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Review Article

REVIEW ON THERAPEUTIC EFFECTS MEDIATED BY OMEGA-3 FATTY ACIDS IN ALZHEIMER'S DISEASE

SATI AARTI[1]*, BHATT PRIYANKA[2]

[1]Department of Pharmacy, Division of Pharmaceutical Sciences, Shri Guru Ram Rai Institute of Technology and Science, Dehradun – 248 001, Uttarakhand, India. [2]Department of Pharmacy, Shri Ram Murti Smarak, College of Engineering and Technology (Pharmacy), Bareilly – 243 202, Uttar Pradesh, India. Email: bhattpriyanka38@gmail.com

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder with relevant unmet therapeutic needs. Both natural aging and AD have been associated with a significant decline in the Omega-3 polyunsaturated fatty acid, docosahexaenoic acid (DHA), and accordingly, administration of DHA has been proposed as a possible treatment for this pathology. DHA and its derivatives like 2-hydroxy DHA-(OHDHA) have a strong therapeutic potential to treat AD. Studies have demonstrated that DHA induced lipid modifications are paralleled with a reduction in amyloid-beta (Aβ) accumulation and full recovery of cognitive impairment. Omega-3 fatty acids also caused alterations in the subcellular distribution of secretases and reduced Aβ-induced tau protein phosphorylation as well. Furthermore, OHDHA enhanced the survival of neuron-like differentiated cells exposed to different insults such as oligomeric Aβ and N-methyl-D-aspartate-mediated neurotoxicity. In conclusion, this review focuses on the pleiotropic effects of Omega-3 fatty acids that might prove beneficial to treat AD.

Keywords: Amyloid beta, Omega-3 fatty acids, Docosahexaenoic acid.

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ALZHEIMER'S DISEASE (AD)

Alzheimer's is the most common cause of dementia [1] in adult life and is associated with the selective damage of brain regions and neural circuits critical for memory and cognition. Epidemiological data show that the occurrence of AD increases with age and doubles every 5 years after 65 years of age and it is predictable that the worldwide dominance of AD will grow four-fold to 106.8 million by the year 2050 [2]. The main risk factors for AD are age, age-related diseases such as cardiovascular disease, diabetes and obesity, head trauma, and exposure to heavy metals such as aluminum, copper, iron, and zinc [3].

The pathogenesis of this disease is complex and involves many molecular, cellular, and physiological pathology [4]. The neurons in the neocortex, hippocampus, amygdala, and the basal forebrain cholinergic system are the most affected brain regions [5]. Research indicates that the disease is associated with plaques and tangles in the brain. At the microscopic level, the characteristic lesions in AD are senile or neuritic plaques and neurofibrillary tangles in the medial temporal lobe structures and cortical areas of the brain, together with a degeneration of the neurons and synapses [6].

Amyloid cascade hypothesis states that the central event in the disease pathogenesis is an imbalance between amyloid beta (Aβ) production and clearance, with increased Aβ production in familial disease and decreased Aβ clearance in sporadic disease [7]. Alzheimer's patients show numerous plaques which are composed of 4 kD Aβ peptides, which are derived from beta-amyloid precursor proteins (APPs). APP is a membrane-associated glycoprotein of 110–135 kDa that is proposed to normally behave in the brain as a cell surface signaling molecule. Presenilins are crucial components of the enzymes that work to cleave APP, and mutations in presenilin's cause the production of Aβ 42 and Aβ 43 peptides (insoluble forms of Aβ). Aβ peptides are generated in the endosomal compartment and the endoplasmic reticulum or Golgi complex by endoproteolytic cleavage of APP by beta, alpha, and gamma secretases. Presenilin 1 and presenilin 2 are highly homologous 43–50 kD proteins with eight transmembrane domains [8]. Presenilins make crucial contributions to neurodegeneration in AD. Aβ oligomers could directly inhibit hippocampal long-term potentiation and impair synaptic function, in addition to the inflammatory and oxidative stress caused by aggregated and deposited Aβ. These processes impair neuronal and synaptic function with resulting neurotransmitter deficits and cognitive symptoms. Tau pathology with tangle formation is regarded as a downstream event but could contribute to neuronal dysfunction and cognitive symptoms [9]. Under pathological conditions, inflammation of the brain is closely involved in pathogenesis of AD. Microglia's are the principal immune effector cells in the central nervous system (CNS) [10]. On phagocytosis of invading bacteria, microglia are activated and produce pro-inflammatory mediators such as tumor necrosis factor-alpha, interleukin-1, interleukin-6, and prostaglandin E_2, as well as nitric oxide and reactive oxygen species (ROS), which are thought to contribute to neuronal injuries and progression of the neurodegenerative diseases [11]. Therefore, the modulation of microglial activation is an effective therapeutic approach against neurodegenerative diseases.

