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REVIEW PAPER

The Effects and Mechanisms of n-3 and n-6 Polyunsaturated Fatty Acids in the Central Nervous System

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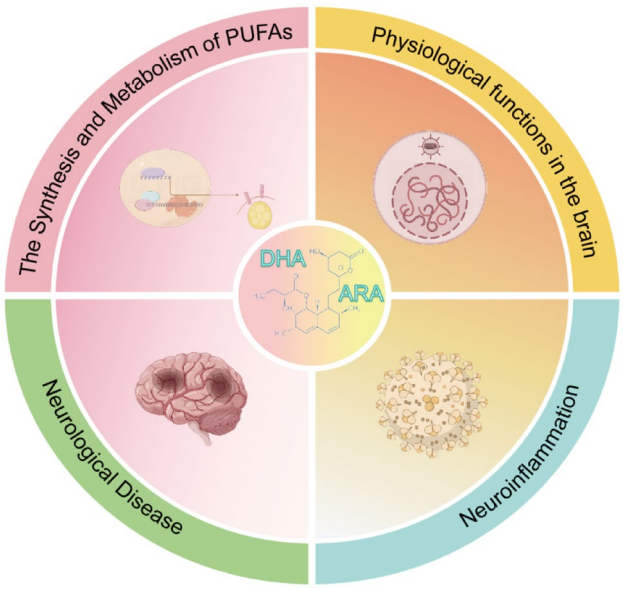
Abstract

The brain is rich in fatty acids (FAs), with polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (C22:6n-3, DHA) and arachidonic acid (C20:4n-6, ARA), and the former predominantly stored in the form of phosphatidylcholine, phosphatidyl ethanolamine (PE, diacyl and plasma phospholipid proform), and phosphatidylserine (PS), while the latter is mainly found in ethanolamine phosphoglycerides (EPG) and contributes to constitute most of phosphoglycerides. When required by the body, PUFAs are liberated from membrane phospholipids (either directly or via their metabolites, which are generated by a series of enzymatic reactions) to participate in various cerebral physiological processes. PUFAs and their derivatives play crucial roles in modulating numerous bodily functions, including neuronal signal transmission, neurogenesis, neuroinflammation, and glucose uptake in the brain, thereby sustaining fundamental brain function. Although PUFAs have been implicated in a spectrum of neurological disorders, including acute brain injury (TBI), multiple sclerosis (MS), and neurodegenerative diseases, their role in conditions such as depression, Alzheimer's disease (AD), and Parkinson's disease (PD) is particularly noteworthy. These disorders are closely linked to critical brain functions, including cognition, memory, and inflammatory processes. Given the substantial body of research elucidating the involvement of PUFAs in the pathogenesis and progression of these diseases, this review will specifically concentrate on their impact within these contexts.

Graphical Abstract



n-3/6 polyunsaturated faty acids (PUFAs) are synthesized by the liver and transported to neurons via the circulatory system. The majority of PUFAs exist in the promoting the differentiation of neural stem cells. Additionally, PUFAs facilitate brain glucose uptake and exert anti-inflammatory effects that influence the progression of neurological disorders such as Alzheimer's disease and Parkinson's disease

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Keywords Polyunsaturated fatty acids · Effects · Mechanisms · Central nervous system

Introduction

Lipids are fat-soluble components of the human body, and their constituent monomers include fatty acids (FAs), which are divided into saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) according to the number of double bonds in the alkyl chain. Depending on the position of the first double bond in the carbon chain, PUFAs are divided into n-3, n-6, and n-9 PUFAs (Table 1). In human brain, n-3 and n-6 PUFAs mainly exist in the cell, organelle membrane (mainly in the form of phosphatidylcholine, phosphatidyl ethanolamine (PE, diacyl and plasma phospholipid proform), and phosphatidylserine (PS)) and myelin. As the PUFAs in the human brain, docosahexaenoic acid (C22:6n-3, DHA) is predominantly distributed in phosphatidylcholine, PE, and PS. In contrast, arachidonic acid (C20:4n-6, ARA) shows relatively lower abundance, primarily localized within ethanolamine phosphoglycerides (EPG). Notably, the human brain harbors trace amounts of EPA, linolenic acid (C18:2n-6, LNA), and α-linolenic acid (C18:3n-3, ALA)—a distinct biochemical profile distinguishing it from peripheral tissues (O'Brien and Sampson 1965; Svennerholm 1968). All of them play crucial roles in the development of neurons, synapses, and endothelial cells, as well as in the maintenance of neuronal differentiation. Traditionally, humans have obtained n-3 PUFAs, such as DHA and EPA, from fish and seafood, and n-6 PUFAs, like ARA, from sources including beef, pork, and eggs. Now, through a specialized process, DHA- and ARA-rich oils derived from fissure microalgae are also available for human consumption (Ren et al. 2022). In early development, the enrichment of DHA in the frontal, occipital, forebrain, and posterior brain regions is very important for brain development, and DHA can regulate the biological processes of embryonic neural stem and progenitor cells (NSPCs) (Taipale et al. 2020). In patients with autoimmune diseases, DHA can also reduce the production of the inflammatory factors interleukin-1 (IL-1) and interleukin-6 (IL-6) and protect the body from inflammatory damage (Hahn et al. 2022). ARA and its metabolites, such as prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs), are important inflammatory mediators involved in the progression of neuroinflammation. Due to the exceptional biocompatibility and unique pharmacological properties, PUFAs have emerged as promising drug carriers in recent antitumour research, including carriers for paclitaxel for treating glioma and melanoma and gemcitabine for the treatment of non-small cell lung cancer (Sun et al. 2017). Recent studies have demonstrated that alterations in PUFA metabolism are strongly associated with the progression of human brain disorders. These metabolic changes significantly impact critical neurological processes, including neurogenesis, synaptic formation, and inflammatory responses in the brain. Furthermore, substantial evidence has revealed distinct patterns of PUFA intake and metabolic level variations across multiple neurological diseases. In light of these findings, researchers have begun to elucidate the molecular mechanisms underlying PUFA transport into neuronal cells and their subsequent regulation within the brain microenvironment. In this review, the metabolism of PUFAs in the brain and their relationships with synaptic function, neuronal stem cell differentiation, brain inflammation, and the progression of nervous system diseases are reviewed.

Table 1 Fatty acid classification

Type	Name	Symbol	Number of double bonds
SFAs	Palmitic acid	C16:0	0
SFAs	Stearic acid	C18:0	0
n-3 PUFAs	α-linolenic acid (ALA)	C18:3n-3	3
n-3 PUFAs	Eicosapentaenoic acid (EPA)	C20:5n-3	5
n-3 PUFAs	Docosapentaenoic acid (DPA) n-3	C22:5n-3	5
n-3 PUFAs	Docosahexaenoic acid (DHA)	C22:6n-3	6
n-6 PUFAs	Linoleic acid (LNA)	C18:2n-6	2
n-6 PUFAs	Arachidonic acid (ARA)	C20:4n-6	4
n-6 PUFAs	DPA n-6	C22:5n-6	5
n-9 MUFAs	Oleic acid (OA)	C18:1n-9	1
n-9 MUFAs	Erucic acid (EA)	C22:1n-9	1

n-3/6 PUFAs are Synthesized in the Liver and Metabolized in the Brain

n-3/6 PUFAs are Synthesized in the Liver and subsequently Transported to the Brain Through Endothelial Cells

