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Omega-3 Fatty Acids as Druggable Therapeutics for Neurodegenerative Disorders

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Abstract

Neurodegenerative disorders are commonly associated with a complex pattern of pathophysiological hallmarks, including increased oxidative stress and neuroinflammation, which makes their treatment challenging. Omega-3 fatty acids (O3FA) are natural products with reported neuroprotective, anti-inflammatory, and antioxidant effects. These effects have been attributed to their incorporation into neuronal membranes or through the activation of intracellular or recently discovered cell-surface receptors (*i.e.*, Free-Fatty Acid Receptors; FFAR). Molecular docking studies have investigated the roles of O3FA as agonists of FFAR and have led to the development of receptor-specific targeted agonists for therapeutic purposes. Moreover, novel formulation strategies for targeted delivery of O3FA to the brain have supported their development as therapeutics for neurodegenerative disorders. Despite the compelling evidence of the beneficial effects of O3FA for several neuroprotective functions, they are currently only available as unregulated dietary supplements, with only a single FDA-approved prescription product, indicated for triglyceride reduction. This review highlights the relative safety and efficacy of O3FA, their drug-like properties, and their capacity to be formulated in clinically viable drug delivery systems. Interestingly, the presence of cardiac conditions such as hypertriglyceridemia is associated with brain pathophysiological hallmarks of neurodegeneration, such as neuroinflammation, thereby further suggesting potential therapeutic roles of O3FA for neurodegenerative disorders. Taken together, this review article summarizes and integrates the compelling evidence regarding the feasibility of developing O3FA and their synthetic derivatives as potential drugs for neurodegenerative disorders.

Keywords

Omega-3 fatty acids; neurodegenerative disorders; prescription therapies; free fatty acid receptor; synthetic agonists

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

1. INTRODUCTION

Neurodegenerative disorders of the Central Nervous System (CNS) are characterized by various pathophysiological hallmarks, such as neuronal cell loss and dysfunction, cognitive impairments and increased oxidative stress and neuroinflammation [1, 2]. Disorders such as Alzheimer's Disease (AD), Multiple Sclerosis (MS), Parkinson's Disease (PD), and Huntington's Disease (HD) are disproportionately observed in elderly populations and severely affect mental and physical health and overall quality of life [3], and age-related decline is associated with an increased proinflammatory cytokine load [4]. A variety of natural products have a broad range of molecular mechanisms through which they exert their neuroprotective effects, such as reductions in oxidative stress and inflammation, which may make them suitable candidates for the management of neurodegenerative disorders that are often multifactorial and require multiple therapies [5–8].

Omega-3 Fatty Acids (O3FA) are essential fatty acids that are the components of neuronal cell membranes in the brain [9–12]. Several studies have highlighted the neuroprotective roles of O3FA in neurodegenerative disorders such as HD [13] and PD [14] as well as AD and Mild Cognitive Impairment (MCI) [15, 16]. There is also evidence for their efficacy in psychiatric disorders such as depression [17, 18] and schizophrenia [19], which similar to neurological disorders, have a neural etiology. Despite the large body of evidence suggesting neuroprotective roles of O3FA for neurodegenerative disorders, there are currently no approved therapies for brain disease, as only Over The Counter (OTC) dietary supplements, which lack standardization and regula tion, are available. Currently, the only approved prescription formulation of O3FA approved by the Food and Drug Administration (FDA) is indicated for hypertriglyceridemia in adults. The availability of a prescription product highlights the relative safety and efficacy of O3FA and the feasibility of their formulation as therapeutic drugs. The aim of this review was to summarize compelling evidence on the importance and feasibility of developing O3FA and their synthetic derivatives as agents for the pharmacotherapy of neurodegenerative disorders, with a major focus on PD, AD and MCI.

2. NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders are a major health concern for society and their prevalence is becoming more common in recent years due to an ever-growing elderly population [20]. While the pathophysiological hallmarks of these disorders are complex and include many factors, the most common hallmarks are neuronal loss and protein impairments. The progressive loss of neurons and protein deposition leads to several alterations in the normal functioning of the brain and peripheral organs. Protein processing impairments are very common in the pathogenesis of neurodegenerative disorders, such as impairments in amyloid-beta, tau protein, and α-synuclein processing. These pathophysiological changes result in complex clinical presentations, suggesting the involvement of various functional systems [21]. Neurodegenerative disorders can sometimes be classified on the basis of clinical features, but often require a neuropathological delineation from the presence of major molecular abnormalities such as tauopathy, amyloid deposition, or alpha-synuclein inclusions [22]. Over the last decade or so, there have been several efforts to discover

biomarkers for CNS disorders, using biofluids such as blood or Cerebrospinal Fluid (CSF), protein markers, and bioimaging. The discovery of early diagnostic biomarkers can vastly aid in drug development efforts and clinical trials for neurodegenerative disorders and promote their timely treatment [23].