OMEGA-3 FATTY ACIDS

Omega-3 (ϖ3) fatty acids are a group of essential fatty acids (EFAs) that are vital to human health. EFAs are fatty acids [12] that humans and other animals must ingest because the body requires them for good health but cannot synthesize them. EFAs help in the formation of healthy cell membranes, proper development and functioning of the brain and nervous system and production of hormone-like substances called eicosanoids, thromboxanes, leukotrienes, and prostaglandins. They are also responsible for regulating blood pressure, blood viscosity, vasoconstriction, and immune and inflammatory responses [13,14].

Omega-3 fatty acid [15] can be obtained from walnuts, wheat germ oil, flaxseed oil/canola oil, fish liver oils/fish eggs, human milk, organ meats, seafood/fatty fish namely albacore tuna, mackerel salmon, and sardines.

ROLE OF OMEGA-3 FATTY ACIDS IN CELL FUNCTION AND BIOLOGY

The Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have different roles in cell function

and biology [16], compared to other fatty acids. This likely derives not only from their longer chain length but also the high number and positioning of double bonds [17], which could impart unique physical and biochemical properties distinct from the more common Omega-6 and Omega-9 fatty acids and short fatty acids. These physical differences could underlie specific properties of Omega-3 fatty acids-rich triglycerides and phospholipids in metabolic pathways [18]. It has been reported that "classical" mechanisms used for Omega-6 fatty acids triglycerides-rich lipoprotein blood clearance are much less important for Omega-3 fatty acid-rich particles [19]. Rather, Omega-3 fatty acid-rich particles use direct lipid-lipid and proteoglycan interactions at the cell surface for blood clearance and cell uptake [20,21]. The long chain fatty acids EPA and DHA can alter cell membrane structure and function generally by increasing fluidity as well as decreasing the amount of membrane occupied by lipid rafts and changing their properties [22].

The Omega-3 fatty acids and their derivatives are potent molecules important in chemotaxis and other aspects of the immune and inflammatory response. They decrease blood pressure and alter vascular resistance [23]. They are important in a large number of metabolic signaling pathways relating to cell proliferation and differentiation and receptor expression.

Recent evidence shows that DHA can interact directly with other transcription factors and specific cell receptors [24,25]. Thus, the Omega-3 fatty acids are potential regulators of a large number of genes. Given the large number of cellular pathways affected by Omega-3 fatty acids, it is clear that they have the ability to regulate cell metabolism through multiple mechanisms as suggested by Calder [26]. Calder justified that at sufficiently high intakes, long-chain Omega-3 polyunsaturated fatty acids (PUFAs), decrease the production of inflammatory eicosanoids, cytokines, and ROS and the expression of adhesion molecules. Long-chain Omega-3 PUFAs act both directly (e.g., by replacing arachidonic acid (AA) as an eicosanoid substrate and inhibiting AA metabolism) and indirectly (e.g., by altering the expression of inflammatory genes through effects on transcription factor activation). Long-chain n-3 PUFAs also give rise to a family of anti-inflammatory mediators termed resolvins. Thus, n-3 PUFAs are potentially potent anti-inflammatory agents. As such, they may be of therapeutic use in a variety of acute and chronic inflammatory settings.

