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REVIEW ARTICLE

Functional and Structural Benefits Induced by Omega-3 Polyunsaturated Fatty Acids During Aging

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Abstract: ***Background*:** Omega-3 polyunsaturated fatty acids (n-3 PUFA) are structural components of the brain and are indispensable for neuronal membrane synthesis. Along with decline in cognition, decreased synaptic density and neuronal loss, normal aging is accompanied by a reduction in n-3 PUFA concentration in the brain in both humans and rodents. Recently, many clinical and experimental studies have demonstrated the importance of n-3 PUFA in counteracting neurodegeneration and age-related dysfunctions.

***Methods*:** This review will focus on the neuroprotective effects of n-3 PUFA on cognitive impairment, neuroinflammation and neurodegeneration during normal aging. Multiple pathways of n-3 PUFA preventive action will be examined.

***Results*:** Namely, n-3 PUFA have been shown to increase the levels of several signaling factors involved in synaptic plasticity, thus leading to the increase of dendritic spines and synapses as well as the enhancement of hippocampal neurogenesis even at old age. In elderly subjects n-3 PUFA exert anti-inflammatory effects associated with improved cognitive functions. Interestingly, growing evidence highlights n-3 PUFA efficacy in preventing the loss of both gray and white matter volume and integrity.

***Conclusion*:** This review shows that n-3 PUFA are essential for a successful aging and appear as ideal cognitive enhancers to be implemented in nutritional interventions for the promotion of healthy aging.

Keywords: Aging, cognitive decline, morphometry, neuroinflammation, neuroplasticity, omega 3 fatty acids.

1. INTRODUCTION

The brain is able to plastically change in response to environmental stimulations [1]. In particular, among the highly environment-responsive structures of the brain is the hippocampus, a region involved in modulating learning, memory and mood [2-4]. The process of long-term potentiation (LTP) is the principal mechanism underlying learning and memory processes in the mammalian brain [5, 6]. The hippocampus, especially in the dentate gyrus (DG), has also the capability of generating newborn neurons in adult individuals due to the process of adult hippocampal neurogenesis [4]. This process is essential for cognitive and emotional processes and its disruption may lead to learning deficits and symptoms of anxiety and depression [7-9]. The generation, migration, and integration of newborn hippocampal neurons into preexisting circuits depend on complex signaling within the neurogenic niche [10]. Neural stem cells in the DG are close to blood vessels and this proximity facilitates the delivery of biochemical stimuli (such as food-derived components or age-related inflammatory markers) from the systemic milieu to the DG [11, 12].

Environmental factors have been shown to alter also other markers of brain plasticity, such as synaptogenesis, dendritic arborization, and spinogenesis [13-16], which in turn provide the biological substrate for adaptation to different environmental stimulations, such as stress or physical exercise [17-19].

Diet is one of the principal environmental factors impacting brain plasticity [20]. Although there is much to be clarified about the specific molecular mechanisms through which dietary components, such as omega-3 polyunsaturated fatty acids (n-3 PUFA), influence brain plasticity, a growing literature supports the idea that diet modulates brain structure and function, exerting its influence throughout the entire lifespan. Recently, the constant growth of the elderly population worldwide has amplified the interest in the prevention and improvement of age-related cognitive decline. In fact, cognitive decline is an hallmark not only of pathological aging, as occurring in Alzheimer's disease (AD) and vascular dementia, but also of non-pathological aging processes [21, 22]. Age-related cognitive decline is due to a progressive impairment of the underlying brain cell

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processes, as neural membrane fluidity reduction, neuroinflammation, oxidative stress, reduced synaptic plasticity and neurogenesis. As a whole these alterations may lead to a consequent and irreversible neuronal loss of gray matter (GM) and white matter (WM) volume [23-25]. Therefore, the identification of modifiable environmental factors that could slow down cognitive decline preceding dementia or AD, such as nutritional factors, is a research priority [26-29]. In particular, nutritional research indicates that Western diets do not provide the aged brain with an optimal supply of n-3 PUFA [30]. Furthermore, aging is associated to decreased cerebral n-3 PUFA levels due to reduced absorption, n-3 PUFA capacity to cross the blood-brain barrier, and capacity to convert shorter chained fatty acids into longer fatty acids [31].

