Omega-3 Fatty Acids' Impact on Neuroinflammation in Neurodegenerative Diseases

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Abstract

Because of their anti-inflammatory properties and effect on the integrity of neuronal membranes, omega-3 fatty acids hold promise for the treatment of neurodegenerative illnesses such as Alzheimer's and Parkinson's. Because they affect neuroinflammation and cognitive function, omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are critical for brain health. A lack of omega-3 polyunsaturated fats is linked to mental illnesses and neurodegeneration. Clinical studies have shown that taking omega-3 supplements, particularly those that contain DHA and EPA, may improve cognitive function and reduce neuroinflammation in patients suffering from Parkinson's and Alzheimer's diseases. Mechanistically, DHA inhibits tau protein phosphorylation and Aβ accumulation, whereas omega-3 PUFAs regulate inflammatory pathways and synaptic function. Fatty fish is one dietary source of omega-3 PUFAs, but supplementation may be necessary, especially in populations with low consumption or conversion capacity. Offering simple ways to incorporate omega-3 fatty acid fortification into regular diets is one beneficial use for it. The potential of omega-3 fatty acids to prevent or treat neurodegenerative disorders requires further research.

Keywords: Omega-3 Fatty Acids, Neuro Degenerative Disorder, Docosahexaenoic Acid, Eicosapentaenoic Acid.

Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (ALS), are progressive disorders of the central nervous system (CNS) characterized by selective and irreversible loss of neurons. Common pathological features include the accumulation of misfolded proteins—such as amyloid-β (Aβ) plaques and hyperphosphorylated tau tangles in AD, and α-synuclein aggregates in PD—synaptic degeneration, mitochondrial dysfunction, oxidative stress, and a chronic state of neuroinflammation.

Neuroinflammation plays a central role in both the initiation and progression of neurodegenerative diseases. It is primarily mediated by innate immune cells of the CNS, especially microglia and astrocytes. Under pathological conditions, these glial cells shift from a homeostatic state to a pro-inflammatory phenotype, releasing a cascade of cytokines and chemokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α). These cytokines further amplify inflammatory signalling, promote neuronal injury, and contribute to synaptic loss.

Another crucial component of the inflammatory response is the activation of inflammasomes, multiprotein complexes that detect cellular stress and damage. The NLRP3 inflammasome, in particular, has emerged as a key mediator of neuroinflammation. It promotes the maturation and release of IL-1β and IL-18, further perpetuating the inflammatory milieu. In addition, damage-associated molecular patterns (DAMPs)—such as extracellular ATP, high-mobility group box 1 (HMGB1), and misfolded protein aggregates—act as endogenous danger signals that sustain glial activation and inflammasome signalling.

Given the central role of chronic inflammation in neurodegeneration, there is growing interest in therapeutic strategies that target inflammatory pathways. Among these, omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been extensively studied.

These long-chain fatty acids are enriched in neuronal membranes and are known to influence membrane fluidity, signal transduction, and gene expression. More importantly, they exhibit anti-inflammatory and pro-resolving properties, modulating glial cell activation, reducing cytokine release, and promoting the clearance of toxic protein aggregates. Moreover, omega-3 PUFAs serve as precursors for specialized pro-resolving mediators (SPMs), such as resolving, protections, and mares ins, which actively drive the resolution of inflammation and support tissue homeostasis.

Preclinical and clinical studies suggest that DHA and EPA may offer neuroprotective and even neurorestorative effects, potentially slowing the progression of neurodegenerative diseases by attenuating inflammation, oxidative stress, and synaptic damage. However, the efficacy of omega-3 PUFAs in human populations remains under investigation, with ongoing studies seeking to clarify optimal dosing, treatment duration, and mechanisms of action.[1]