SFAs and MUFAs can be actively synthesized within the brain, whereas PUFAs are primarily supplied by the blood. LNA and ALA, which serve as precursors for the synthesis of PUFAs and are essential FAs for humans, can be obtained only via external supplementation. In the liver, ALA and LNA can synthesize DHA, n-3 docosapentaenoic

acid (C22:5n-3, DPA n-3) and ARA under the actions of Δ6 desaturase, elongases (including elongases 2 and 5), Δ5 desaturase, and β-oxidation, respectively. Subsequently, as a result of the activities of transporter proteins, these PUFAs enter the bloodstream in the form of lipoproteins and can ultimately be used to maintain normal brain and retinal function (Song et al. 2022). Circulating lipoproteins gain entry into endothelial cells through three distinct mechanisms: (i) Sodium ion-dependent activation of the major facilitator superfamily domain-containing protein 2A (MFSD2A), inducing its outward-open conformation to facilitate transport(Bergman et al. 2023); (ii) Passive diffusion of non-albumin-bound esterified fatty acids across the endothelial membrane, mediated by specific transport proteins (Murphy 2017); (iii) Receptor-mediated endocytosis, where very low-density lipoproteins (vLDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs) undergo cellular internalization following binding to their cognate receptors (vLDLR, LDLR, and HDLR, respectively). Within endothelial cells, fatty acids (FAs) are sequestered by cytoplasmic fatty acid-binding proteins (FABPs) and subsequently transported across the blood–brain barrier through two distinct mechanisms: (i) carrier-mediated transport via specific fatty acid transport proteins (FATPs) localized in the endothelial basement membrane, or (ii) passive diffusion along concentration gradients. Following cellular uptake, these FAs undergo dynamic metabolic cycling through the Lands cycle, a continuous process of esterification and de-esterification catalyzed by the long-chain acyl-CoA synthetase (ACSL) activity intrinsic to FATPs. Additionally, interactions with peroxisomes or mitochondria enable beta-oxidation, thus providing energy for the brain (Fig. 1).

The Biosynthesis of Both n-3 and n-6 PUFAs is Rate-Limited by the Enzymatic Activity of Δ6 Desaturase

The biosynthesis of n-3 and n-6 PUFAs, exemplified by DHA and ARA, exhibits distinct metabolic kinetics due to differential substrate specificity of key enzymes. The

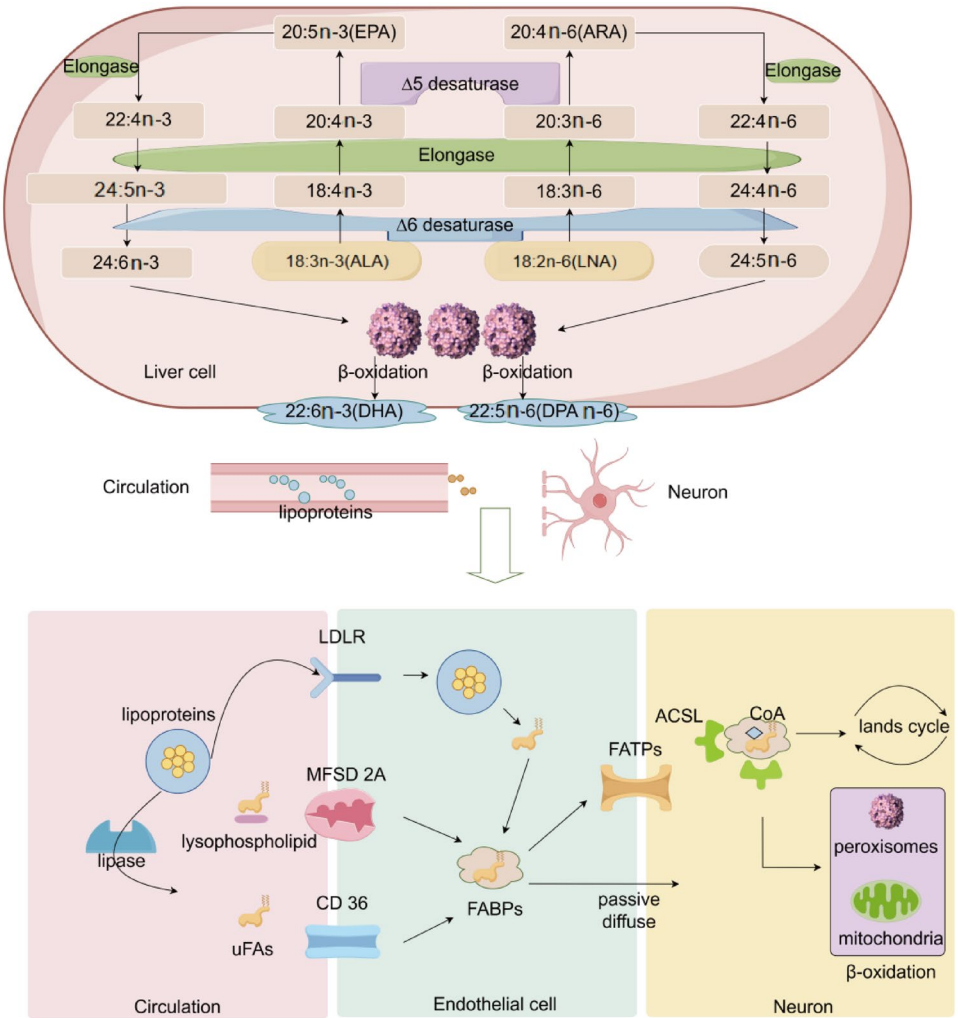

Fig. 1 Metabolic processes of n-3/6 PUFs in the liver and brain. ALA and LNA synthesize various n-3/6 PUFAs under the action of various enzymes, most of these PUFAs are bound to lipoproteins, and a small part of them are transported throughout the body in the form of lysophospholipids throught the blood. PUFAs transported to the blood–brain barrier can cross the BBB in the following ways: (i) bind directly to lipoprotein receptor recognition; (ii) PUFAs in the form of lysophospholipids enter through MFSD 2A; (iii) entry into endothelial cells via the transporter CD36. In endothelial cells, lipoproteins are hydrolysed to fatty acids and bound to fatty acid binding proteins (FABPs), either by fatty acid transporters (FATPs), or by passive transport into neurons. After entering the neuron, it is directed towards esterification and defat or β oxidation under the action of long-chain fatty acid CoA synthetase (ACSL)

enzymes in PUFA metabolism, including Δ6 desaturase, elongases (including elongases 2 and 5), and Δ5 desaturase, demonstrate preferential binding affinity for n-3 PUFAs, resulting in enhanced synthesis rates and systemic circulation of n-3 derivatives, particularly DHA, within and beyond hepatic tissues. This metabolic asymmetry may be attributed to multiple regulatory factors: (1) ALA bioavailability and utilization efficiency; (2) Retroconversion of DHA to EPA (Metherel and Bazinet 2019); (3) Modulation by oxidative stress status (Barrera et al. 2020); (4) Protein sufficiency and insulin-mediated activation of Δ5 desaturase and Δ6 desaturase; (5) Downregulation of Δ5 desaturase and Δ6 desaturase expression by epinephrine and glucocorticoids (Nakamura and Nara 2002); (6) Nutritional inhibitors including protein deficiency and excessive intake of trans fatty acids, fructose, cholesterol, and ethanol (Videla et al. 2022). Δ6 desaturase, the pivotal enzyme in C14 and C22 fatty acid desaturation, exhibits substrate preference that influences subsequent enzymatic reactions. The preferential binding of elongases 2 to n-3 PUFAs is secondary to Δ6 desaturase selectivity, with elongases 2 demonstrating 5.1-fold greater catalytic efficiency than Δ6 desaturase for n-3 substrates and 11.4-fold higher activity for n-6 substrates, establishing Δ6 desaturase as the primary rate-limiting factor in n-3/6 PUFA biosynthesis (Valenzuela et al. 2025). The enzymatic machinery for n-3/6 PUFA synthesis is differentially expressed across tissues, with highest abundance and activity in hepatic tissue, followed by brain, testicular, and renal tissues (Valenzuela et al. 2024), Consequently, hepatic steatosis and oxidative stress significantly impact n-3/6 PUFA biosynthesis in both hepatic and cerebral tissues (Zuniga-Hernandez et al. 2024).