Although the etiology of neurodegenerative disorders is not clearly understood, studies have reported that neuroinflammation [24–26] is a common pathophysiological change that is observed across different disease states. Moreover, neuroinflammation is an attractive drug target because it has a partially understood molecular and cellular basis. Micro-glial cells and inflammasomes are key mediators of inflammation [1]. Neuronal degeneration is often associated with the chronic activation of microglial cells, the resident macrophages found in the CNS. The hyperactivation of microglial cells, or microgliosis, is associated with increased inflammation, which can be associated with neurotoxic effects [27]. In the context of neurodegenerative disorders, for example, in the primary mesencephalic neuron-glia culture system, aggregated alpha-synuclein activates microglia, which can lead to progressive neurodegeneration in the substantia nigra in PD [28]. Neuroinflammation is also an attractive target for neurodegenerative disorders because it may provide objective biomarkers of treatment efficacy. Markers that can be measured from blood, such as increased levels of the proinflammatory cytokine interleukin-1β (IL-β) [29], may reflect central proinflammatory changes. Similarly, Positron Emission Tomography (PET) has emerged as a tool for detecting neuroinflammation *in vivo* using PET radioligands to help clarify the role of inflammation in neurological disorders [30]. A clinical trial reported that systemic markers of inflammation such as IL-6 and the soluble IL-6 receptor as well as oxidative stress markers like malondialdehyde in PD patients were associated with alterations in iron metabolism, with malondialdehyde, plasma haptoglobin, and ferritin reportedly the most significant biomarkers of PD [31]. This suggests that anti-inflammatory drugs that specifically target neuroinflammation may be viable new treatments for neurodegenerative disorders because they can potentially be augmented by novel biomarkers and may target specific molecular and cellular signaling pathways.

Oxidative stress is another hallmark of neurodegenerative disorders [32] and is associated with the overproduction of Reactive Oxygen Species (ROS). When the natural antioxidant enzyme system of the body cannot balance the ROS generation, the increased oxidative stress leads to the destruction of cellular structures, lipids, proteins and genetic material such as DNA and RNA [33]. ROS can cause cellular damage either by direct destruction of cell proteins or components, or indirectly by disrupting cellular pathways. Studies have determined the presence of nitrotyrosine in neurofibrillary tangles, an important pathophysiological hallmark of AD. This finding links oxidative stress, and excitotoxicity to neuronal cell death in AD [34]. Observational studies in a healthy human population also indicate a relationship between increased oxidative stress and impairments in executive functioning [35], which can degrade in neurodegenerative disorders. A survey reviewing studies probing the underlying mechanisms of oxidative stress as a central player in neurodegenerative disorders confirmed the key role of oxidative stress in the pathophysiology of neurodegenerative disorders. Several markers of neuronal dysfunction, including protein oxidation, microgliosis, Aβ plaque deposition, apoptosis, and proteasome dysfunction, were linked to oxidative stress, thereby suggesting strongly that mitigating

oxidative stress and free radical generation play a pivotal role in targeting neurodegenerative disorders [36]. These studies together implicate a pivotal role of oxidative stress in neurodegenerative disorders and suggest that therapeutics for neurodegenerative disorders should possess sufficient antioxidant properties.

Dysregulation or frank loss of O3FA themselves in the brain has also been linked to neurodegenerative disorders. Increased lipid peroxidation and decline of O3FA have been associated with AD [37]. Increased lipid peroxidation results in the formation of the strong electrophile acrolein, which reacts with DNA bases to form products such as acrolein-deoxyguanosine, and has been found in the brain tissues of AD patients [38, 39]. Hippocampal levels of the major brain fatty acid docosahexaenoic acid (DHA) decrease with age in rats [40], which is associated with learning and memory deficits [41]. PD is characterized by the progressive loss of dopaminergic neurons, particularly in the substantia nigra, leading to significant dopamine depletion in the striatum, which is responsible for the motor symptoms of PD [42]. The concentration of O3FA decreases in the substantia nigra of patients with PD, whereas the concentration of malondialdehyde, a lipid oxidation marker, increases. This lipid peroxidation could be associated with an accelerated metabolism of dopamine, thereby playing a vital role in the pathogenesis of PD [43]. Another study reported that adult rats raised from conception on diets containing negligible O3FA had significantly lower tyrosine hydroxylase-positive cells in the substantia nigra and ventral tegmental as compared to rats fed a control diet [44]. Studies have also reported that rats consuming diets deficient in the O3FA α-Linolenic Acid (ALA) had a significantly lower density of D2 receptors and significantly lower levels of endogenous dopamine as compared to control rats [45–47]. Altered lipid metabolism is also associated with other neurological disorders such as HD [13] and MCI [48] as well as schizophrenia [49]. These studies highlight the link between depletions of O3FA and neurodegenerative conditions, thereby supporting the hypothesis that they might be suitable therapeutics for neurodegenerative disorders.

Recent studies suggest that diet and nutrition play a vital role in the development of neurodegenerative disorders, and consumption of diets that are good sources of antioxidants and anti-inflammatory components may reduce age-associated cognitive decline and the development of neurological disorders [50]. Additionally, there is emerging evidence suggesting that impaired nutrition is associated with the promotion of neurodegenerative disorders such as AD, PD, and HD [51]. While the interplay between metabolic conditions such as dyslipidemia and atherosclerosis and diet is well characterized, the neuronal implications of diet remain to be understood clearly. Studies indicate that nutraceuticals target multiple pathophysiological markers and pathways that are associated with multifactorial neurodegenerative disorders, and thus represent an effective treatment strategy [52]. This further strengthens the hypothesis that dietary components, including O3FA, can be potential druggable therapeutics for neurodegenerative disorders.