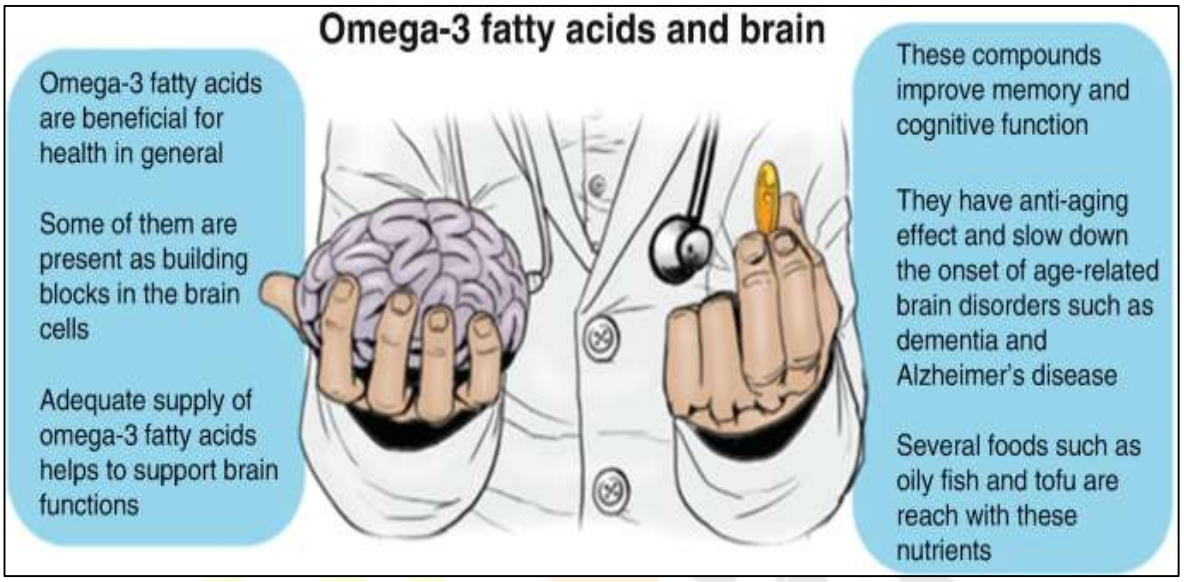

Fig. 1. Omega-3 Fatty Acid & Brain[2]

Mechanisms

The Regulation of Neuroinflammation by Omega-3sThere are several mechanistic routes that have been suggested or validated.
The pro-inflammatory "M1" phenotype of microglia is changed to an anti-inflammatory/phagocytic "M2" phenotype by omega-3 fatty acids.
This facilitates the removal of protein clumps, including as tau and Aβ.
Competition with lipids that promote inflammation and a decrease in their production: Arachidonic acid and other omega-6 fatty acids compete with omega-3s for the enzymes that generate inflammatory eicosanoids. Therefore, higher omega-3 tends to lower pro-inflammatory prostaglandin and leukotriene levels.
Resolvins, protectins, maresins, and docosanoids—all downstream metabolites of omega-3 fatty acids—help resolve inflammation rather than merely reduce it.
In actuality, DHA can change cellular and physiological functions such neurotransmitter release, gene expression, myelination, membrane fluidity, neuroinflammation release, and neuron proliferation. DHA is made from ALA, whereas ARA is made from LA by desaturation and carbon chain elongation. Humans can synthesize both saturated and monounsaturated fatty acids (MUFAs), which are required to produce ALA and LA, because they lack the conversion enzyme 3-desaturase. There is competitive inhibition between the two substrates as a result of LA and ALA making the same requests for conversion enzymes.Delta-6-desaturase facilitates the conversion of omega-3 fatty acids into omega-6 fatty acids. However, consuming more LA could tilt the scales in favor of converting omega-6 PUFA, which would stop ALA from turning into DHA. Intestinal lipases in the small intestine release the free, unesterified form of DHA (DHA-FFA) from food after it has undergone intestinal and hepatic metabolism. Additionally, it can be found esterified in triglycerides and phosphotidylcholine, or as free DHA connected to albumin or low-density lipoprotein.
Using both active and passive methods, endothelial lipases, fatty acid-binding proteins (FABP), and

apolipoprotein E (ApoE) separate the different forms in the blood-brain barrier (BBB).FABP and ApoE, which are produced by astrocytes, transport the DHA throughout the central nervous system. DHA is mainly incorporated into membrane phospholipids at the stereospecific numbered-2 position by means of coenzyme A. However, phospholipase-assisted hydrolysis activities can release DHA from membrane phospholipids. Both synthesis and hydrolysis serve as mechanisms in response to dynamic cellular events and challenges that arise during development and aging.

This synthesis from DHA, EPA, and ARA (prostaglandins, thromboxanes, and leukotrienes) is also essential to the role of eicosanoids in inflammation. Enzymes called phospholipase A2 (PLA2) hydrolyze phospholipids, releasing fatty acids in the process. The implication is that inflammatory stimulation involving specific cell activation leads to an increase in free fatty acid levels. Generally speaking, bioactive lipid release is linked to three types of PLA2: the cytosolic calcium-dependent PLA2 that Thestereospecifically numbered-2 position of membrane phospholipids is where coenzyme A, DHA, predominantly integrates its activity. However, phospholipase-assisted hydrolysis activities can release DHA from membrane phospholipids. Both synthesis and hydrolysis serve as mechanisms in response to dynamic cellular events and challenges that arise during development and aging.