Active Derivatives of n-3/6 PUFAs

Under conditions of stress, phospholipase A1 (PLA1) and phospholipase A2 (PLA2) cleave the ester linkages at the sn-1 and sn-2 positions of phospholipids, respectively. The liberated PUFAs are subsequently converted into various bioactive derivatives by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 enzymes (Cyt P450). COX-2 is prominently expressed in neural tissue and facilitates the conversion of ARA into PGs and TXs. LOX enzymes convert ARA into LTs and specialized pro-resolving mediators such as lipoxins (LXA4 and LXB4), whereas Cyt P450 enzymes generate various hydroxyeicosatetraenoic acids (HETEs). Currently, the active metabolites derived from n-3 PUFAs in the brain comprise resolvin D (RvD), neuroprotectin D1 (NPD1), maresin 2 (MaR2), 14S-hydroxy-docosahexaenoic acid (14-HDHA), 17-HDHA, and maresin 1 (22-COOH-MaR1). RvD can enhance the phagocytosis of microglia and reduce the accumulation of neutrophils in cerebral ischemic diseases (Li et al. 2023). Additionally, injections of NPD1 into ischemic stroke rats can decrease the ischemic area and atrophy, suppress mitochondrial BCL-2-associated X protein (BAX) expression, and mitigate mitochondrial apoptosis following brain injury (Zirpoli et al. 2021). DPA, biosynthesized from EPA and ARA through elongation reactions catalyzed by specific elongase enzymes, undergoes extensive oxidative metabolism via multiple enzymatic pathways. LOX-mediated oxidation generates various hydroxylated derivatives, including 11-hydroxylDPA (11-HDPA), 14-hydroxylDPA(14-HDP), and 8,14-dihydroxylDPA (8,14-HDPA). Additionally, COX-2 in conjunction with dehydrogenase activity catalyzes the formation of 13-hydroxylDPA and 13-oxo-DPA (EFOX-D5). Notably, acetylated COX-2 and dehydrogenase mediate the production of 17-HDPA and 17-oxo-HDPA (17-EFOX-D5), which function as potent peroxisome proliferator-activated receptor gamma (PPARγ) agonists. Furthermore, DPA serves as a precursor for specialized pro-resolving mediators (SPMs) through sequential COX and LOX catalysis, generating protective metabolites and maresin analogs such as resolvin D1 DPA (RvD1 DPA) and maresin 1 DPA (MaR1 DPA) (Dyall 2015; Weylandt 2016). In pathological states such as brain injury and local inflammation of the brain, these active derivatives are significantly increased and can even be increased to higher levels, which can be utilized to combat neuronal damage and serve a neuroprotective role (Fig. 2).

n-3/6 PUFAs Maintain the Functions of the Brain

n-3/6 PUFAs are Associated with Synaptic Formation and Neuronal Differentiation

Neuronal axons and synapses are essential structures for sustaining efficient neural information transmission and normal brain function. The most prominent pathological characteristic of slow nervous system degeneration is synaptic impairment. DHA and EPA play vital roles in the synthesis of phosphatidylserine (PS) to preserve the stability of the synaptic membrane, and EPA can increase the expression of synaptic amides to maintain the plasticity of the synaptic membrane (Wang et al. 2023). The synthesis of synaptic amides initiates with the binding of serine and palmitoyl coenzyme A. PS undergoes enzymatic hydrolysis, facilitated by enzymes such as phospholipase, to release free serine. This serine serves as a crucial precursor for the synthesis of ceramides and other sphingolipids, including sphingosine. These sphingolipids, in conjunction with PS, contribute to the formation of lipid rafts. These lipid rafts play a pivotal role in the aggregation of signaling molecules and receptors, thereby enhancing the efficiency of signal transduction.

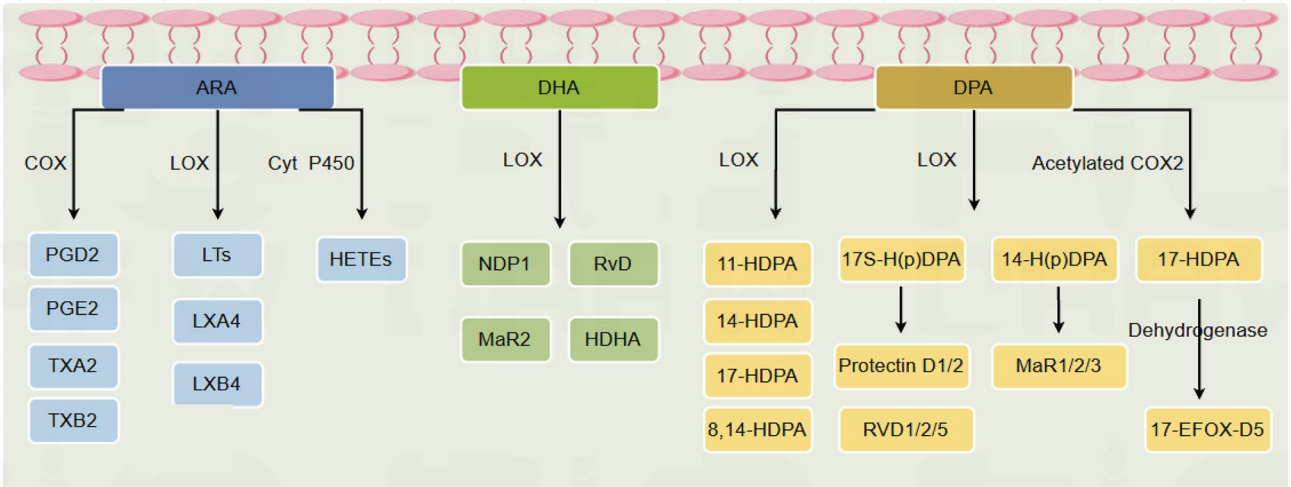

Fig. 2 Active derivatives of n-3/6 PUFAs. ARA forms prostaglandins (PGs), thromboxanes (Txs), leukotrienes (LTs), lipoxins (Lxs) and hydroxy-eicosateraenoic acid (HETEs) under the action of cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P4502 (Cyt P450), respectively, and DHA is mainly formed Resolvin D (RvD), neuroprotection D1 (NPD1), and COX-2, DPA undergoes metabolic transformation into various bioactive compounds, including hydroxyl derivatives, protectors, and MaR analogues. These metabolites play significant roles in the regulation and maintenance of neuronal functions

Furthermore, as a synthetic precursor of synaptic amides, PS is integral to the stability and remodeling of synaptic structures. It influences membrane bending and fusion processes, promotes the release of synaptic vesicles, and indirectly contributes to the formation and consolidation of memory (Kim et al. 2022; Kim and Spector 2018). In addition, DHA can promote synaptic formation by increasing the expression of drebrin (a dendritic spine marker protein) and PSD95 (a postsynaptic density protein). Wen et al. proposed that the expression of PSD95 and synaptic amides was increased and that synaptic development was improved in 3-week-old mice supplemented with DHA (Wen et al. 2021). In cases where injury leads to a loss of dendritic spines, DHA supplementation can help to restore dendritic spinal density and maintain the structural integrity of synaptic connections. A previous study demonstrated that when sevoflurane was administered to six-day-old mice for three consecutive days, a reduction in the prominent synaptic marker known as PSD95 and abnormal synaptic morphology could be observed. At this point, exogenous DHA was added, and the comprehensive synaptic morphology was subsequently analyzed using fluorescence electron microscopy (Tao et al. 2016). Moreover, the integrity of the mitochondrial structure is crucial for sustaining synaptic information transmission. When cardiolipin (a primary component of the mitochondrial membrane) undergoes peroxidation, synaptic circuit function becomes compromised. DHA can protect cardiolipin from peroxidation, thereby preserving synaptic function (Chang et al. 2015). Under the action of calcium ion-activated PLA2, phospholipid molecules release unesterified DHA. This DHA molecule is subsequently passively transported into the nuclear membrane, where it binds to retinoic acid receptor α (RXRA). This binding enhances the expression of immediate early genes (IEGs) and increases synaptic density (Cao et al. 2020). Furthermore, some scholars have noted that DHA activates the Nrf-Nqo1 pathway to maintain axon growth (Drolet et al. 2021). DHA can also stimulate the growth of neuronal dendrites by elevating the expression of proteins associated with neurotransmitter development. Human progenitor cells pretreated with DHA/EPA have demonstrated enhanced hippocampal cell activity and maintain more intact neural structures when being subjected to cytokine damage, such as that caused by interleukins (Borsini et al. 2021). PUFAs can also reduce the level of the axon growth inhibitor Nogo-A, increase the expression of synaptic amides, suppress microglial activity, and facilitate the recovery of the synaptic structure (Thau-Zuchman et al. 2019). As an agonist of RAF proto-oncogene serine/threonine protein kinase (RAF-1) and growth factor receptor, DHA significantly activates downstream signaling pathways and supports neuronal growth and development. Moreover, when the levels of PUFAs in the neuronal membrane decline, the activity of RAF-1 compromised, thereby leading to substantial inhibition of neuronal development (Fig. 3). DHA is also critically important for synaptic development in young children. Supplementation with DHA can markedly increase the lengths and numbers of individual hippocampal neuron branches in newborns, induce synaptic formation, and facilitate the functions of synapsin and glutamate receptors (rather than GABA receptors), thereby improving hippocampal-related cognitive function. During brain development and cell membrane expansion, the