Gut dysbiosis is shown to augment the release of proinflammatory cytokines, T helper cells and monocytes, which causes an increase in the intestinal and Blood Brain Barrier (BBB) permeability through the microbiota-gut-brain axis and contributes to neuroinflammation [53]. Neuroinflammation promotes the accumulation of misfolded proteins and axonal

damage and is associated with neurodegenerative disorders [54]. Interestingly, probiotics have shown to help in maintaining the integrity and structural components of the intestine and BBB through the microbiota-gut-brain axis, thereby mitigating the pathogenesis of neurodegenerative disorders [55]. Thus, the role of microbiota, a healthy gut environment and the maintenance of a well-balanced coexistence state between the microbiota and host should be studied further in relation to chronic inflammatory processes, and especially disorders that are of an autoimmune origin such as HD and MS [56].

3. O3FA AND DIET

The findings described above show that O3FA have anti-inflammatory and antioxidant effects and their loss seems to be associated with neurodegeneration, which naturally leads to the logical conclusion that dietary O3FA may be beneficial for neurodegenerative disorders. O3FA are natural compounds that can be obtained from several dietary sources and are commonly available as nutritional supplements [57–59]. ALA is a dietary fatty acid that is commonly found in plant oils such as mustard seed oil and flaxseed oil, while Eicosapentaenoic Acid (EPA) and DHA are the major lipid constituents of fish oil [60]. DHA is an essential component of fish oil and is associated with roles integral to brain development and cognition [61]. In line with the expectation that they may be beneficial for neurodegenerative disorders, several studies report the benefits of dietary O3FA for brain aging and cognitive dysfunction [62–65]. This literature is discussed in detail later in this article. Moreover, although these studies provide a compelling basis for the use of dietary O3FA for neurodegenerative disorders, the use of natural compounds for neurodegenerative disorders is often limited by their poor bioavailability and limited penetration across the BBB. The recent development of targeted CNS drug delivery systems [66–68] has aided in improving the CNS bioavailability of natural compounds such as O3FA [69, 70]. In addition, molecular docking studies with natural compounds have also helped in better characterizing ligand/receptor interactions and selecting compounds with higher activity at desired targets, thereby aiding the development of natural products against neurodegenerative disorders [71].

4. NEUROPROTECTIVE EFFECTS OF O3FA

Recent studies have established a link between the intake of dietary O3FA and a decreased incidence of neurodegenerative diseases such as AD [86, 87]. Studies have also reported that transgenic models of AD are more vulnerable to DHA depletion as compared to healthy controls, and DHA exerted protective effects against pathophysiological hallmarks of AD such as cognitive dysfunction, amyloid-beta plaque accumulation and tau protein hyperphosphorylation [88]. Additionally, O3FA have been shown to improve amyloid-β phagocytosis by macrophages in subjects suffering from MCI [16].

Cognitive impairments are a common feature of several neurodegenerative disorders such as PD, MCI and AD [89–91] and there are reports of supplementation of O3FA having beneficial roles in improving cognitive function. Another study [92] reported significantly improved cognitive function in patients suffering from MCI with DHA supplementation (2g/day) for 12 months. Similar results were reported in other studies [93, 94]. However, a contrary report noted an overall negligible benefit for cognitive impairment and dementia in

individuals with cognitive impairments [95]. Additionally, it shows the effects of supplementation of O3FA on cognitive decline depending on the stage of cognitive decline. A longitudinal observational study reports that patients with mild MCI had positive results when provided with DHA and EPA. However, no benefits were reported in patients with established AD [96]. Similarly, a meta-analysis study reported marginal evidence for beneficial effects of supplementation of O3FA in patients deficient in O3FA, while no conclusive effects were obtained in patients with neurocognitive deficits such as Attention Deficit Hyperactivity Disorder (ADHD) [97]. Another systematic review reported beneficial effects of supplementation of O3FA in predominantly mild AD cases, with very few studies reporting improved scores of cognitive functions in more severe cases [98]. Similar studies have been reviewed extensively to discuss the beneficial effects of O3FA in AD which confirm the overall beneficial effects of O3FA in very mild AD [99]. A survey of 21 studies that reported risks for MCI, cognitive decline, dementia, PD or AD and utilized nutraceutical formulations of O3FA as interventions was included in a systematic survey. The survey reported that a 0.1-g/d increment of dietary DHA intake was associated with lower risks of dementia and AD [100]. On the contrary, a meta-analysis study assessing the efficacy of supplementation of O3FA for the treatment of people with dementia showed no evidence of a benefit from O3FA supplementation on cognitive function when measured at six months using different measures such as AD Assessment Scale - Cognitive subscale and Clinical Dementia Rating. There were also no differences found on mental health when measured with the Montgomery-Åsberg Depression Rating Scale. The authors report one small study which showed beneficial effects of O3FA in instrumental activities of daily living at 12 months post supplementation of O3FA [101]. On similar lines, [102] reported DHA supplementation did not slow the rate of cognitive and functional decline in patients with mild to moderate AD. Similar effects were reported in another study where supplementation of O3FA did not delay the rate of cognitive decline in patients with mild to moderate AD [103]. Thus, there have been mixed reports regarding the effects of supplementation of O3FA on cognitive function and AD. Furthermore, it shows that the beneficial role of supplementation of O3FA for cognitive function and AD is largely determined by the extent of cognitive dysfunction and the stage and severity of AD. O3FA have also been shown to prevent behavioral and neurochemical disturbances induced by the neurotoxin 6-hydroxydopamine (6-OHDA) in animal models of PD, presenting a potential neuroprotective action against PD [14]. The proposed mechanism of the beneficial effects of O3FA for PD involves their antioxidant and anti-inflammatory properties [104]. A study comprising 1053 individuals with self-reported idiopathic PD reported an association between fish oil and reduced PD progression, suggesting evidence between targeted nutrition and PD progression [105]. Additionally, studies have reported beneficial effects of administration of fish oil, as a promising nutraceutical agent to delay the onset of mitochondrial dysfunction in the brain, which is often related to age or pathological conditions such as increased oxidative stress [106].