The production of eicosanoids from DHA, EPA, and ARA (prostaglandins, thromboxanes, and leukotrienes) is also essential to their involvement in inflammation. The Phospholipase A2 enzymes (PLA2) hydrolyze the phospholipid, releasing fatty acids in the process.

Consequently, an inflammatory stimulus involving specific cell activation results in an increase in free fatty acid levels. Three types of PLA2 are primarily linked to bioactive lipid release: cytosolic calcium-dependent PLA2, which is one of the forms of PLA2 that shows substrate preference for phospholipids, including arachidonic acid (AA). Although phospholipids containing EPA may also be hydrolyzed by cPLA2, in certain situations, the low concentration of this fatty acid allows cPLA2 to release AA. Prostaglandins, leukotrienes, and thromboxanes are metabolized by cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), which regulate inflammation (Figure 1). The 2-series prostaglandins, thromboxanes, and 5-series leukotrienes are all descended from ARA.

Males typically convert less than 5% of ALA to DHA when they reach adulthood, while females convert more efficiently. This variation has an impact on the fetus's nutrition during pregnancy. Women often eat less omega-3 than men do, and as they become older, their ability to convert, especially delta-6 desaturase activity, declines. This indicates that preformed omega-3 dietary supplements are required for older adults in particular to obtain adequate intake of EPA and DHA. When paired with a decline in physical activity, modern diets high in omega-6 and low in omega-3 have a negative impact on aging and cognitive performance. Current recommendations place a strong emphasis on maintaining an adequate intake of EPA and DHA.[3]

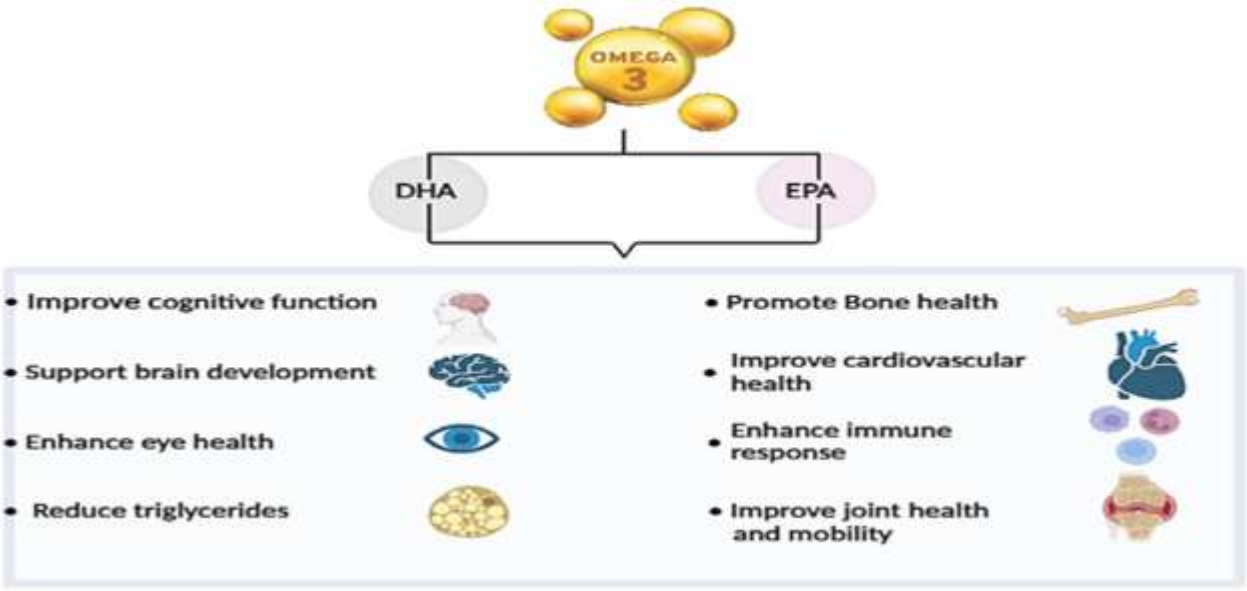

Fig.2. DHA and EPA, two omega-3 fatty acids, have therapeutic advantages.[4]