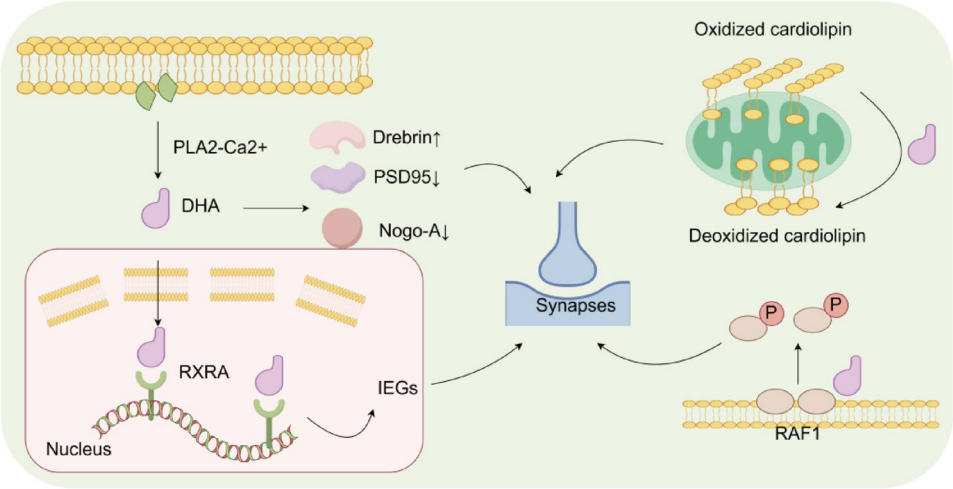

Fig. 3 DHA maintains synaptic integrity. Under PLA2 action, DHA from membrane phospholipids is released and maintains synaptic integrity in the following ways: (i) DHA promotes Drebein expression and inhibits Nogo-A and PSD95 expression. (ii) DHA binds to retinoic acid receptor α (RXRA) gene in nucleus to promote immediate early genes (IEGs) expression; (iii) DHA is involved in the reduction process of oxidized cardiolipin; (iv) DHA interacts with RAF proto-oncogene serine/threonine protein kinase (RAF-1) to promote the growth of synapses and maintain their integrity

physiological doubling that occurs during the S phase of mitosis is a necessary condition for these processes, and DHA is also involved in these processes. Once n-3 PUFA levels are depleted, the rates of phospholipid synthesis and decomposition during this process significantly decline, and DHA significantly accelerates esterification, which is not conducive to the growth and development of neurons (Andersen et al. 2021).

Except the n-3/6 PUFAs, their derivatives are also indispensable for neurogenesis. Studies have demonstrated that rats with nerve injury exhibit significantly reduced levels of synaptic amines. However, when these amines are supplemented with a diet rich in DHA, the differentiation rate of neural stem cells is markedly accelerated. As a metabolite of DHA, NPD1 not only inhibits the expression of pro-inflammatory genes but also upregulates antiapoptotic genes, thereby preserving neuronal structural integrity and promoting synaptic formation under pathological conditions (Bosviel et al. 2017). In addition, the endocannabinoids (eCBs) synthesized from PUFAs play a vital role in maintaining neuronal activity and regulating synaptic function in the basolateral amygdala (BLA) of the basal ganglia (Watkins et al. 2023). These eCBs significantly influence intersynaptic communication. The process involves phospholipase A2 (PLA2) hydrolyzing phospholipid molecules in the postsynaptic membrane, leading to the synthesis of eCBs. These eCBs are then released into the synaptic cleft through exocytosis, where they bind to cannabinoid receptor 1 (CB1) in the presynaptic membrane, modulating neurotransmitter release (Fig. 4). Additionally, eCBs interact with brain-derived neurotrophic factor (BDNF) (which is produced through the hydrolysis and metabolism of DHA via phospholipase), maintain synaptic integrity, and prevent synaptic breakdown. In a lateral fluid percussion injury model used to simulate nerve damage in the BLA of female mice, researchers observed disrupted eCB signaling, significantly reduced synaptic activity, increased ARA levels in tissues, and enhanced inflammatory signaling. Interestingly, supplementation with exogenous DHA or eicosapentaenoic acid (EPA) restored eCB levels and enhanced synaptic activity in the BLA of female mice. These effects are likely mediated through the antagonistic actions of DHA and EPA on arachidonic acid (ARA) metabolism (Stielper et al. 2021).

The orchestrated differentiation of neural stem cells (NSCs) into various cells (particularly glial cells) is a pivotal aspect of neuronal development, and DHA or EPA can effectively induce the differentiation of NSCs into astrocytes. Following treatment with DHA or EPA, the differentiation process of NSCs is characterized by a progressive increase in glial fibrillary acidic protein (GFAP)-positive cells, elevated levels of phosphorylated cyclic AMP response element-binding protein (CREB), and a significant upregulation of BDNF. Notably, the DHA- or EPA- induced phosphorylation of CREB remains unaffected by cyclic adenosine monophosphate (cAMP) antagonists. These observations collectively suggest that DHA and EPA enhance the levels of neurotrophic factors and sustain the differentiation of NSCs into astrocytes, thereby supporting neurogenesis (Yu et al. 2021). Furthermore, DHA and ARA play regulatory roles in the differentiation process of NSPCs. While both DHA and AA maintain the proliferation capacity of NSPCs, their influence on differentiation is more nuanced. Specifically, DHA