Impaired levels of O3FA in the brain can affect and alter the brain dopamine system in a manner that may augment the risk of developing both neurological disorders such as PD and HD as well as neuropsychiatric disorders related to dopamine such as schizophrenia, substance dependence, and depression, especially when coupled with contributing genetic

and environmental factors [110]. Similarly, recent studies have shown the benefits of anti-inflammatory agents for neuropsychiatric disorders [111, 112]. Exposure to drugs of abuse is also known to disrupt brain dopamine systems and dopamine-related behavior [113–115], which may be reversible with DHA treatment. DHA and other O3FA are ligands for nuclear receptors such as the retinoid X receptor (RXR) [116]. The RXR heterodimerizes with the nuclear receptor-related-1 protein (Nurr1) and nerve growth factor 1B (Nur77), are highly expressed in brain regions involving dopamine synthesis such as the substantia nigra and ventral tegmental area, thereby implicating possible roles of O3FA in dopaminergic neuron survival and development [117] as well as implications for neurological and neuropsychiatric disorders.

In spite of all this promising literature in support of O3FA in neurodegenerative disorders, the exact nature of these associations and mechanisms of action for the neuroprotective effects of O3FA is not completely elucidated, and some studies have yielded mixed results. For instance, a study [106] reported that fish oil treatment in aged mice led to increased levels of neuroprotectin D-1, a neuroprotective compound derived from unesterified DHA, which may be implicated in its neuroprotective mechanisms. Meanwhile, Taghizadeh and colleagues (2017) reported co-supplementation of O3FA and vitamin E improved levels of glutathione, an antioxidant enzyme, which could have favourable outcomes for neurodegenerative disorders such as PD and AD that are characterized by increased oxidative stress [118]. EPA and DHA give rise to compounds such as resolvins and protectins through pathways involving cyclooxygenase and lipoxygenase enzymes, which are implicated in the anti-inflammatory effects of O3FA [119]. On the contrary, some studies have reported no beneficial effects of O3FA supplementation on conditions commonly associated with neurodegenerative disorders. A study [120] reported supplementation with 1400 mg EPA+DHA failed to reduce common systemic inflammation markers in healthy adults. Similar results were reported in another study evaluating the anti-inflammatory effects of supplementation of O3FA on other inflammatory markers, such as tumor necrosis factor (TNF)-α and IL-6 [121]. Another study [122] reported that supplementation of O3FA reduced triglyceride levels in type-2 diabetes patients, yet there was no significant effect on inflammatory and oxidative stress markers. A systemic review and meta-analysis evaluated the effect of supplementation of O3FA on Expanded Disability Status Scale (EDSS) and proinflammatory cytokines such as IL-1β, IL-6 and TNF-α in MS. This study revealed that O3FA supplementation had no significant effect on the EDSS scale and serum levels of IL-1β and IL-6 as compared to placebo. However, supplementation of O3FA significantly lowered serum levels of TNF-α, suggesting some therapeutic potential of O3FA for the management of MS warranting further study [123]. Another study [124] reported that supplementation of O3FA did not lead to any significant effect on psychological health and neurocognitive functioning among US soldiers. However, it is interesting to note that while some studies use supplemental or nutraceutical O3FA as treatments in their study designs, others use prescription O3FA. These two classes are not interchangeable, and their differences may be a major contributing factor to discrepancies observed across different studies, as described in detail in the following section.

5. NUTRACEUTICAL VERSUS PHARMACEUTICAL O3FA

Dietary supplements are a very common source of O3FA in the US and typically contain DHA and EPA in varying proportions and have different lipid effects [125]. Additionally, they may also have varying quantities of impurities and additives, which may not have undergone stringent quality control tests. These issues are of utmost importance given that many OTC supplements of O3FA contain only minor compositions of O3FA, with larger amounts of other fats, specifically pro-inflammatory omega-6 fatty acids (O6FA) and omega-9 fatty acids (O9FA), comprising the majority of the dietary fats per dose. Additionally, O3FA are prone to oxidation and some studies have indicated that the consumption of fish oil capsules with increased levels of peroxidized lipids may have adverse health effects, thereby highlighting the need for proper quality control, storage, and expiration of these supplements [126]. Despite their popularity as nutritional supplements, there are currently no prescription products of O3FA available in the US for neurodegenerative disorders. O3FA are currently prescribed for triglyceride reduction as monotherapy or in combination with statins in patients with hypertriglyceridemia [127]. Prescription O3FA are supported by robust clinical trial data and several safety monitoring programs, while on the other hand, neutraceuticals of O3FA containing DHA, EPA, and other fatty acids are not required to demonstrate safety, efficacy, and FDA approval prior to marketing [128].