n-3 PUFA are classified as essential since their levels depend on dietary intake. Although fish is the major source of n-3 PUFA, these nutrients are also contained in other foods, such as shellfish, seafood, seaweed, flax, soy, rapeseeds, nuts and certain animal products (such as meat and eggs) dependent on the animal's diet [32, 138]. As neuronal membrane major components, they exhibit a wide range of regulatory functions [32]. Up-to-date, although somewhat conflicting, a growing number of animal and human studies has indicated that n-3 PUFA may exert beneficial effects on the aging brain [32-37]. Namely, in rodents n-3 PUFA deficiency have been associated with memory deficits and hippocampal plasticity reduction, while n-3 PUFA supplementation may improve learning and memory abilities, and neurogenic and synaptogenic functions [27, 32, 33, 36, 38]. As for human studies, several longitudinal studies based on the assessment of regular consumption of fish [39] or on blood biomarkers of n-3 PUFA have suggested the potential preventive role of n-3 PUFA against age-related cognitive decline [40-45]. Recently in human studies using morphological MRI-based techniques a putative neuro-protective effect of n-3 PUFA in aging is emerging, with positive associations between peripheral n-3 PUFA levels and more favorable GM and WM volumetric measures [46-53]. However, interventional studies of supplementary n-3 PUFA showed contradictory results on the relationship between n-3 PUFA administration and cognitive performances in older adults [54-59].

This review will primarily examine neuroprotection exerted by n-3 PUFA on cognitive impairment and markers of reduced brain plasticity and neurodegeneration during non pathological aging. Multiple pathways of n-3 PUFA preventive action will be taken into account. In particular, n-3 PUFA have been shown to increase the levels of several signaling factors involved in synaptic function, thus leading to the increase of dendritic spines and synapses as well as to the enhancement of hippocampal neurogenesis even at old age. Attention will be also paid to the n-3 PUFA anti-inflammatory effects exerted by reducing neuroinflammation and oxidative stress markers in elderly subjects. Finally, growing evidence highlights n-3 PUFA efficacy in preventing age-related loss of GM and WM volume and integrity in both animal and human studies.

2. OMEGA-3 FATTY ACIDS AND SYNAPTIC PLASTICITY DURING AGING

n-3 PUFA have been observed to reverse age-related synaptic plasticity changes [20, 32, 60, 61]. For instance, n-3 PUFA supplementation for 12 weeks in aged rats (24 months old) reverses age-related decrease in levels of docosahexaenoic acid (DHA), the most abundant n-3 PUFA in the brain, and of the GluR2 and NR2B subunits of respectively N-methyl-D-aspartate (NMDA) receptors and the a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors in the hippocampus [62]. Signaling through these receptors plays an important role in synaptic plasticity underlying learning and memory, such as LTP. On the contrary, n-3 PUFA deficiency worsens the age-induced degradation of glutamatergic transmission in the CA1 of the hippocampus [63].

Interestingly, dietary enrichment of aged rodents with n-3 PUFA has been shown to have positive effects on aged-related impairments in LTP. For example, n-3 PUFA supplementation for 8 weeks reverses age-related disruption of depolarization-induced glutamate release and LTP in aged rats (22 months old) supplemented with DHA or eicosapentaenoic acid (EPA) [64, 65]. Moreover, EPA and its metabolite docosapentaenoic acid (DPA) have been demonstrated to be equally able to reverse age-related impairment in spatial learning and LTP [66].

Age-related learning and memory impairments have been related to the strong decrease in the production of new neurons due to stem-cell-intrinsic factors that change within the aging stem-cell pool and systemic and microenvironmental factors modulating the neurogenic niche [67, 68]. Notably, n-3 PUFA supplementation has a beneficial effect on adult neurogenesis [69]. Age-related decreases in neurogenesis as well as in transcription factors involved in learning and memory, such as retinoic acid receptors, retinoid X receptors, and peroxisome proliferator-activated receptors, are even reversed by EPA/DHA-enriched diets for 12 weeks in 25-26 months old rats [70]. n-3 PUFA neurogenic and synaptogenic properties are reported also by Robson *et al*. [71] which demonstrate that EPA and DHA exert a neurite-enhancing action on rat dorsal root ganglion cells even at old stage (18-20 months). More recently, it has been demonstrated that DHA may increase newborn neurons production and/or survival in rats fed a DHA supplemented diet from 2 to 18 months [72]. In aged mice (19 months old) a 2-month EPA+DHA+DPA supplementation ameliorated hippocampal-dependent mnesic functions in the context of an enhanced hippocampal cellular plasticity (increased neurogenesis and dendritic arborization of newborn neurons, neuronal density) and reduced neurodegeneration (decreased apoptosis and lipofuscin accumulation) [73]. This n-3 PUFA neuro-protective action exerted on hippocampal neuroplasticity was further associated to the increase of metabolic correlates, such as brain DHA and EPA levels, and blood Acetyl-L-Carnitine (ALC) concentrations [73]. Notably, additive effects of ALC and PUFA supplementation in reducing age-related retinal degeneration [74] and brain damages caused by oxidative stress [75] have been reported. Furthermore,

n-3 PUFA may increase the signaling factors involved in neurogenesis, such as BDNF, CREB, or CaMKII [27, 76, 77], and exert their bioactivity even through syntaxin 3 that mediates membrane expansion at the growth cone giving rise to neurite outgrowth [78].