The Omega-3 fatty acids have important roles relating to human health and disease. In infancy, they improve cognitive development [27] and learning as well as visual development. Again, long-chain EPA and DHA have been reported to be beneficial in terms of decreasing the risk of depression and suicide and delaying the onset of the neurological degeneration of aging [28-30]. It has been suggested that these fatty acids decrease the risk of certain forms of cancer. Although not recognized to improve manifestations of Type 2 diabetes once developed, these fatty acids have beneficial effects on some of the parameters associated with metabolic syndrome [31]. The Omega-3 fatty acids are reported in a number of studies to have beneficial effects in decreasing stroke and coronary heart disease [32,33]. A number of intervention trials have shown positive effects from supplementation with Omega-3 fatty acids after cardiac events. Dietary fatty acids are increasingly recognized as major biologic regulators and have properties that relate to both health outcomes and disease [34,35].

OUTCOMES OF OMEGA-3 DEFICIENCY IN HUMAN BODY

The first reported case of Omega-3 deficiency [36] was induced by an Omega-3 preparation. A girl, 6 years of age, experienced an accidental abdominal gunshot wound and underwent repeated surgical repairs. Recovery time increased with each surgery. By 1982, the food and drug administration had approved the use of total parenteral nutrition (TPN) with lipid emulsions to provide EFAs, and two preparations were then available, one containing soybean oil, a source of 18:3 Omega 3. The other contained safflower oil, almost devoid of 18:3 Omega 3, but with a very high content of 18:2 Omega 6. After 5 months of TPN with safflower oil, the girl exhibited episodes of numbness, tingling, weakness, inability to walk, leg pain, psychological disturbances, and blurred vision. The clinicians suspected that her intravenous alimentation was inducing an Omega-3 deficiency and requested a fatty acid analysis of her plasma phospholipids. Her profile showed Omega-3 deficiency, with a level of total Omega-3 EFAs at 34% of control value and total Omega-6 at 75% of its control value. When TPN was changed to the soybean oil preparation, the neuropathy disappeared, and subsequent analysis showed that the Omega-3 deficiencies were restored toward normal.

Ralph T. Holman measured significant deficits of Omega-3 EFAs in humans with neuropathy or impairment of the immune system [37]. During the embryonic phase in humans (until 7 weeks) the structure of the brain is defined, while growth during the fetal phase (start at 8 weeks) is characterized by functional development [38,39]. At birth, the brain is fully developed but only 25% of its definitive volume; postnatally, the brain expands by an increase in glial cells, outgrowth of axons and dendrites, and myelination of nerve fibers. This human brain growth spurt starts prenatally in the third trimester of pregnancy [40]. At this time, the infant brain starts accumulating DHA (DHA, 22:6 ω-3) in utero and this continues up to the first 24 months of neonatal brain growth, although the postnatal DHA accumulation occurs at a slower rate [41]. In this period, neural development is most dependent on an adequate supply of long-chain PUFA.

POTENTIAL OF OMEGA-3 PUFAS IN THE TREATMENT OF AD

A decreased level of plasma DHA is associated with cognitive impairment with aging [42-44]. Many animals, epidemiological and clinical studies have shown that high DHA consumption is associated with reduced AD risk [45-47]. In the rat, a DHA containing diet [48] enhanced the effects of exercise on cognition and brain-derived neurotrophic factor-related synaptic plasticity [49,50].

DHA (22:6 n-3) is the most abundant Omega-3 PUFA in the brain, and it is involved in the functioning of the CNS [51], particularly in neurogenesis, synaptogenesis, and synaptic transmission [52,53]. This fatty acid is obtained through the diet, and its deficiency is associated with age-related cognitive decline and with neurodegenerative diseases, such as AD [54,55].