The variation in the composition and type of fish oil supplements is a major barrier in the attainment of therapeutic goals for O3FA for neurodegenerative disorders [129]. The fish oil supplements that are commonly used in clinical trials for neurodegenerative disorders have lower concentrations of the active ingredients, which are EPA (about 18%) and DHA (about 12%), as compared to prescription O3FA. Almost 70% of supplement product composition can be composed of other ingredients such as saturated fats, other O3FA, O6FA, O9FA, and impurities that may affect the therapeutic potential [130]. For instance, to achieve a dose equivalence to 4g per day of Vascepa, the approved prescription EPA product, a patient would need to consume at least 20, 1 gram units of fish oil supplements (assuming 18% EPA per unit), to achieve comparable amounts of EPA from a daily dose of Vascepa [131]. Thus, it might be more beneficial to evaluate the therapeutic potential of regulated prescription formulations of O3FA for neurodegenerative disorders in clinical trials, rather than evaluating nutraceutical formulations of O3FA that are characterized by a lack of standardization and are inherently susceptible to variations in the amount of EPA and DHA present in them. Interestingly, an extensive assessment of the effects of O3FA on cardiovascular health was performed [132]. Most of the evidence was collected from supplement trials of EPA and DHA and the results of the assessment indicated that increasing EPA and DHA had little or negligible effects on mortality or cardiovascular effects. This study further supports the notion that the variations in the composition and type of fish oil supplements and their non-uniformity may probably be the largest barrier in the attainment of therapeutic goals for O3FA for neurodegenerative disorders.

Studies in human subjects have indicated that the coadministration of O3FA with statins decreased triglyceride levels in patients with type-2 diabetes [133], as well as subjects suffering from hypertriglyceridemia [134]. Several studies have indicated a link between

cardiac events such as diabetes, hypertriglyceridemia and atherosclerosis, and brain damage [135, 136]. In addition, studies have also indicated relationships between conditions such as stroke and cardiac myopathy, indicating links between brain health and cardio vascular events [137]. Studies have indicated type-2 diabetes as a risk factor for cognitive dysfunction and dementia [138]. Both type-1 and type-2 diabetes are known to contribute to the acceleration of cerebral atrophy and increased white matter abnormalities [139]. While the exact nature of these associations remains to be known, several studies suggest probable mechanisms. A study [140] reported mechanisms related to alterations in insulin and related proteins impairing the degradation of amyloid-beta plaques and contributing to AD-like pathology. Studies also suggest the roles of amyloid-beta and hyperphosphorylated tau accumulation in pancreatic islet beta cells in causing insulin insensitivity and impaired glucose uptake by the cells, promoting type-2 diabetes [141].

An unbiased search on https://clinicaltrials.gov entering the “condition” as “hypertriglyceridemia” and “drug” as “omega-3 fatty acids” revealed that clinical trials that have assessed the roles of O3FA for hypertriglyceridemia, have not evaluated their efficacy for neurodegenerative conditions or cognitive dysfunction which have been shown to be closely related to hypertriglyceridemia as discussed above. Thus, moving forward, it might be favorable to assess the effects of O3FA on secondary measures of cognitive decline in clinical trials studying the effects of O3FA on cardiac events, such as hypertriglyceridemia, considering the great overlap between cardiac health and brain health. Most studies evaluating the therapeutic efficacy of O3FA for neurodegenerative disorders use neutraceutical O3FA or fish oil. In contrast, the majority of the studies evaluating the therapeutic potential of O3FA for hypertriglyceridemia utilize prescription O3FAs, which are tightly regulated and have standardized amounts of O3FA. Moving forward, it might be beneficial to use standardized prescription O3FA in place of supplements, to obtain more reliable results, which can then aid in developing O3FA as prescription therapies for neurodegenerative disorders.

6. O3FA AND FREE FATTY ACID RECEPTORS (FFAR)

O3FA, have traditionally been associated with neuroprotective roles owing to their incorporation in the neuronal membranes, and different O3FA have distinct and sometimes synergistic neuroprotective effects [142, 143]. O3FA are associated with membrane properties such as membrane strength and fluidity [144]. Being the structural components of the membrane, they are also associated with neuronal membrane synthesis [145]. DHA, for example, has been shown to alter membrane properties such as fluidity and permeability, as well as interact with other membrane lipids such as cholesterol [10].