Furthermore, age-related decline in learning and memory is accompanied by a decrease in c-Fos expression reflecting a decreased neuronal response to extracellular signals triggered during action potentials [79]. DHA and EPA enriched diet for 2 months has been shown to restore age-related spatial memory deficits and increase hippocampal c-Fos expression in 22-month-old mice [80].

The decrease in hippocampal spine density seen either in aged rats and humans is another morphological mechanism underlying memory impairments that characterizes normal aging [81-83]. It has been demonstrated that in adult gerbils DHA oral supplementation for 4 weeks results in an increase (>30%) in the number of hippocampal dendritic spines accompanied by a parallel increase in membrane phosphatides and in pre- and post-synaptic proteins [84]. Unfortunately, no studies have yet addressed the role of n-3 PUFA on spine density during aging.

Overall the discussed studies indicate potential mechanisms through which n-3 PUFA help in the maintenance of learning and memory performances by preventing age-related synaptic plasticity changes. However, there is still little direct evidence of how n-3 PUFA affects synaptic structure in aged individuals.

3. OMEGA-3 FATTY ACIDS AND NEURO-INFLAMMATION DURING AGING

The aging brain is particularly apt to inflammatory and oxidative alterations, which may underlie decreased learning and memory as well as increased risk of developing neuropsychatric disorders in elderly subjects [60, 85]. This process of gradual deterioration of the immune system brought on by natural age advancement is referred to as immunosenescence and is accompanied by an increase in proinflammatory cytokines production [86, 87].

It has been demonstrated that dietary intake of n-3 PUFA is strictly linked to inflammation [88]. In fact, excessive levels of omega-6 (n-6) PUFA relative to n-3 PUFA is correlated with inflammation, arthritis, and cancer [88-91]. Modern Western diets typically have an excessive n-6:n-3 PUFA ratio of 10/1 to 20-25/1 with a consequent over-production of arachidonic acid (AA) derivatives favoring the emergence of a pro-inflammatory status in the aging brain [33, 92]. Epidemiological, observational and preclinical studies have demonstrated that both higher plasma levels of n-3 PUFA and lower plasma n-6:n-3 PUFA ratio are associated with a reduced proiflammatory cytokine production [93-96]. Interestingly, also telomere length, which is regulated by exposure to proinflammatory cytokines and oxidative stress, increases with decreasing n-6:n-3 ratio and increasing n-3 PUFA blood levels during aging [97-99].

Many studies have shown that the positive effects of n-3 PUFA upon age-related cognitive decline are linked to their anti-inflammatory properties [20, 100]. For example, age-related increase of neuroinflammation markers, such as interferon-γ and interleukin-1β, is overcome by EPA supplementation and associated to restored LTP in aged rats (22 months old) [101]. Additionally, a 2-month EPA/DHA treatment increases n-3 PUFA levels in the brain, prevents cytokines expression and astrocytes morphology changes in the hippocampus, and restored spatial memory deficits in aged mice (22 months old) [80]. Similarly, EPA enriched diet prevents the age-related increase in cortical and hippocampal IL-1β and IL-4 in aged rats (22 months old) [102, 103].

Astrogliosis is considered a hallmark of brain aging found in the brain of aged rodents [104-106], primates [107] and humans [108]. The astrogliosis is associated with microglial activation and a low-grade inflammatory state occurring in the aging brain [33]. Many studies have reported a decrease in high affinity glutamate transport and in the expression of glial glutamate transporters in the brain of aged rodents [63, 109]. Astrocytes are a target cell for the effects of n-3 PUFA in the brain given the high concentration of DHA in their membrane phospholipids. Notably, n-3 PUFA deficiency worsens age-related hippocampal astrocytosis and promotes neuroinflammation [63, 110]. On the contrary, the diffuse astrocytosis as well as microglial activation occurring with age is markedly reduced in n-3 PUFA supplemented aged rodents [73, 101, 111]. DPA and EPA are reported to reduce age-related spatial memory decline as well as microglial activation [66]. It has been advanced that the production of protective docosanoids (DHA derivatives) may regulate microglial activation, thus facilitating glial reparative activation in response to the disruption of synaptic glutamate homeostasis [110, 112]. Furthermore, a recently identified DHA-derived messenger, neuroprotectin D1 (NPD1), has been demonstrated to be involved in regulating brain cell survival and repair through neurotrophic, anti-apoptotic and anti-inflammatory signaling [113]. NPD1 also prevents β-amyloid formation, protects synapses and reduces the number of activated microglial cells [114].