Omega-3 Fatty Acids' Function in Brain Health

The strong antioxidant qualities of certain vitamins and the possible health benefits of polyunsaturated fatty acids (PUFAs) have garnered attention. Omega-3 and omega-6 fatty acids are classified as polyunsaturated fatty acids (PUFAs) because their carbon chain backbone contains two or more double bonds. Arachidonic Acid (AA), γ-Linolenic Acid (GLA), and Linoleic Acid (LA) are examples of omega-6 fatty acids. Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA) are two varieties of omega-3 fatty acids. However, these fatty acids need be acquired from diet or supplements because humans can only manufacture a certain amount of them. Effects on development, aging, and cognitive function.

Insufficiency in omega-3 fatty acids is. This emphasizes how important omega-3 fatty acids are. On the other hand, deficiencies in docosahexaenoic acid (DA) and eicosapentaenoic acid (EA) control inflammatory processes and mental health and cause mental diseases. Additionally, they have a direct impact on brain membrane fluidity and receptor function. Omega-3 supplements and enriched foods have long been acknowledged for their vital role in preserving brain homeostasis, but their use in psychiatry has been restricted since randomized clinical trials investigating their potential for treatment have not shown conclusive results. We urgently need high-quality clinical trials to determine whether omega-3 fatty acids are helpful in preventing and treating NDs.

Additionally, they have a direct impact on brain membrane fluidity and receptor function. Omega-3 fatty acids have long been acknowledged for their vital function in preservingbrainhomeostasis. Because randomized clinical trials investigating the therapeutic potential of supplements and fortified meals have not shown conclusive results, their use in psychiatry is limited. There is an urgent need for high-quality clinical trials to determine if omega-3 fatty acids are helpful in preventing and treating NDs.

DHA prevents the formation of neurofibrillary tangles and the breakdown of intraneuronal microtubules by blocking the phosphorylation of tau proteins. Additionally, DHA can reduce the amount of Aβ that builds up in neurons and stop it from developing, which decreases Aβ toxicity and neuronal death. According to a recent study, DHA, but not AA, can prevent the production of reactive oxygen species, the synthesis of inducible nitric oxide synthase, the activation of tumor necrosis factor α in microglia cells, the formation of oligomeric Aβ (oAβ), and the rise in phosphorylated cytosolic phospholipase A2 that oAβ causes.

DHA can control AA metabolism in oAβ-stimulated microglia by upregulating the Nrf2/heme oxygenase-1 antioxidative pathway and downregulating oxidative and inflammatory pathways.

In a group of patients with mild cognitive dysfunction and organic brain lesions but no AD diagnosis, 240 mg/day of AA and DHA supplementation resulted in a significant improvement in immediate memory and attention score; however, no significant differences were seen when compared to the AD group.

Supplementing with EPA and DHA preserved the generation of resolvings, preventing detrimental alterations in cognitive function, according to an analysis of mononuclear cells from the peripheral blood of patients.[5]

Common Dietary Sources[7]

Food	Omega-3 Type	Notes
Fatty fish (salmon, mackerel, sardines)	EPA & DHA	Most bioavailable form
Flaxseeds, chia seeds	ALA	Plant-based; limited conversion to EPA/DHA
Walnuts	ALA	Good vegetarian option
Algal oil (from algae)	DHA	Suitable for vegans
Fish oil supplements	EPA & DHA	Popular for heart and joint health

