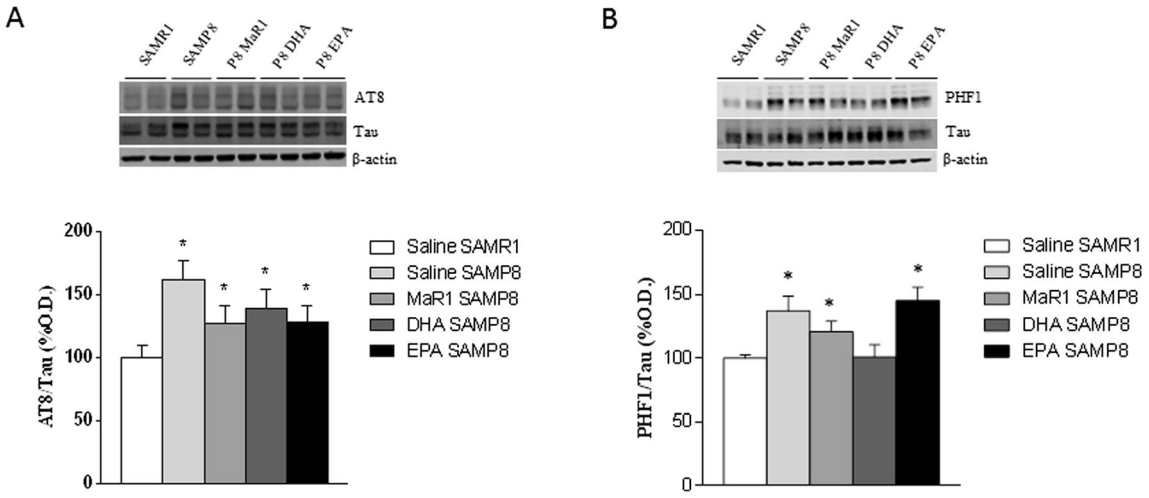

Fig. 4 Differential effects of ω-3 PUFAs (DHA and EPA) and MaR1 (a DHA-derived SPM) on phosphorylated tau levels using the AT8 antibody (**a**), or PHF-1 antibody (**b**). A representative picture of western blot is shown. Results are expressed as % optical density (O.D.) of correspondent controls (SAMR1 mice) and normalized to total levels of protein. *vs. SAMR1 saline, one-way ANOVA, Tukey $p < 0.05$

In the present work, the SAMP8 mouse model has been chosen. The causes of aging remain unknown, but they are probably intimately linked to a multifactorial process that affects cell networks to varying degrees. Although a growing number of aging and AD animal models are available, a more comprehensive and physiological mouse model is required. In this context, the senescence-accelerated mouse prone 8 (SAMP8) has a number of advantages, since its rapid physiological senescence means that it has about half the normal lifespan of a rodent. Indeed, this mouse model has drawn attention in gerontological research of dementia since it manifests irreversible senescence and share similar characteristics with aged humans, such as a reduced lifespan, lordosis, hair loss, and reduced physical activity [34, 35], altered emotions and abnormality of the circadian rhythm [36], elevated biomarkers of oxidative stress [37–39], neuronal cell loss [40], inflammation [41, 42], mitochondrial dysfunction [43], impaired antioxidant defense [37, 44], and blood–brain barrier dysfunction [45, 46]. However, the main phenotypic characteristic is the progressive cognitive decline and the neurodegenerative changes that have led to the proposal of the SAMP8 mouse as a good model of neurodegeneration [46]. In addition, according to data gathered over the last 5 years, some of its behavioral traits and histopathology resemble AD human dementia. SAMP8 has remarkable pathological similarities to AD and may prove to be an excellent model for acquiring more in-depth knowledge of the age-related neurodegenerative processes behind brain senescence and AD in particular. Therefore, there is increasing evidence that SAMP8 is an acceptable model for sporadic Alzheimer's disease (AD) showing several advantages over the gene-modified models as it may represent the complex multifactorial nature of AD [17, 47–50].

Even though current evidence suggests that consumption of ω-3 PUFA, particularly DHA, may enhance cognitive performance, there is a lack of consensus on the benefits of the use of ω-3 PUFA supplementations on cognition in experimental mouse models [51–53]. Previous studies using transgenic models have reported the beneficial impact of diet enriched in ω-3 PUFAs on cognition [54–56]. Similarly, SAMP8 mice fed with ω-3 PUFA-enriched fish oil during 2 months demonstrated memory improvement in the passive avoidance cognitive test. Specifically, these beneficial effects were attributed to DHA and not to other dietary fatty acids (EPA, DPA, or ALA) since DHA was the only fatty acid that appeared increased in the brain lipid composition of these animals [57].