A progressive accumulation of oxidative damage to cellular molecules is a primary mechanism involved in most senescence-associated modifications [115]. Oxidative damage occurs when free radicals produced within an organism are not completely destroyed by the appropriate endogenous defense systems. Because lipids are a major component of neuronal membranes [116], lipid peroxidation might play an important role in initiating and/or mediating some aspects of the brain aging process. It has been widely demonstrated that there is an age-associated increase in the steady-state concentrations of lipid peroxidation products [117-119]. However, dietary n-3 PUFA may counteract aging brain modifications by promoting membrane homeostasis and this effect is associated with a reduced cognitive decline [120]. In fact, DHA administration for 10 weeks in previously n-3 PUFA deficient aged rats (25 months old) enhances mnesic performances along with a reduction in hippocampal lipid peroxidation [121]. Similarly, DPA and EPA ameliorate spatial memory performances and reduce oxidative stress [66]. Moreover, n-3 PUFA effectively improve the reference memory-related learning ability associated with increased brain DHA-derived docosanoids

in aged rats [122]. As for human studies it has been demonstrated that erythrocyte membranes derived from nonagenarian offspring display a reduced lipid peroxidation and increased membrane integrity compared to that of the general population [123]. Inverse correlations have been found between DHA and EPA intake and plasma lipid hydroperoxide levels among mild cognitive impairment (MCI) patients [124]. Furthermore, EPA and DHA reduce oxidative stress in patients affected by hypertension, type 2 diabetes and/or hypertriglyceridemia, pathological conditions linked with aging [125, 126]. Finally, in middle-aged subjects both n-3 and n-6 PUFA are inversely associated with concentrations of plasma C-reactive protein, an index of oxidative stress [127].

Taken together the discussed studies indicate that n-3 PUFA may help in the maintenance of learning and memory performance by reversing age-related inflammation and oxidative stress changes, further reinforcing the idea that increased n-3 PUFA intake may provide protection to the brain of aged subjects.

4. OMEGA-3 FATTY ACIDS AND BRAIN VOLUME INTEGRITY DURING AGING

Reduced brain volume is an essential element of MCI and AD pathology, and brain atrophy is frequently observed during aging before symptomatic impairment [128]. Being one of the main component of synaptic membranes, n-3 PUFA have an important role in maintaining brain structure and function during aging. Many studies highlighted n-3 PUFA efficacy in preventing hippocampal neuronal loss in AD-like neurodegenerative models [32, 33, 36, 61]. In addition, the few human studies addressing the relations between n-3 PUFA intake and brain volumes converge on detrimental effects of n-3 PUFA deficiency and beneficial effects of their presence. Namely, in mood disorders the n-3 PUFA deficiency is associated with reduction of the GM volume in the prefrontal cortex inducing in turn alterations in cortico-limbic projections [129]. Conversely, in healthy subjects positive associations between n-3 PUFA intake and GM volumes in hippocampus, amygdala and anterior cingulate cortex were reported [130].

As for human aging studies, many correlational studies have shown positive associations between n-3 PUFA and GM and WM volumes in elderly subjects [46-53]. To the best of our knowledge only one interventional study by Witte *et al*. [58] reported n-3 PUFA beneficial effects on WM microstructural integrity and GM volume in frontal, temporal, parietal, and limbic areas associated with improvements in executive functions. The lack of improvements in memory performances following n-3 PUFA administration in this study [58] is at odds with previous studies in elderly [34, 59], even if other studies fail to reveal any effect of n-3 PUFA supplementation both on mnesic and executive functions [54-57]. Human interventional studies addressing n-3 PUFA effects on cognitive decline and brain volumes have even not provided conclusive information about emotional correlates, as depression levels. In this regard recent interventional studies in mice demonstrated that n-3 PUFA supplementation at old age is able to counteract atrophy in specific brain regions linked either to age-dependent cognitive decline and mood disturbances (such as hippocampus, medial prefrontal, orbitofrontal and restrosplenial cortices) [73, 131]. Interestingly, the ameliorated brain volume patterns observed in n-3 PUFA supplemented aged mice were associated not only to better mnesic and cognitive performances, but also to beneficial effects on emotional behaviors with increase in active coping responses [131]. These neuroimaging findings are in line with human and animal studies demonstrating that increased dietary intake of n-3 PUFA is able to ameliorate depression symptoms [50, 132-134].