The Effect of Omega-3 Fatty Acids on Insulin Resistance

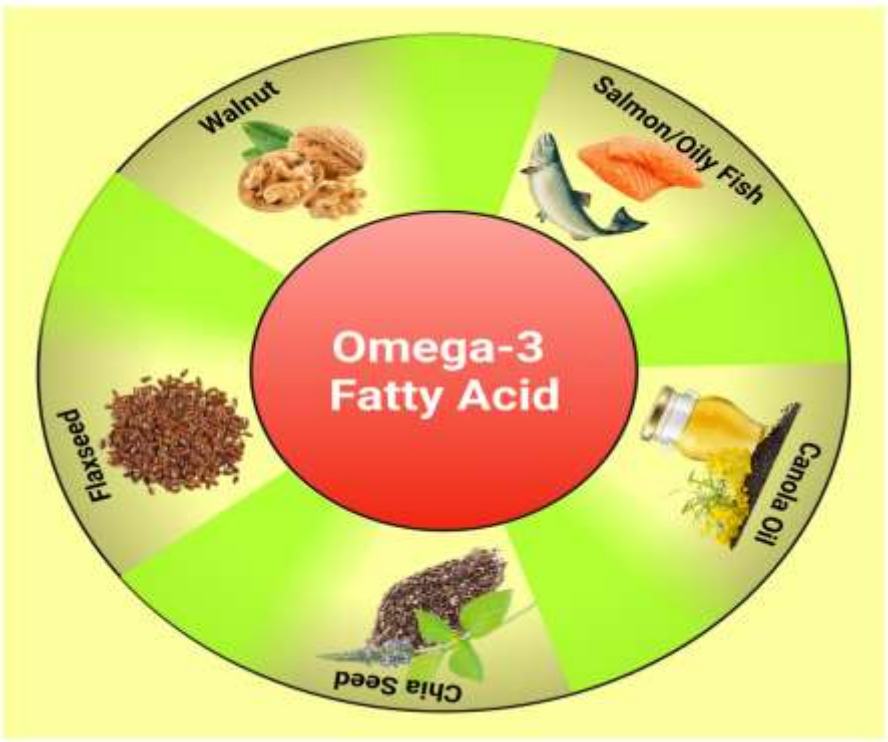

Fig.3. The Effect of Omega-3 Fatty Acids on Insulin Resistance[6]

Preclinical / Animal Evidence

There is strong evidence from animal models and cell studies in support of the anti-neuroinflammatory effects of omega-3s:

✓ Traumatic Brain Injury (TBI) models: ω-3 PUFA supplementation after TBI leads to lower levels of HMGB1 release, lower NF-κB activation, reduced expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), increased IL-10, and shift of microglia toward M2 phenotype.

✓ Inflammasome & NLRP3: In TBI and other CNS-injury models, ω-3s reduce caspase-1 activation, IL-1β secretion, mitochondrial localization of NLRP3 (which is important in its activation), via GPR40 etc.

✓ Macrophage studies (non-CNS but relevant mechanisms): DHA reduces inflammasome activation for multiple types (NLRP3, AIM2, NAIP5/NLRC4) in macrophages; requires functional autophagy machinery.

✓ Ageing, microglia, Alzheimer's disease models: In vitro and ex vivo studies show DHA/EPA reduce microglial pro-inflammatory activation and increase phagocytosis of Aβ, reduce markers like CD40, CD86, increase CD206, CD163 etc.

✓ Prenatal / gestational models: ω-3 supplementation during gestation in rats reduces neuroinflammation induced by stress, reduces NLRP3 / NF-κB in specific brain regions. [8]

Consequences for Parkinson's, Alzheimer's, and Other Conditions

✓ Alzheimer's disease (AD): Inflammation is fueled by key abnormalities (tau and Aβ). According to some preclinical studies, ω-3s may be beneficial by lowering tau phosphorylation, encouraging phagocytosis of Aβ, and lowering cytokine burden. The cognitive clinical benefit is slight and more noticeable in the early stages of the illness.

✓ Parkinson's disease (PD): Preclinical models indicate ω-3s can decrease oxidative stress, microglial activation, and α-synuclein aggregation, although there is less clinical data on this topic. More experiments on humansarerequired.

✓ Additional neurodegenerative conditions, such as multiple sclerosis, Huntington's, and ALS: There is limited human evidence, but there are some studies (mostly from animal models) demonstrating the anti-inflammatory and antioxidant benefits of ω-3s.[11]

New and Recent Perspectives

Autophagy and mitophagy's function as vital mediators: For instance, ω-3s decrease inflammatory triggers and ROS by promoting the elimination of damaged mitochondria and lowering inflammasome activation.

The pathways mediated by Sirtuin-1 (SIRT1): Because ω-3s increase SIRT1, HMGB1 is deacetylated, which lowers its extracellular release and NF-κB activation downstream.
PMC

GPR40/GPR120 and β-arrestin-2 receptors: These are becoming important ω-3 signal sensors and transducers that have anti-inflammatory effects later on. For instance, GPR40 and β-arrestin-2 bind to NLRP3 to decrease activity, which is at least one way that ω-3 mediates effects in TBI.
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The function of lipid mediators and lipidomic alterations in microglia: how the makeup of membranes influences microglial reactions to injury, and how ω-3 levels decrease with age in AD brain. [12]

Mechanistic Understanding

1. Glial polarization (microglia & astrocytes): According to recent research on animals, aging is linked to a change in pro-inflammatory microglial (M1) and astrocytic (A1) phenotypes; these changes can be reversed or attenuated by DHA (and to a lesser extent, EPA).Dietary omega-3 fatty acids can enhance microglial phenotypes with improved phagocytic/clearance capabilities in Alzheimer's-type mice, lowering aggregation of tau, Aβ, and other proteins.