In our hands, only DHA treatment was able to reverse cognitive impairments in SAMP8 mice while EPA was ineffective. Notably, and supporting our data, in a clinical randomized trial it has been shown that only DHA and not EPA is able to prevent AD development in the elderly population [58]. By contrast to the present results, it has already been described that EPA-enriched diet during 3 months restored cognitive function and SAMP8 mice [59]. However, in that study younger animals (7 vs. 10 months) and longer treatments (3 months vs. 20 days) were used. Our study has also uncovered differential effects between DHA and its derivative MaR1. While both were able to reverse the decreased discrimination index observed in SAMP8 mice (with MaR1 acting at thousands of times lower dose), only DHA ameliorated the cognitive impairments in SAMP8 animals observed in MWM. It is possible to speculate that maybe a higher dose and/or longer treatment would be essential to detect a positive effect of MaR1 or EPA.

Different mechanisms have been proposed as responsible for the beneficial effects of ω-3 PUFAs. Among them, ω-3

PUFAs have been proposed as natural JNK inhibitors [26]. JNK has already been involved in the cognitive deficits in the SAMP8 mouse model as the administration of DJNKi, a synthetic JNK inhibitor, ameliorated the cognitive deficits shown by SAMP8 mice in the MWM [18]. In parallel to the results obtained in the cognitive tests, increased pJNK levels in the hippocampus of SAMP8 mice have been presently found which were reversed only by DHA treatment. Interestingly, higher pJNK levels correlate negatively with performance in the cognitive test, further supporting the implication of this kinase in cognitive status. On the other hand, Zhang et al. [60] showed that EPA induces apoptosis in HepG2 cells through activation of JNK, further supporting the notion that inhibition of JNK could be a selective effect of DHA.

It has been suggested that the accumulation of misfolded proteins, such as Aβ, initiates IRE1α activation and subsequent unfolded protein response (UPR) which is the adaptive response to ERS. The effect of the IRE1 pathway results in JNK activation [61]. According to a recent study, elevation in ERS markers in the SAMP8 model has been found, assessed as higher IRE1α phosphorylation [62]. However, as DHA treatment was not able to reverse this increased IRE1α phosphorylation, it is proposed that DHA is a direct JNK inhibitor, not affecting upstream ERS-associated mechanisms of JNK activation. In the same line, Torres et al. [63] did not find significant changes in pIRE1α levels in SH-SY5Y cells after DHA derivate metabolite treatment.

Once activated, JNK may act at the cytosolic level, but it may also perform a translocation to the nucleus with the aim to perform its kinase activity in this cell compartment [64]. JNK acts on transcription factors such as ATF2, FOXO3, FOXO4, or Stat3, although c-Jun has been described as the first and main substrate of JNK [65]. Previous studies have shown that JNK inhibitors succeed in decreasing c-Jun phosphorylation in the SAMP8 model or that induced by cellular stress [66, 67]. Therefore, it is plausible that DHA, by modulating JNK activation, could regulate the transcription of many target genes involved in differentiation, growth, or apoptosis, altering the balance between survival and neuronal death, suggesting the mechanism of action through which DHA can exert its beneficial effects on cognition.

Increased phosphorylation of JNK could lead to hyperphosphorylation of tau, contributing therefore to AD pathology. Tau can be phosphorylated at multiple sites by several kinases, but in particular, JNK is known to phosphorylate Tau at Ser202/Thr205 and Ser422 and these two sites are