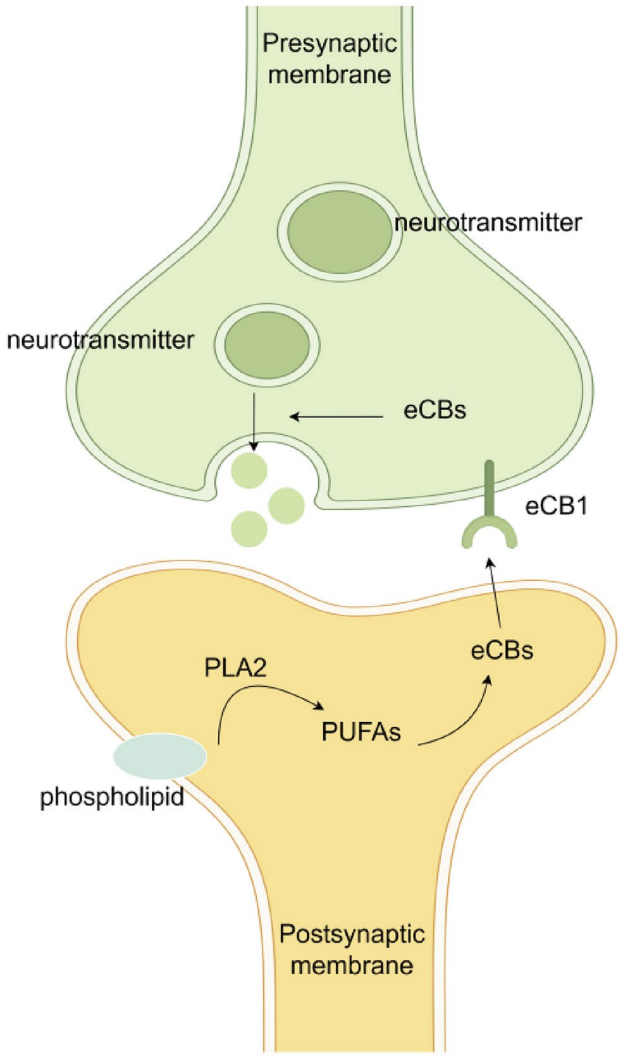

Fig. 4 PUFAs affect endocannabinoid mediated synaptic communication. Endocannabinoids (eCBs) are signalling lipids produced by PUfas present in phospholipids in neuron cell membranes. PUFA is released from the postsynaptic membrane by PLA in response to neuronal activity. eCB is released into the synaptic space and can then bind to the presynaptic cannabinoid receptor type 1 (CB 1) on the presynaptic neuron. Activation of CB 1 leads to the release of neurotransmitters and the inhibition of synaptic activity

facilitates the maintenance and neuronal differentiation of NSPCs, whereas AA promotes their differentiation into astrocytes. Additionally, the transcriptional repressor hairy and enhancer of split 1 (Hes1) is implicated in NSCs differentiation. EPA modulates the differentiation of NSCs into neural progenitor cells (NPCs), neurons, and various glial cells through the activation of Hes1, whereas DHA tends to suppress the expression of Hes1. Moreover, EPA has been shown to upregulate the Hes1 expression, while concurrently promoting Hes6 expression. The interplay between Hes1 and Hes6 establishes a positive feedback loop, significantly enhancing neuronal differentiation (Ferguson et al. 2016).

n-3/6 PUFAs and Myelination

Myelination represents a fundamental process in human neural development, serving as the structural and functional cornerstone of the nervous system. The composition of myelin is primarily characterized by a complex array of lipids, including cholesterol, galactosylceramides, thioglycosides, gangliosides, phosphatides, and very long-chain fatty acids (VLCFAs), particularly PUFAs. Notably, the fetal brain actively stores these essential fatty acids in preparation for myelination (Schneider et al. 2022). During the critical period of the third trimester, the fetal brain undergoes a remarkable acceleration in PUFA accumulation, with DHA reaching substantial levels of 50–70 mg per day. This developmental window is so crucial that infants born prematurely before 29 weeks of gestation are deprived of normal DHA supplies. Clinical evidence demonstrates that when these preterm infants receive appropriate DHA supplementation, they exhibit significantly higher IQ scores at 5 years of age compared to their non-supplemented counterparts, underscoring the vital role of DHA in neurocognitive development. (Gould et al. 2022). The rapid accumulation of DHA in the fetal brain during gestation, coupled with its abundant presence in breast milk, synergistically supports the development of cognitive, neurological, and psychological functions in the fetus. The critical role of fatty acids, particularly DHA, in fetal brain development has been extensively documented in numerous scientific reviews (Devarshi et al. 2019; Lauritzen et al. 2016).

n-3/6 PUFAs and Cognition

Cognitive decline poses a significant challenge associated with aging. A previous research has demonstrated that mild cognitive impairment (MCI) patients receiving exogenous high-dose (810 mg) DHA supplementation for three to six months exhibited notable improvements in clinical cognitive scores, offering promising insights and potential therapeutic approaches for addressing cognitive impairment in elderly populations (Stavrinou et al. 2020). Another study revealed that after two years of supplementation with DHA/EPA, the elderly supplement group demonstrated fewer errors in working cognition compared to the placebo group. Moreover, as cognitive load increased, the supplement group consistently outperformed the placebo group (Power et al. 2022). These findings suggest that appropriate supplementation with n-3 PUFAs may mitigate age-related cognitive decline. Beyond their effects on age-related cognitive dysfunction, numerous studies have investigated the impact of PUFAs on cognitive function in various disease states. For instance, cognitive insufficiency in Alzheimer's disease (AD) is frequently associated with alterations in brain PUFA levels. Analyses of cerebrospinal fluid (CSF) and plasma

PUFA components in AD patients have revealed that higher CSF DHA levels are correlated with a reduced risk of cognitive impairment. A longitudinal evaluation of n-3 PUFAs intake and cognition among participants in the AD Neuroimaging Initiative (ADNI) demonstrated that long-term supplementation with n-3 PUFAs (particularly DHA) could prevent 60% of AD onset and reduce cognitive decline by 20% (Wei et al. 2023). In addition, the intestinal microbiota is an important environmental factor for the normal immune function of microglia. Cognitive dysfunction in AD patients is frequently accompanied by intestinal microbiota disturbances, which can influence the secretion of amyloid beta peptide (Aβ) or tau protein and promote the progression of AD via ARA-mediated neuroinflammation (Chen et al. 2022). Additionally, using a mouse model of depression, a previous study demonstrated that changes in the glymphatic system and the expression of aquaporin-4 (AQP4) in cerebrovascular cells with reduced compliance jointly affected the mice's cognitive function. Exogenous DHA supplementation was able to rescue changes in the glymphatic system, thereby improving the cognitive decline of mice with depression (Wei et al. 2023). Recent studies have also indicated that the cognitive decline during menopause can be improved through exogenous supplementation with n-3 PUFAs and that the reduction in estrogen during menopause affects the synthesis of BDNF, impacting the formation of neuronal axons and dendritic tree spines. In ovariectomised (OVX) mice, exogenous supplementation with choline-DHA, increased BDNF secretion and dendrite intersections in CA1 and CA3 pyramidal neurons in the hippocampus, leading to improve cognitive function (Konuri et al. 2021). However, the detailed mechanism by which n-3/6 PUFAs affect cognition still requires further investigation.

n-3/6 PUFAs and Mood

Clinical studies have demonstrated the involvement of PUFAs in emotion regulation. A controlled trial revealed that patients with depression exhibit significantly lower serum levels of EPA and DHA (Gao et al. 2024). Furthermore, the serum concentrations of ARA were observed to be significantly lower in patients with bipolar disorder (BD) compared to controls. Genome-wide association studies have identified fatty acid desaturase (FADS) as a susceptibility gene for BD, which significantly alters ARA concentrations, potentially contributing to BD pathogenesis (Ashizawa et al. 2024). However, the etiology of these serum PUFA alterations in depression and BD patients remains unclear, with potential contributions from both fatty acid metabolism disorders and dietary modifications. Epidemiological studies indicated that reduced dietary intake of n-3 PUFAs is associated with increased prevalent of affective disorders. Meta-analytic studies have consistently demonstrated that lower n-3 to n-6 PUFAs ratio correlates with higher depression rate (Wang et al. 2022). Consequently, significant research attention has been directed toward the mood-regulating potential of n-3 PUFA supplementation. A 52-week randomized, double-blind trial revealed that DHA supplementation reduces initial brain entropy in the left posterior cingulate gyrus (PCG) of patients with depression (Lin et al. 2024). Previous investigations have shown that the etiology of these serum PUFA alterations in depression and BD patients remains unclear, with potential contributions from both fatty acid metabolism disorders and dietary modifications (Mischoulon et al. 2022). A recent clinical cohort study investigating the exogenous supplementation of DHA/EPA and vitamin D in patients with depression revealed no significant difference in depressive symptoms compared with those receiving a placebo (Vyas et al. 2023), suggesting potential dose- or formulation-dependent effects. The therapeutic potential of n-3 PUFA supplementation on mood has also been investigated in animal studies. In a chronic unpredictable mild stress (CUMS)-induced depression model, CUMS significantly elevated corticosterone levels while reducing the concentration of 5-hydroxytryptamine (5-HT) in hippocampal neurons—effects that were mitigated by DHA/EPA supplementation. Notably, EPA supplementation demonstrated superior efficacy in ameliorating depression-like behaviors compared to DHA (Peng et al. 2020). Additionally, in a sleep deprivation, rats subjected to 7-day sleep deprivation exhibited depressive behaviors and reduced CB1 protein expression, which were reversed following DHA supplementation (Wang et al. 2020b). Therefore, n-3 PUFAs are more likely to be useful for treating mood disorders; however, the clinical use of n-3 PUFAs still requires further mechanistic studies and pharmacokinetic analyses.