Recent studies have indicated that O3FA are also agonists for a subfamily of G protein-coupled receptors (GPCR), termed FFAR [146], indicating that some of their roles might actually be receptor-mediated and involve specific intracellular signaling pathways [147]. Currently, there are five GPCR that have been identified to be activated by fatty acids. FFA1 (GPR40) and FFA4 (GPR120) are selectively stimulated by long-chain fatty acids, including O3FA, whereas FFA2 (GPR43) and FFA3 (GPR41) are selectively stimulated by short-chain fatty acids, and GPR84 is selectively stimulated by medium chain length fatty acids [148].

Several beneficial effects of O3FA, including reduced inflammation, have been attributed to their effects on FFAR [149, 150]. While these receptors have garnered great interest recently, further studies are needed to elucidate their receptor pharmacology and regulation in more detail [151], particularly in the brain.

Research on the regulation of FFA1 gene expression at the transcriptional level has highlighted the role of FFA1 in the regulation of glucose metabolism [152]. Conformational studies have helped in further understanding the complexes formed between partial agonists such as MK-8666 and Ago-PAM and the intracellular loops and helixes of FFA1, helping further elucidate agonist binding with this receptor [153]. Stimulation of FFA1 with nonspecific agonists such as DHA or agonists such as GW9508, administered by intracerebroventricular (ICV) infusion, attenuated inflammatory pain induced by formalin and increased the release of β-endorphins [154].

Recent studies reported that O3FA, such as ALA and DHA, are agonists of FFAR and participate in receptor activation, intracellular signaling, and receptor regulation [155–157]. Supplementation with O3FA has also been shown to increase colonic FFA4 and actin expression, along with the suppression of inflammatory mediators such as TNF-α, thereby highlighting their anti-inflammatory potential through FFA4 agonism [158]. Studies report the involvement of the FFA4 in insulin sensitization and anti-diabetic effects of O3FA *in vivo* through the suppression of macrophage-induced tissue inflammation [159]. Furthermore, studies have reported vital structure-function and signaling differences between the two FFA4 isoforms, as well as links between FFA4 and proinflammatory ROS production in macrophages [160]. However, it has also been reported that FFA4 and GP84 gene expression in human adipocytes is very sensitive to proinflammatory mediators including TNF-α and IL-1β, which can reduce FFA4 expression. This inflammation-induced inhibition of FFAR may negatively impact the proposed anti-inflammatory activities of agonists of FFAR [161].

Although the complete mechanism of action of O3FA on FFAR is not completely elucidated, phosphorylation of FFAR leads to interactions between FFAR and β-arrestin-2, which can induce downstream disruption of the inflammatory cascade [162]. O3FA stimulate the activation of PLC-β/IP_3/Ca^{2+} pathways and are associated with downstream effects such as the release of brain-derived neurotrophic factor (BDNF) [163], which is involved in several vital brain functions, such as neuronal survival and growth, synaptic plasticity, and learning and memory [164–166]. BDNF is a member of a large family of neurotrophic growth factors, mainly found in the hippocampus and cerebral cortex of the brain. Studies have linked the loss of BDNF and cognitive dysfunction, as well as intake of O3FA and BDNF production. Docking studies indicate that the metabolites of O3FA have greater effects on the modulation of BDNF activity than the parent O3FA [167]. While the potential of agonists of FFAR as therapeutic targets for metabolic and inflammatory disorders is promising, the termination of Phase III clinical trials of the FFA1 agonist TAK-875/fasiglifam due to non-specific off-target effects highlights the need to further clarify the role and mechanisms involved in the development of these receptors as therapeutic targets [162, 168].

In attempts to reduce non-specific off-target effects of agonists of FFAR, novel structural models of the FFAR are being developed which highlight properties of the binding cavity such as hydrophilicity and the residue function involved in binding of FFAR, which aid in drug delivery of specific allosteric modulators [169, 170]. Drug discovery methods such as pharmacophore searches and docking studies have led to the identification of specific compounds that are active at FFA1 and identified their functionality as either full agonists, partial agonists, or pure antagonists. Site-directed mutagenesis and docking studies led to the identification of different patterns of ligand-receptor interactions and further elucidate the roles and functions of particular amino acids that are involved in the binding and activation of FFA1 [171]. Similarly, well-validated models have been developed to study ligand-FFA4 interactions that will help in identifying novel ligands and the subsequent development of FFA4 as a therapeutic target [172].

7. SYNTHETIC AGONISTS OF FFAR

While synthetic selective agonists of FFAR may not have been widely studied for neurodegenerative disorders, they have been studied for a closely related metabolic and inflammatory disorder such as type-2 diabetes [173–175]. The positive results for these peripheral disorders strongly support their potential for neurodegenerative disorders, because of the overlap in inflammation and metabolic dysregulation between neurodegenerative and cardiovascular disorders [27].

TUG-424 is an FFA1 agonist and at a concentration of 100 nM, increases glucose stimulation. Another FFA1 agonist, compound 22, has been shown to have a favorable physicochemical and pharmacokinetic profile, and has displayed potent effects on glucose tolerance in diet-induced obese mice [176]. MR1704 is another FFA1 selective agonist that has been reported to improve glucose homeostasis in rats through improved glucose-dependent insulin secretion [177]. Additionally, FFA1 full agonists such as AM-1638 and AM-6226 have shown to stimulate glucose-dependent insulino-tropic peptide (GIP) and glucagon-like peptide (GLP-1) secretion from intestinal enteroendocrine cells leading to enhanced glucose control in a streptozocin mouse model of type-2 diabetes [178].