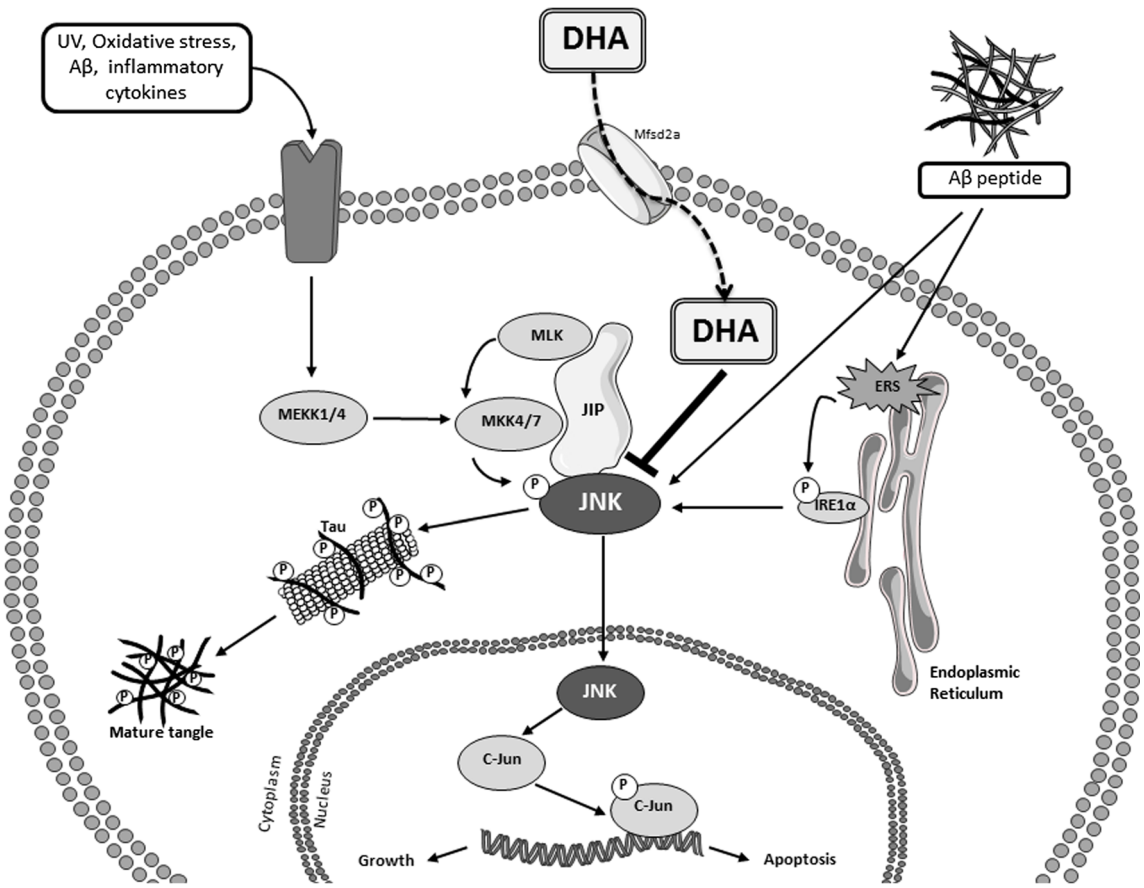

Fig. 5 Proposed mechanisms for the beneficial effects of DHA treatment in the SAMP8 model. DHA acts inhibiting JNK phosphorylation and, in consequence, decreasing c-Jun activation. ERS: endoplasmic reticulum stress. JIP: JNK interacting protein

strictly associated with AD pathogenesis. Phosphorylation at Ser202/Thr205 residues of tau, recognized by the AT8 antibody, is displayed at the early stage of the disease [27, 68]. It has been previously shown that brains of SAMP8 strains present hyperphosphorylation of tau protein [19, 69]. However, although our data reveals that SAMP8 mice presented the expected increased levels of AT8 immunoreactivity, DHA EPA or MaR1 was not able to reverse this effect. Consequently, it was checked whether other tau phosphorylation (Ser396/Ser404 or PHF-1) could be restored after DHA-induced JNK inhibition in SAMP8 mice. Indeed, the JNK inhibitor SP600125 significantly inhibits tau phosphorylation at the PHF-1 site in SH-SY5Y cells [70]. Therefore, from the present study, it could be suggested that the beneficial effects of JNK inhibition by DHA target tau hyperphosphorylation in the Ser422 epitope (PHF-1).

Concluding Remarks

In summary, the JNK cascade could be understood as an axis in the molecular development of AD and other neurodegenerative pathologies. Its implication at different stages of the disease makes clear its importance within neuronal dysregulation, metabolic disruption, and development of pathological structures. In the present work, it has been shown that the beneficial actions of DHA could be related to JNK inhibition. As depicted in Fig. 5, DHA could enter the brain through the Mfsd2a transporter [71] and it exerts its action directly inhibiting JNK phosphorylation and, as consequence, decreasing p-c-Jun levels which promotes survival in neurons and decreasing tau hyperphosphorylation.

Altogether, DHA could represent a new approach for the treatment of AD through JNK inhibition. Supporting this suggestion, a decrease in DHA content in both humans and SAMP8 model associated to cognitive decline has been found [39, 72]. Thanks to its lipidic nature, DHA is able to cross the blood–brain barrier and to disseminate into the neuron [57], allowing JNK inhibition. However, it has also been described that activation of the G protein-coupled receptor 120 (GPR120) by omega 3 PUFAs specifically inhibits transforming growth factor-beta-activated kinase (TAK) activation, which in turn would lead to a decreased JNK activation [73]. Nevertheless, further investigation is needed in order to better elucidate the mechanism of action of DHA and to determine the real extension of the rationale behind proposing DHA inhibition of JNK as specific treatments of AD.

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Compliance with Ethical Standards

Experimental procedures were conducted in accordance with the European and Spanish regulations (2003/65/EC; 1201/2005) for the care and use of laboratory animals and approved by the Ethical Committee of University of Navarra (068-11)

Conflict of Interest The authors declare that they have no conflict of interest.

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