n-3/6 PUFAs and Glucose Uptake in the Brain

An alteration in DHA levels within the brain may lead to neuronal damage due to hindered glucose absorption and utilization by neurons. An examination of the glucose absorption rates in lemurs supplemented with exogenous DHA revealed that, in comparison with the control group, an elevation in DHA levels notably increased glucose uptake across all brain regions (Pifferi et al. 2015). Furthermore, prior research conducted by Pifferi et al. revealed that decreased levels of DHA result in the suppressed expression of the endothelial glucose transporter protein (GLUT1), thus consequently diminishing glucose uptake (Pifferi et al. 2007). These findings suggest that exogenous DHA supplementation may improve brain glucose uptake in the context of disease.

n-3/6 PUFAs Play Significant Roles in the Progression of Neuroinflammation

The cerebral immune system of the brain is activated in response to various stimuli, including pathogens and other factors. This activation leads to the release of pro-inflammatory cytokines and chemokines, which subsequently interact with their cognate receptors within the central nervous system, thereby initiating a cascade of inflammatory responses collectively termed neuroinflammation. Mild neuroinflammation promotes the recovery of damaged nerves and glial cells, whereas excessive neuroinflammation can result in neuronal dysfunction. Devane et al. (1988) initially demonstrated the existence of the cannabinoid system in the brain and identified cannabinoid receptors 1 and 2 (CB1/2) (Devane et al. 1988). CB1 is predominantly localized to the terminals of nerve axons, where it principally modulates synaptic neurotransmission. In contrast, CB2 is located on the microglial cell membrane and contributes to the regulation neuroinflammation. The biosynthesis of endocannabinoids (eCBs), including anandamide (AEA) and 2-arachidonoylglycerol (2-AG), is mediated through the enzymatic hydrolysis of membrane phospholipids. This process is catalyzed by N-acylphosphatidylethanolamine-specific phospholipase D-like hydrolase (NAPE-PLD) and diacylglycerol lipase (DAGL), under the regulation of phospholipase A2 (PLA2). Recently, the pharmacological inhibition of the hydrolysis of eCBs was shown to promote the COX-2-mediated metabolic pathway of AEA conversion to PGs, consequently ameliorating neuroinflammatory responses. (Wen et al. 2023). Additionally, eCBs can bind to transient receptor potential vanillin-1 (TRPV1), modulating the activation process of microglia (Uliana et al. 2016). Moreover, G protein-coupled receptor 120 (GPR120), a specific receptor of n-3 PUFAs, exerts anti-inflammatory effects. Exogenous DHA administration has been demonstrated to alleviate the neuroinflammation in mouse glial cells induced by Japanese encephalitis virus infection via GPR120 (Chang et al. 2021). Furthermore, GPR120 activation has been found to suppress the nuclear translocation of NF-κB in microglia following lipopolysaccharide (LPS), thereby reducing the production of inflammatory factors and inhibiting microglial activation activation (Nakajima et al. 2023). Interestingly, LPS can also downregulate GPR120 expression in microglia by activating the Toll-like receptor 4 and p38 MAPK pathways (Zhao et al. 2020). The PUFA analog diethyl (9Z,12Z)-octaenediene-9,12 -diene-1-acylphosphonate (NKS3) has been demonstrated to inhibit the LPS-induced TAB1/TAK1/JNK pathway in macrophages via GPR120-dependent mechanisms. This intervention leads to the reduced production of interleukin-1β (IL-1β), interleukin-6 (IL-6), and nitric oxide (NO) (Boutanquoi et al. 2024). These findings suggest that the anti-inflammatory properties of n-3 PUFAs in neuroinflammatory conditions may be mediated through GPR120 upregulation in microglia, resulting in the attenuation of LPS-induced inflammatory responses. Furthermore, emerging evidence revealed that microglia express substantial levels of haematopoietic prostaglandin D synthetase (H-PGDS), and mice with GPR120 knockdown exhibit obvious hippocampal neuronal inflammation, which is possibly due to the fact that the knockdown of GPR120 upregulates the expression of H-PGDS, thereby resulting in the production of the pro-inflammatory factor PGD2 and the activation of microglia. In addition, upregulated PGD2 downregulates the expression of SOD2, and the production of reactive oxygen species (ROS) in hippocampal neurons is not inhibited, which exacerbates nerve damage (Iwasa et al. 2021). In addition to GPR120-mediated mechanisms, DHA and its derivative NPD1 have been shown to modulate macrophage-mediated inflammatory responses through peroxisome proliferator-activated receptor (PPAR) pathway activation, thereby protecting neurons from damage caused by inflammatory factors (Bosviel et al. 2017) (Fig. 5).

n-3/6 PUFAs and Neurological Diseases

AD

AD represents a prevalent neurodegenerative disorder, with global prevalence projected to triple by 2025. During the initial cellular phase of AD, the pathological accumulation of Aβ peptides coincides with the hyperactivation and proliferation of microglial cells, which subsequently facilitates the propagation of tau pathology. Currently, therapeutic strategies targeting Aβ and tau proteins are undergoing advanced-stage clinical trials (Scheltens et al. 2021). Neurochemical analyses in AD patients revealed significant reductions in DHA concentrations across multiple brain regions, particularly in hippocampal unesterified DHA pools, along with decreased levels of LOX and NPD1. A longitudinal cohort study of 129 AD patients demonstrated an inverse correlation between plasma DHA/EPA ratios and the rate of cognitive decline, with patients maintaining higher baseline DHA/EPA levels exhibiting slower progression of cognitive impairment. These findings suggest that DHA/EPA status may serve as a potential biomarker for AD progression and is closely associated with the neuropathological hallmarks of AD (Chu et al. 2022). Pathophysiological investigations have established that DHA depletion is mechanistically linked to the accumulation of Aβ plaques and neurofibrillary tau tangles. Quantitative analysis revealed that 6 months post-Aβ/