In recent years, PUFAs like DHA have gained much attention due to promising results that suggest they may be useful to treat AD. In this sense, several studies have demonstrated that oral intake of DHA or fish oil [56,57] reduces AD-associated brain pathology, for instance, improving cognitive deficits, protecting against synaptic degeneration, and lowering Aβ levels in transgenic AD mouse models [58,59].

Moreover, these results are supported by epidemiological studies [60,61] indicating an inverse relationship between DHA intake and AD incidence, which correlate high DHA levels with reduced risk of cognitive dysfunction.

A prospective study conducted from 1993 through 2000, of a stratified random sample from a geographically defined community, was conducted by Morris *et al.* [62]. Participants were followed up for an average of 3.9 years for the development of AD. The results proved that in laboratory studies, animals fed diets enriched with Omega-3 PUFAs had better regulation of neuronal membrane excitability, increased levels of neurotransmitters and higher density of neurotransmitter membrane receptors, increased hippocampal nerve growth, greater fluidity of synaptic membranes, higher levels of antioxidant enzymes, decreased levels of lipid peroxides, reduced ischemic damage to neurons, and increased cerebral blood flow. In behavioral models, animals fed diets enriched with n-3 fatty acids had superior learning acquisition and memory performance over animals fed control diets.

Johnson and Schaefer unpublished observations from the Framingham Heart Study suggest that ≥180 mg/d of dietary DHA (≈2.7 fish servings/week) is associated with an ≈50% reduction in dementia risk. At least this amount of DHA is generally found in one commercially available 1-g fish oil capsule given daily [63].

However, direct administration of DHA in clinical trials only showed improved cognition of a small subgroup of patients with very mild cognitive dysfunction, and there was no clear effect in most patients, even though DHA administration improves the physiological, but not pathological, age-related cognitive decline [64]. In this context, there would appear to be a link between AD and lipid alterations in neuronal membranes, especially diminished DHA levels. Therefore, molecules that are effective in restoring DHA and normalizing the membrane lipid composition could constitute therapeutic tools to treat AD.

Torres *et al.* [65] illustrated that the novel hydroxyl-derivative of DHA (2-hydroxy DHA-OHDHA) has a strong therapeutic potential to treat AD. They proved that OHDHA administration increases DHA levels in the brain of a transgenic mouse model of AD (5×familial AD [FAD]), as well as those of phosphatidylethanolamine species that carry long PUFAs. In 5×FAD mice, administration of OHDHA induced lipid modifications that were paralleled with a reduction in Aβ accumulation and full recovery of cognitive scores. OHDHA administration also reduced Aβ levels in cellular models of AD, in association with alterations in the subcellular distribution of secretases and reduced Aβ-induced tau protein phosphorylation as well. Furthermore, OHDHA enhanced the survival of neuron-like differentiated cells exposed to different insults, such as oligomeric Aβ and N-methyl-D-aspartate-mediated neurotoxicity.

In a recent study Fiol-de Roque *et al*. [66] have shown that (OHDHA) regulates membrane lipid composition and structure, cell signaling and, additionally, it improves cognitive scores in animal models of AD thereby representing a novel therapeutic candidate for the treatment of this disease.

Omega-3 PUFAs and fish oil, the major dietary source of Omega-3 PUFA have been extensively studied as dietary supplements suggesting beneficial effects for the treatment of inflammation [67-69], macular degeneration [70,71], AD [72-75] depression [76] anxiety disorders [77], and psychotic disorders [78]. Optimum maintenance of the synaptosome, brain cell functions, and general health of human CNS are potentially facilitated by Omega-3 PUFA [79-81].