2. Lipid mediators and inflammatory signalling: Omega-3 fatty acids are competitive inhibitors of inflammatory lipid mediators generated from arachidonic acid (omega-6). Reversing the balance (reducing ω-6 / ω-3 ratios) affects the net inflammatory milieu and decreases the production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6). Recent research indicates that omega-3 fatty acids may act through epigenetic regulators. For instance, when omega-3 fatty acids are used to treat spinal cord injury in rats, they decrease endoplasmic reticulum stress-induced neuroinflammation via the HDAC3/PGC-1α pathway.

3. Blood-brain barrier (BBB) and lymphatic clearance: There is mounting evidence that omega-3 fatty acids contribute to the maintenance or repair of the integrity of the BBB by affecting tight junction proteins, aquaporins, and matrix metalloproteinases (MMP9). Neuroinflammation and neurodegeneration are exacerbated by disruption of the blood-brain barrier. Deteriorated microvascular and clearance system (glymphatic) dysfunction are becoming significant factors in Alzheimer's disease models and clinical dementia situations. Through glymphatic routes, omega-3 fatty acids may help improve the removal of protein and metabolic waste.

4. Stress, ER stress, and homeostasis in cells Omega-3 fatty acids can lower ER stress and subsequent inflammatory reactions, as demonstrated by the spinal cord injury model (above). Academic OUPWhen it comes to cellular aging, omega-3 fatty acids lower oxidative stress, enhance mitochondrial function, lower lipid peroxidation, and other factors that are upstream causes of neuroinflammation.

5. Sex differences and lipid levels in human disease: According to recent research, women with Alzheimer's disease have far lower levels of unsaturated lipids, such as omega-3s, than women in good health. Male patients do not exhibit this difference. This raises the possibility of a sex-specific need or vulnerability.[13]

Human and Animal Data

Models of animals In elderly rats, DHA and EPA have been compared; DHA is generally more effective than EPA alone for a number of outcomes, including memory, the suppression of several pro-inflammatory cytokines, and improved glial polarization. Mice with high ω-6:ω-3 ratios exhibited higher behavioral

abnormalities and brain inflammation than mice with more balanced or low ratios when fed high omega-6/omega-3 diets.

Deficient levels of omega-3 (particularly DHA and EPA) are linked to worse cognitive outcomes and greater inflammatory markers in Alzheimer's, Parkinson's, and other diseases, according to human, clinical, and epidemiological reviews. Although results are inconsistent, supplements show potential in decreasing cognitive deterioration. The majority of RCTs are small, have conflicting objectives, or are not long enough to provide conclusive evidence of disease-modifying effects in human neurodegenerative diseases.[14]

Limitations

✓ Stage of disease: Effects are more likely (and stronger) when administered early (during mild cognitive impairment or early AD) rather than in later stages where neuronal loss and pathology are extensive. Once damage is advanced, anti-inflammatory action alone may not reverse lost neurons.

✓ Dose, formulation, ratio of EPA vs DHA: Not all studies used the same dosage or ratio. Some indications suggest EPA-dominant ω-3s may have particular benefit. Also whether ω-3s are delivered as free fatty acids, triglycerides, ethyl esters, etc., may affect bioavailability.

✓ Duration: Many trials are relatively short (months), neurodegenerative diseases progress slowly; longer intervention may be needed to observe meaningful changes.

✓ Biomarkers: There is a lack of consistent, sensitive biomarkers in human trials to capture neuroinflammation and resolution. Measuring CSF vs plasma vs imaging correlates, etc.

✓ Inter-individual differences: Genetics (e.g. APOE genotype), diet, baseline ω-3 status, background inflammation, co-morbidities may influence the response. For instance, those with low baseline ω-3 or high inflammation may benefit more.

✓ Mechanistic translation: While preclinical studies identify pathways (NLRP3, HMGB1, NF-κB, SIRT1, GPR40 etc.), whether similar dynamics operate in human neurodegenerative disease is still being established.

✓ Safety, side effects: Generally, ω-3s are safe, but high doses may have issues (like bleeding risk, gastrointestinal problems) depending on formulation. Also, interaction with other medications should be considered.[15]

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