Considering the overlap between cardiac and brain health, these compounds should be tested for neurodegenerative roles [179]. TAK-875 is an FFA1 agonist and was terminated in phase III studies due to off-target hepatotoxicity side effects of liver toxicity. Additionally, attempts were made to develop FFA1 agonists with lower lipophilicity by carrying out structural modifications and by molecular modelling techniques. One such compound developed was compound 44, which had a strong hypoglycemic effect in type-2 diabetes mellitus mice and showed lower risks of inducing liver toxicity [180]. Previously, it was believed that a single binding site exists for fatty acids and synthetic FFA1 agonists. However, recent studies have revealed that partial and full agonists bind differently at different sites and exhibit positive heterotropic cooperativity [181].

GW9508 was the first synthetic ligand of FFA4 identified [182]. However, it was not selective for FFA4, and shows a considerable affinity for FFA1, which restricts its application to some extent. Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist

derivatives, such as NCG21, have shown high selectivity for FFA4 over FFA1, although not complete selectivity. Other FFA4 agonists, such as GSK137647A and grifolic, have been developed, although their selectivity for FFA4 is not completely established [183, 184].

TUG-891 is a selective FFA4 synthetic agonist and has displayed properties of stimulating calcium mobilization, recruitment of the protein β-arrestin 1, as well as extracellular kinase phosphorylation [185]. All of these functions have been shown to play numerous roles in the CNS and their alterations are implicated strongly in several neurodegenerative disorders [186, 187]. Despite its moderate potency, it has very high lipophilicity and limits its solubility in suitable solvents for drug delivery, which highlights the need for more druggable FFA4 agonists [172]. Efforts were made to screen more than 80 natural compounds, to identify novel, selective ligands for FFA1 and FFA4 by drawing comparisons to MEDICA16, an FFA1 agonist to further probe the pharmacological and physiological functions of these receptors [188].

Such efforts to develop synthetic ligands for FFAR with more specific activity, increased potency, suitable physio-chemical and pharmacokinetic properties and reduced off-target side effects can aid the development of O3FA as druggable targets for neurodegenerative disorders. Many synthetic ligands of FFAR have been tested as potential therapeutics for type-2 diabetes, and other metabolic conditions. However, considering the great overlap between these conditions and neurodegenerative disorders, it is necessary to study these ligands in the context of neurodegenerative disorders. Several synthetic agonists of FFA1 and FFA4 have been reviewed extensively and literature supports further investigation and future studies to explore their potential development as pharmacotherapeutics for neurodegenerative disorders and other metabolic conditions [168, 174, 188–191].

8. DRUG DELIVERY SYSTEMS TO INCREASE THE BIOAVAILABILITY OF O3FA

Bioavailability is defined as the amount of drug or substance that is available at the site of activity, or that reaches systemic circulation [195]. The concentration of O3FA in the plasma serves as an indicator of the fatty acid supply in the diet, while the concentration of O3FA in blood cells is usually a marker of long-term bioavailability [196]. While there are several ways to express the bioavailability of O3FA, the three most commonly employed ones are the omega-3 index, C_{max} and Area Under the Curve parameters [197]. O3FA are highly lipophilic molecules, containing long carbon chain structures, and can cross the BBB. This aspect makes them suitable candidates for CNS drug delivery [12]. Additionally, the use of specific carriers in conjunction with O3FA further enhances their brain delivery. Molecules, such as 1-lyso, 2-docosahexaenoyl-glycerophosphocholine (LysoPC) and Ace-DoPC (1-acetyl,2-docosahexaenoyl-glycerophosphocholine), have shown to increase the intracerebral DHA transport by almost 10-fold, thereby facilitating DHA transport selectively to the brain [126].

The half-life of EPA and DHA after repeated administration is reported to be 37 h and 48 h, respectively [198]. There are several factors that can affect the bioavailability of O3FA, which needs to be considered for their development as pharmacotherapeutics for

neurodegenerative disorders. O3FA in specific drug formulations could interact with dietary fatty acids, thereby impacting their bioavailability [199]. Additionally, the fish oil formulations that are marketed as soft gelatin capsules may have different amounts of DHA and EPA across formulations [200]. Furthermore, O3FA are available in different forms and the recommendations on their consumption vary substantially. Variability in the frequency of dosing can also lead to variations in the bioavailability of O3FA. A study using rats reported that a large dose of long-chain O3FA once a week was more effective in increasing the whole-body long-chain content of O3FA as compared to smaller doses delivered daily [201]. Concerning the issues discussed above, there are methodological challenges that exist with current bioavailability studies of O3FA. The major ones include limitations with standardization of analytical methods and protocols, different sample sources for the detection of O3FA such as blood and plasma, non-standardized amounts of O3FA present in the formulations, differences between dosage forms, batch to batch variations in supplements, lack of standardized doses on the basis of body weights, challenges associated with measuring fatty acid content in membranes, and failure to control the total dietary fat intake [201, 202].