The converging evidence on n-3 PUFA anti-depressant action at old age is important since mood disorders, such as depression, can be linked to aging, metabolic disorders and dementia [132], and are often associated with age-related atrophy in the hippocampus and the prefrontal cortex [127, 135, 136]. Despite the mechanisms of n-3 PUFA anti-depressant action are not yet clarified, it has been reported that DHA deficiency is associated with dysfunctions of neuronal membrane stability and serotonin, norepinephrine and dopamine neurotransmission [137]. In addition, EPA is important in balancing the immune function and physical health by reducing membrane AA and prostaglandin E 2 synthesis [137]. These dietary n-3 PUFA deficiencies may be linked to the aetiology of mood disorders.

Although dietary factors are important modifiers of brain plasticity and can have an impact on central nervous system pathophysiology, a growing body of evidence indicates that nutrients can complement the beneficial effects of exercise on neural damage [138]. A recent pilot study provides preliminary evidence that n-3 PUFA intake combined with aerobic exercise and cognitive stimulation is able to prevent atrophy in AD-related brain regions in MCI patients, promising findings that deserve validation in future interventional trials [139].

Overall, the discussed studies account for a protective function of dietary n-3 PUFA on brain atrophy during aging, thus corroborating not only the emerging view of n-3 PUFA as pro-cognitive nutritional agents, but also underlining their efficacy against age-related mood disorders vulnerability.

5. DISCUSSION

The aging brain is characterized by functional and metabolic changes associated with cognitive decline, impaired brain plasticity and severe neuronal loss [20]. Beneficial effects on brain health and function have been reported as an outcome of increased n-3 PUFA dietary intake across the lifespan [32]. In fact, n-3 PUFA are important structural component of neural cell membranes, essential to appropriate neuronal functioning, membrane fluidity, and modulation of signal transduction processes, strictly linked to optimal cognitive functioning [61, 140]. Thus, given the pressing question of how the elderly can maintain their cognitive functions as their life expectancy increasingly raises, n-3 PUFA has been tested in human and animal studies as cognition-enhancing nutraceuticals.

Namely, n-3 PUFA have been implicated in enhancing brain plasticity and cognitive function in aged rodents [20, 32, 60, 61]. The positive effects of n-3 PUFA upon age-

related cognitive decline are likely promoted by antioxidant and anti-inflammatory mechanisms, as demonstrated by several studies in animals [20, 66, 80, 100, 111] and few studies in humans [124, 127]. Furthermore, n-3 PUFA intake has been positively associated with both cognitive performance and GM and WM structural integrity [46-53, 58, 131].

However, not all studies have reported positive relationships between n-3 PUFA consumption and cognitive performance in elderly subjects [37, 54-57] and in patients with AD [141]. It is possible that a beneficial effect of n-3 PUFA intake on cognitive decline may be apparent only with marked cognitive decline, as age advances, or with trials of longer duration. Furthermore, uncontrolled confounding factors (such as socio-economic status, genetic background as well as healthy habits and lifestyle), the enormous variation in n-3 PUFA supplement kind and dosage, and a general failure in controlling the n-6 PUFA dietary intake may also account for the inconsistent results in clinical and interventional studies [33, 49]. As a result, the impact of n-3 PUFA supplementation on cognitive functions in the aging human brain is still a matter of debate, and underlying mechanisms on the systemic and neuronal level remain unclear. In this framework, animal studies under controlled environmental and genetic conditions can help to identify the cellular and molecular mechanisms through which n-3 PUFA counteract brain aging, thus laying the groundwork for future studies in humans.

CONCLUSION

The rise of life expectancy has amplified the interest in the prevention and improvement of age-related brain dysfunctions. This review shows that n-3 PUFA are essential for a successful aging and appear as ideal candidates for cognition-enhancing nutritional and anti-depressant interventions aimed to promote healthy aging. However, whilst growing evidence accounts for the crucial role played by these dietary factors in promoting brain plasticity, much remains to be elucidated at the mechanistic level in both animals and humans.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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