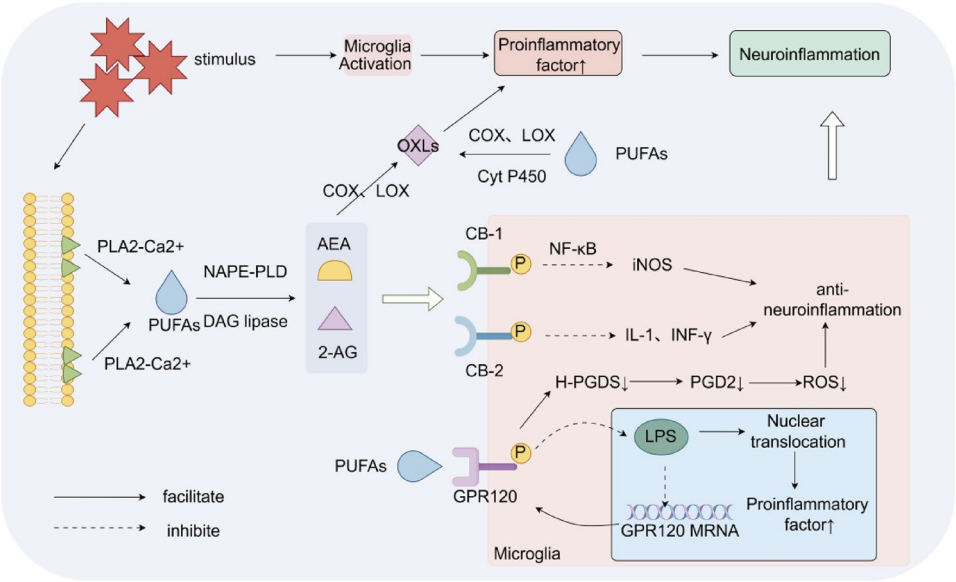

Fig. 5 PUFAs are involved in the progression of neuroinflammation. External stimulation causes the stress of neurons, microglia are activated, secrete and produce a variety of inflammatory facors, and promote the occurrence of neuroinflammation. Neuronal stimulation leads to hydrolysis of membrane phospholipids. Under the action of N-acylphosphatidylglycerol-specific phospholipase D-like hydrolase (NAPE-PLD) and diacylglycerol lipase (DAG) lipase, dissociated PUFAs form anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which can activate CB-1 and CB-2 receptors om microglia cell membrane. Activated CB-1 and CB-2 inhabit the production of inflammatory factors such as iNOS, IL-1 and IFN-γ. AEA and 2-AG can also form lipoxyprotein under the action of COX and LOX, which affects the occurrence of neuroinflammation. PUFAs also activates its specific receptor G protein-coupled receptor 120 (GPR120), which inhibits lipopolysaccharide (LPS)—induced nuclear translocation, thereby inhibiting the production of pro-inflammatory factors, and LPS inhibits the expression of GPR120 in microglia

tau deposition, significant reductions were observed in DHA and its bioactive metabolites, including RVD6 and NPD1, while PE species containing ARA showed marked elevation. Furthermore, a neuroinflammatory cascade involving COX-2, IL-1β, and chemokine ligand 2/3 (CCL2/3) was identified to potentiate Aβ and tau pathology, establishing a vicious cycle wherein proteinopathies and neuroinflammation mutually exacerbate AD progression (Do Carmo et al. 2024). Moreover, DHA have attracted attention in the treatment of AD because of their ability to inhibit neuromembrane plasticity and synaptic changes caused by inflammatory factors in the brain (Song et al. 2016). A clinical study involving 163 patients with AD demonstrated that EPA administration significantly reduces the levels of CCL4, a well-established biomarker of neuroinflammation. (Lin et al. 2022). Moreover, clinical evidence demonstrates that low-dose purified DHA (800 mg/day) or DHA-enriched supplementation exhibits therapeutic potential in ameliorating age-related cognitive decline among healthy elderly populations. However, a randomized controlled trial administering 2 g/day DHA monotherapy over an 18-month intervention period showed limited efficacy in improving cognitive performance in patients with mild-to-moderate AD. In contrast, combined supplementation with DHA (1.3 g/day) and EPA (0.45 g/day) for 12 months demonstrated significant improvements in both immediate verbal recall and delayed memory functions among individuals with mild cognitive impairment (MCI). Importantly, therapeutic intervention with optimal DHA dosage (1–2 g/day) has been shown to attenuate the progression of physiological cognitive decline and enhance cognitive outcomes in AD patients presenting with MCI. (Lee et al. 2013). DHA can enhance the phagocytosis activity of microglia, facilitating the clearance of Aβ deposits and stimulating the production of BDNF. This process leads to a reduction in the levels of the pro-inflammatory factor TNF-α, thereby promoting transition of microglia from the M1 phenotype (pro-inflammatory effect) to the M2 phenotype (anti-inflammatory effect). Moreover, EPA mitigates the hyperactivation of microglia and suppresses the conversion of ILs (such as IL-1β and IL-4). Analysis of inflammatory mediators in the plasma of AD patients indicates that both DHA and EPA are capable of lowering the concentrations of inflammatory invisible cytokines. Notably, DHA exerts a stronger effect in inhibiting single cytokines, and EPA tends to reverse inflammatory activity in AD patients (Serini et al. 2012). Compared to the control group, PS rich in DHA and EPA significantly inhibits the expression of amyloid precursor protein (APP), presenilin 1 (PS1), and β-site APP cleaving enzyme 1 (BACE1), reducing Aβ production in CHO-APP/PS1 cells. It also suppresses the

mitochondria-dependent apoptotic pathway, protecting hippocampal neurons from Aβ-induced damage. Additionally, it decreases the expression of inflammatory factors (TNF-α, IL-1β) and apoptosis, thereby alleviating the progression of AD (Che et al. 2018; Xu et al. 2021). Experimental evidence indicates that DHA administration markedly Aβ plaque deposition and downregulates the expression of caspase-3 and catalase in cerebral tissues, resulting in the suppression of neurofibrillary tangle formation and subsequent improvement of cognitive function in AD transgenic mice. Furthermore, DHA supplementation exhibits systemic metabolic regulatory properties, effectively modulating blood lipid profiles and normalizing serum uric acid and urea concentrations, suggesting its potential as an early treatment option for AD (Ruiz-Roso et al. 2018; Xiao et al. 2022). The neuroprotective effects of DHA against β-amyloid plaque formation are mediated through multiple distinct mechanisms: (i) its active metabolite, NPD1, modulates amyloid precursor protein-β (APPβ) processing through downregulation of BACE1 activity, while concurrently enhancing α-secretase ADAM10 and soluble APPα (sAPPα) production, thereby promoting a shift in APP processing from the amyloidogenic to the non-amyloidogenic pathway; (ii) activation of the receptor-interacting protein kinase 1/3 (RIPK1/RIPK3) signaling pathway results in attenuation of β-amyloid-induced microglial activation and subsequent neuroinflammatory responses; and (iii) upregulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, in conjunction with suppression of CD36 and FABP5 expression, ameliorates β-amyloid-induced neuronal oxidative stress and associated cellular damage (Huang et al. 2019; Yuan et al. 2020; Zhao et al. 2011). In contrast, ARA exhibits a pro-inflammatory effect that exacerbates the progression of AD. This detrimental effect is mediated through two distinct pathways: firstly, phosphatidylglycolamine, a metabolic derivative of ARA, interacts with phosphatidylethanolamine presents on neuronal cell membranes, thereby disrupting the nuclear factor NRF2 nucleation process and potentiating neuronal damage. Secondly, ARA oxygenated lipase-15 (ALOX-15), a crucial mediator of phospholipid peroxidation, modulates the redox homeostasis and reprograms the ferroptosis pathway, consequently accelerating AD pathogenesis. (Lane et al. 2021). Recently, the efficacy of dietary DHA supplements in AD patients and the results of animal models differ greatly, the reason may be that the control group in animal experiments is a complete lack of DHA diet, and the human diet cannot avoid the intake of DHA, but because of the particularity of lipids, animal models are still the best method.