There are several prescription products of O3FA available for reducing hypertriglyceridemia and non-prescription nutritional supplements that are currently available and are well summarized in the review [129]. Ethyl ester formulations of O3FA, containing EPA and DHA are poorly absorbed, unless they are consumed with meals that contain dietary fat to aid absorption [203]. However, this approach might not be feasible in patients with increased cardiovascular risk as they are advised to reduce the consumption of fats. This led to technological advancements to enhance EPA and DHA absorption, such as *in-situ* emulsification, which improves bioavailability [204], and incorporation within nanoparticles and nanocapsules to improve the absorption of fatty acids in a low-fat environment [205]. Additionally, as O3FA are prone to oxidation, microencapsulation helps in stabilizing the fish oil mixture, thereby protecting it from oxidation [206, 207]. Thus, newer formulation strategies coupled with concrete bioavailability studies can aid in the therapeutic development of O3FA.

CONCLUSION

Neurodegenerative disorders are very common in the elderly population and are characterized by several pathophysiological hallmarks such as protein misfolding, neuroinflammation, increased oxidative stress, neurotoxicity, cognitive deficits, and mood alterations [3]. Owing to the numerous interconnected hallmarks, and very complex interplay between all these features, the treatment of neurodegenerative disorders remains very challenging. Natural product O3FA exhibit anti-inflammatory, antioxidant, and neuroprotective properties that make them suitable candidates for the treatment of multifactorial disorders such as AD and PD [7]. O3FA have traditionally been associated with neuroprotective roles and neuronal membrane strengthing owing to their incorporation into neuronal membranes [12]. However, over approximately the last 10 years, their agonist effects at FFAR have gained great attention and attempts have been made to evaluate their therapeutic benefits for several inflammatory and metabolic disorders. Apart from studying the naturally occurring O3FA, such as DHA and EPA, attempts have been made to use

molecular docking and pharmacophore binding studies to develop selective, targeted agonists for FFAR as potential pharmacotherapeutics [172]. Several studies have highlighted the promising neuroprotective roles of O3FA in both pre-clinical, as well as clinical studies studies. Inspite of all the data available, O3FA are currently not available as prescription drugs for CNS conditions. They are commonly available as nutraceuticals, intended for general health benefits such as improvements in cognitive function [125]. However, these supplements do not undergo robust testing to prove their safety and efficacy and may have varying concentrations of EPA and DHA [128]. Additionally, it will be more beneficial to use prescription O3FA in clinical studies to evaluate their therapeutic potentials for neurodegenerative disorders, as commonly occurs in clinical trials evaluating efficacy of O3FA for hypertriglyceridemia. This will assist in increasing the rigor of the findings and minimize the variability observed owing to the use of non-validated and non-standardized dietary supplements.

Considering that prescription O3FA have been approved by the FDA for triglyceride reduction, clinical studies have established their safety and efficacy, and the overlap between cardiac health and normal brain function, considerable advances could be made through the application of prescription O3FA for neurodegenerative conditions. In addition, O3FA are drug-like molecules with current prescription use, the capacity to be formulated in suitable pharmaceutical drug delivery systems [208], and sufficient BBB penetrance to be used for CNS disorders [209]. It is now known that O3FA have specific molecular targets and specific ligands for FFAR could show improved efficacy and reduced off-target effects [169]. In the future, biotechnology could provide novel O3FA from plants and single-cell organisms [210]. Based on all of this, the development of O3FA as prescription therapeutics for neurodegenerative disorders seems plausible and warranted, especially if they can be repurposed from prescription therapies for lowering triglycerides.

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Table 1.

Summary of studies comparing various parameters for natural product omega-3 fatty acids and synthetic agonists of free fatty acid receptors.

Parameter	Natural Product O3FA	Synthetic Agonists of FFAR	Refs.
Proposed Mechanism of Action	Membrane incorporation and activation of FFAR	Activation of FFAR	[192]
Receptors	FFA1 and FFA4 – medium and long-chain FA (EPA and DHA)	FFA1 – GW9508, AM4668, TAK-875, AMG-837 FFA4 – TUG-891, GW9508	[173]
Half Life	Approximate values of ALA, EPA and DHA are 1, 50, and 20h, respectively	Largely unknown	[180, 181]
Brain Transport Coefficient	[^{14}C]-DHA: 48 ± 3 μl g^{-1} s^{-1} [^{14}C]-EPA: 52 ± 4 μl g^{-1} s^{-1}	Largely unknown	[182]
Routes of Administration	Oral, Parenteral, IP	Oral, IP, ICV,	[182]
Prescription Therapies	Lovaza, Vascepa, Epanova Omtryg	None	[67]
Indications	Hypertriglyceridemia	None	[193]
Dose	2–4g/day	Largely unestablished	[193]
Commonly Reported Adverse Effects	Infections, skin rashes, eructation, nausea/ vomiting, dyspepsia, taste perversion	Largely unestablished TAK-875 – liver toxicity	[194]

FFAR=Free Fatty Acid Receptors; FFA1=Free Fatty Acid Receptor 1; FFA4=Free Fatty Acid Receptor 4; EPA=Eicosapentaenoic Acid; DHA=Docosahexaenoic Acid; ALA=Alpha-Linolenic Acid; IP =Intraperitoneal; ICV= Intracerebroventricular; O3FA= Omega-3 Fatty Acids.