A clinical trial on Alzheimer's patients supplemented by Omega-3 PUFA enriched diets failed to deliver a robust outcome. The trials found Omega-3 PUFA effective only if it was administered during the early onset of the AD. A number of clinical, epidemiological, and laboratory studies linked the health benefits of Omega-3 PUFA to various dietary compositions, including EPA alone [82,83], the EPA:DHA ratio [84], the AA:EPA ratio [85,86] the AA: Alpha-linolenic acid ratio [87] and the overall Omega-3 PUFA; Omega-6 PUFA ratio [88]. The appropriate dietary composition is still a subject of ongoing investigation. Many studies reported the increased levels of EPA and DHA accompanied by decreased AA in the brain tissues of rats fed on fish oil-enriched diets [89,90]. The Omega-3 PUFA enriched diet helped balancing behavioral plasticity [91], improved cognitive function and working memory [92], enhanced neuroprotection [93,94], and reduced anxiety and depression-like traits [95,96] *in vitro*. Hence Omega-3 PUFA can be effective in Alzheimer's treatment. The comprehension of the underlying molecular mechanism is potentially critical to understand the effect of the fish oil on neuronal activities. Toward this goal, Hammamieh *et al*. [97] studied the effects of high dietary intake of fish oil on the genomic regulations in the mouse brain and characterized the potentially associated molecular events focused on the nervous system and neuro functions. They found that fish oil potentially augmented the nervous system's development and functions by selectively stimulating the Src-mediated calcium-induced growth cascade and the downstream PI3K-AKTPKC pathways. Moreover, fish oil rich diet reduced the amyloidal burden, attenuated oxidative stress, and assisted in somatostatin activation-the signatures of attenuation of AD, Parkinson's disease, and affective disorder.

More recent studies showed that dietary DHA could be protective against beta-amyloid production, deposition in plaques and cerebral amyloid angiopathy in an aged AD mouse model and increases cerebral blood volume [98]. In other transgenic AD mouse models DHA also protects against dendritic pathology [99,100].

In a small pilot study by Shinto *et al.* [101] combining Omega-3 with alpha lipoic acid slowed both cognitive and functional decline in mild to moderately impaired AD participants over 12 months, and the combination appears to be safe at the doses evaluated.

Rainger *et al*. [102] illustrated that Omega-3 (n-3) PUFAs (n-3 PUFAs) have well documented anti-inflammatory properties, and consequently therapeutic potential in chronic inflammatory diseases. As we know that there is marked oxidative stress accompanied with neurodegeneration in AD, so the anti-inflammatory activity of Omega-3 fatty acid can be very beneficial in retarding the progression of AD [103].

Souvenaid (Nutricia N.V., Zoetermeer, the Netherlands), containing the specific nutrient combination Fortasyn Connect, has been designed to enhance synapse formation and function in AD compared to control product without the specific nutrient [104,105]. Souvenaid is a product intended as a medical food for oral consumption under medical supervision with the purpose of addressing disease-specific nutrient requirements. A medical food is a food formulated for enteral intake by patients, taken under physician supervision, and intended to meet the specific nutritional requirements identified for a disease or condition, which cannot be met by a modification of the normal diet. The specific nutrient combination Fortasyn connect comprises DHA, EPA, uridine monophosphate (UMP), choline, phospholipids, folic acid, and Vitamins B6, B12, C, E, and selenium, which are the precursors and cofactors for the formation of neuronal membranes. Preclinical studies have shown that administration of DHA, EPA, UMP, and choline can increase phosphatide synthesis [106], neurite outgrowth [107], the number of dendritic spines and the levels of pre- or post-synaptic proteins [108]. This proves that Souvenaid is an excellent neuroprotective agent.

CONCLUSION

Omega-3 fatty acids could provide therapeutic benefits for a number of neurodegenerative diseases, while there is a valid concern about its therapeutic efficacy in treating certain other illnesses. The comprehensive investigation to confirm these findings are exigent and the effectiveness of this PUFA rich diet should be validated by introducing this diet type to specific disease models.

AUTHOR'S CONTRIBUTION

All the author have contributed equally.

CONFLICT OF INTEREST

'The author(s) declare(s) that there is no conflict of interest.

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