Parkinson's Disease (PD)

Parkinson's disease (PD), which is the most prevalent neurological degenerative disorder following AD, is characterized by the degeneration of nigrostriatal dopaminergic neurons. The pathological hallmark of PD involves the formation of Lewy bodies (LBs), eosinophilic cytoplasmic inclusions composed primarily of α-synuclein (α-syn) aggregates, which disrupt synaptic communication and dopamine (DA) metabolism. Recent advances in PD research have identified multiple contributing factors, including oxidative stress, mitochondrial dysfunction, and neuroinflammation. A comprehensive lipidomic using liquid chromatography-mass spectrometry (LC–MS) has demonstrated significant alterations in FA metabolism in PD patients, specifically downregulation of triacylglycerol and neuromide alongside upregulation of fatty acyl metabolites. These metabolic disturbances in PUFAs have been implicated in PD progression (Sinclair et al. 2021). The susceptibility of PUFAs to reactive oxygen species (ROS)-induced damage is particularly relevant in the context of synaptic membrane integrity. ROS can initiate the autoxidation chain reaction of PUFAs at their diallyl sites; however, this process can be effectively inhibited through isotopic reinforcement by substituting hydrogen atoms with deuterium at these vulnerable positions. A clinical investigations have demonstrated that long-term supplementation with deuterium-reinforced PUFAs (D-PUFAs), particularly D-linolenic acid (D-LNA) and hydrogenated linolenic acid (H-LNA), significantly ameliorates DA neuronal damage in PD patients. Furthermore, a controlled study comparing 33,674 PD patients with 449,056 non-PD patients reported that increased supplementation with AA and EPA tended to lead to PD development (Zhu et al. 2023). Researchers employing 6-hydroxydopamine (6-OHDA) to induce PD-like symptoms in murine models demonstrated that ALA facilitates lipid droplet formation, enhances autophagic activity, and exerts potent antioxidant effects, thereby attenuating dopaminergic neuronal degeneration. Furthermore, DHA supplementation was shown to augment striatal dopamine synthesis through activation of secondary messenger systems involving protein kinase A (PKA) and protein kinase C (PKC). This mechanism regulates the expression of catecholamine synthase, specifically counteracting dopamine depletion and ameliorating clinical manifestations in 6-OHDA-induced PD mice (Alarcon-Gil et al. 2022; Chitre et al. 2020). Dietary supplementation with DHA has been demonstrated to upregulate complement component C1q expression while attenuating pro-inflammatory responses, thereby enhancing microglial phagocytosis and subsequent degradation of α-syn aggregates. This therapeutic intervention has shown efficacy in ameliorating α-synucleinopathy in transgenic mouse models, with concomitant neuroprotective effects on DA neurons and synaptic integrity (Zhang et al.

2023a). Nevertheless, conflicting evidence from alternative studies suggests that DHA supplementation primarily modulates the brain's susceptibility to oxidative stress without significantly influencing α-syn pathology. Furthermore, in a murine model of PD, dietary supplementation with DHA demonstrated significant therapeutic effects. Specifically, DHA administration led to a marked reduction in rotational behavior, concomitant with the restoration of dopaminergic activity as evidenced by normalized dopamine levels and tyrosine hydroxylase (TH) activity. At the molecular level, DHA supplementation was found to upregulate nuclear factor NRF2 expression, subsequently enhancing the production of 19,20-dihydroxydocosapentaenoic acid (19,20-DHDP). This bioactive lipid metabolite, mediated through NRF2 signaling pathways, facilitated the transcriptional activation of key antioxidant enzymes, including superoxide dismutase 1 (SOD1) and catalase, thereby ameliorating the functional deficits associated with PD pathology (Oguro et al. 2021). Abnormalities in the mitochondrial oxidative respiratory chain (particularly complex I) can lead to dopaminergic neuronal degeneration and even death, thus triggering PD onset. Hence, the restoration of the mitochondrial oxidative respiratory chain may impede PD progression. After Neuro 2A cells were subjected to starvation culture, DHA or EPA notably inhibited caspase-3 expression and reduced dopaminergic neuronal death. Neuroinflammation has also emerged as a predisposing factor for PD, with microglial activation spanning from the early to late stages of the disease. Furthermore, dietary supplementation with DHA exerts modulatory effects on glial cell activation in PD models, significantly attenuating astrocytic and microglial proliferation within the striatum and substantia nigra (SN) pars compacta, thereby ameliorating neuroinflammatory responses (Hernando et al. 2019). The neuroinflammatory cascade induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in murine PD models is primarily mediated through TNFR1-dependent activation of receptor-interacting protein kinase 1 (RIP1). DHA administration has been shown to downregulate RIP1 expression, enhance the survival of TH-positive dopaminergic neurons, and suppress the production of pro-inflammatory cytokines, particularly IL-1β and tumor necrosis TNF-α. Mechanistic studies have further elucidated that DHA exerts neuroprotective effects against MPTP-induced dopaminergic neuronal apoptosis through mitochondrial-dependent pathways and modulation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) signaling cascades (Kartik et al. 2023; Wang et al. 2020a). However, research on the ability of DHA supplements to alleviate symptoms and slow the progression in PD patients remains limited to animal studies.

Clinical trials investigating the efficacy of n-3 PUFAs supplements in the treatment of neuropsychiatric disorders, including depression, AD and PD, have been conducted for over two decades (Table 2). However, clinical trials of n-3 PUFAs supplements face significant challenges, including numerous complex factors that need consideration such as age stratification, gender differences, baseline DHA levels, inflammatory markers, neurotrophic factor levels, and FAs metabolism enzyme profiles.

Beyond AD and PD, n-3/6 PUFAs have also been shown to play a critical role in acute brain injury and repair processes. For instance, in traumatic brain injury (TBI) and stroke, n-3 PUFAs such as DHA and EPA have been demonstrated to reduce neuroinflammation, promote neurogenesis, and enhance functional recovery. Similarly, in other neurodegenerative diseases like multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS), n-3/6 PUFAs have been shown to modulate immune responses and protect against

Table 2 Association of n-3 PUFAs supplements with disease progression

Disease	Time	The amount	The efficacy
Depression	6 weeks	EPA 2 g + DHA 1 g/day	Effective in mild cases
	8 weeks	EPA 1.5 g + DHA 1 g/day	Depressive symptoms were significantly improved and BDI score was decreased ($p < 0.01$)
	12 weeks	EPA 1 g + DHA 0.5 g/day	Depressive symptoms were significantly improved and HAM-D score was decreased ($p < 0.05$)
AD	6 months	EPA 1.7 g + DHA 0.6 g/day	Mild cognitive function improved, but the effect was not significant in moderate to severe patients
	12 months	DHA 1 g/day	There was no significant improvement in cognitive function, but there was some effect in APOE4-negative patients
	18 months	DHA 2 g/day	Cognitive function decline slowed down, ADAS-Cog score improved ($p < 0.05$)
AD	3 months	DHA 1 g/day	Inflammatory markers were significantly reduced, but motor function was not significantly improved
	6 months	EPA 1 g + DHA 0.5 g/day	Motor function improved and UPDRS score decreased ($p < 0.05$)
	12 months	EPA 1.2 g + DHA 0.8 g/day	Cognitive function improved significantly, but motor symptoms did not change significantly

neuronal damage. These findings underscore the broad therapeutic potential of n-3/6 PUFAs across a spectrum of neurological conditions, warranting further investigation into their mechanisms of action and clinical applications.

Conclusion

In recent years, extensive research has been conducted on the role of PUFAs in brain physiology and pathology, consistently demonstrating their significant neuroprotective effects. Scientific evidence indicates that PUFAs play a crucial role in promoting the differentiation of neural stem cells into glial cells, enhancing the secretion of neurotrophic factors, and supporting neuronal growth and development. Furthermore, endocannabinoids derived from PUFAs have been shown to stimulate dendritic growth and maintain optimal synaptic membrane fluidity, thereby promoting the stability of interneuronal conduction—a critical factor in inhibiting the progression of neurodegenerative diseases. Notably, n-3 PUFAs have demonstrated remarkable therapeutic potential through their ability to inhibit microglial activation, reduce neuroinflammation, and suppress Aβ production, consequently improving clinical outcomes in patients with AD. The pathogenesis of PD frequently involves lipid metabolic disorders, and emerging evidence suggests that n-3 PUFA supplementation may offer therapeutic benefits for these conditions. However, the scientific community has yet to reach a consensus regarding optimal dosing regimens and administration methods. Future research directions should prioritize the elucidation of PUFAs signaling mechanisms in central nervous system disorders and the development of innovative strategies to enhance PUFAs stability in vivo, which may pave the way for novel therapeutic interventions in neurological diseases.

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Declarations

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