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Docosahexaenoic acid (DHA): An essential nutrient and a nutraceutical for brain health and diseases

Grace Y. Sun[a,*], **Agnes Simonyi**[a], **Kevin L. Fritsche**[b], **Dennis Y. Chuang**[c], **Mark Hannink**[a], **Zezong Gu**[d], **C. Michael Greenlief**[e], **Jeffrey K. Yao**[f], **James C. Lee**[g], **David Q. Beversdorf**[h]

[a] Biochemistry Department, University of Missouri, Columbia, MO, United States

[b] Department of Nutrition and Exercise Physiology, University of Missouri, Columbia, MO, United States

[c] Department of Neurology, University Hospitals Cleveland Medical Center and Case Western Reserve University, Cleveland, OH, United States

[d] Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, Columbia, MO, United States

[e] Chemistry Department, University of Missouri, Columbia, MO, United States

[f] Medical Research Service, VA Pittsburgh Healthcare System, and Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

[g] Department of Bioengineering, University of Illinois at Chicago, Chicago, IL, United States

[h] Department of Radiology, Neurology, and Psychological Sciences, and the Thompson Center, William and Nancy Thompson Endowed Chair in Radiology, University of Missouri School of Medicine, Columbia, MO, United States

Abstract

Docosahexaenoic acid (DHA), a polyunsaturated fatty acid (PUFA) enriched in phospholipids in the brain and retina, is known to play multi-functional roles in brain health and diseases. While arachidonic acid (AA) is released from membrane phospholipids by cytosolic phospholipase A_2 ($cPLA_2$), DHA is linked to action of the Ca^{2+}-independent iPLA2. DHA undergoes enzymatic conversion by 15-lipoxygenase (Alox 15) to form oxylipins including resolvins and neuroprotectins, which are powerful lipid mediators. DHA can also undergo non-enzymatic conversion by reacting with oxygen free radicals (ROS), which cause the production of 4-hydoxyhexenal (4-HHE), an aldehyde derivative which can form adducts with DNA, proteins and lipids. In studies with both animal models and humans, there is evidence that inadequate intake of maternal n-3 PUFA may lead to aberrant development and function of the central nervous system (CNS). What is less certain is whether consumption of n-3 PUFA is important in maintaining brain health throughout one's life span. Evidence mostly from non-human studies suggests that DHA intake above normal nutritional requirements might modify the risk/course of a number of diseases of the brain. This concept has fueled much of the present interest in DHA research, in particular, in attempts to delineate mechanisms whereby DHA may serve as a nutraceutical and

* Correspondence to: Biochemistry Department, University of Missouri Columbia, 117 Schweitzer Hall, MO 65211, United States.

confer neuroprotective effects. Current studies have revealed ability for the oxylipins to regulation of cell redox homeostasis through the Nuclear factor (erythroid-derived 2)-like 2/Antioxidant response element (Nrf2/ARE) anti-oxidant pathway, and impact signaling pathways associated with neurotransmitters, and modulation of neuronal functions involving brain-derived neurotropic factor (BDNF). This review is aimed at describing recent studies elaborating these mechanisms with special regard to aging and Alzheimer's disease, autism spectrum disorder, schizophrenia, traumatic brain injury, and stroke.

Keywords

Docosahexaenoic acid (DHA); Polyunsaturated fatty acids (PUFA); IPLA$_2$; Alox 15; Oxylipins; Neuroprotectin 1 (NPD1); Resolving; Neuroinflammation; Signaling pathways; Oxidative metabolites; 4-hydoxyhexenal (4-HHE); Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); Nuclear factor (erythroid-derived 2)-like 2 (Nrf2); Antioxidant response element (ARE); Heme oxygenase-1 (HO-1); Brain-derived neurotropic factor (BDNF); Brain development; Life spectrum

1. Docosahexaenoic acid (DHA) – an essential (n-3) polyunsaturated fatty acid (PUFA) enriched in the mammalian brain

The brain is a fatty tissue with higher proportions of lipids than proteins. Brain lipids, including phospholipids, sphingolipids, and cholesterol, are known to play critical roles in the structure and functions of cell membranes. Phospholipids in mammalian brain, including phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylethanolamine plasmalogen (PEpl), phosphatidylserine (PS) and phosphoinositides (PI, PIP and PIP2) have polyunsaturated fatty acids (PUFA) esterified in the sn-2 position (Fig. 1). Although all phospholipids have PUFA, each one has specific profile. For example, fatty acids in PS are comprised of high levels of palmitic acid (16:0) and docosahexaenoic acid (DHA; 22:6 n-3), whereas fatty acids in PI have high levels of stearic acid (18:0) and arachidonic acid (AA; 20:4 n-6) [1–3]. Besides being an integral part of the membrane structure, PS and PI have unique functions. PI and its phosphorylated derivatives are linked to G-protein coupled phospholipase C (PLC) for the release of inositol trisphosphates (IP3) and diacylglycerol (DG), which in turn serve as second messengers for mobilization of intracellular calcium stores and activation of protein kinase C (PKC), respectively. In contrast, PS is an anionic phospholipid present mainly in the inner monolayer of the plasma membrane, but its translocation to the outer monolayer serves as an indication of cell apoptosis [1,4].

The PUFAs in membrane phospholipids are metabolically active and undergo turnover through a deacylation-reacylation mechanism mediated by phospholipases A$_2$ (PLA$_2$) and ATP-dependent acyl-CoA acyltransferases [5,6] (Fig. 1). Under pathological conditions such as stroke, stimulation of PLA$_2$ together with depletion of ATP can perturb the deacylation-reacylation cycle and resulting in a rapid accumulation of free fatty acids [7]. The release of PUFA from membrane phospholipids is mediated by two major groups of PLA$_2$, namely the group IV cytosolic PLA$_2$ (cPLA$_2$) and the group VI calcium-independent PLA$_2$ (iPLA$_2$) (Fig. 1). Although each PLA$_2$ family is comprised of multiple isoforms, studies have

focused mainly on the cPLA$_2$α and iPLA$_2$β [8–10]. cPLA$_2$α is linked to inflammatory pathways through cell-specific receptors and activation of protein kinases, including the mitogen activated protein kinases (MAPK) and protein kinase C (PKC) [10]. This enzyme prefers acting on PC and releases AA, which serves as a substrate for cyclooxygenases (COX1/ COX2) and lipoxygenases (LOX). In turn, this leads to production of a large number of lipid mediators including prostanoids, thromboxanes, lipoxins and leukotrienes [11]. The Ca^{2+}-independent iPLA$_2$β does not exhibit obvious substrate specificities and is not regulated by protein kinases. However, there is evidence that this PLA$_2$ is the major source for the release of DHA [12,13]. In rodents, dietary deprivation of n-3 PUFA for 15 weeks can cause a decrease in iPLA$_2$ mRNA and protein in the brain [14]. Genetic depression of iPLA2 and inhibition of its activity by its specific inhibitor, bromoenol lactone (BEL) indicated a relationship between iPLA2 with oxidative stress and mitochondrial functions [15]. iPLA2 is highly expressed in the prefrontal cortex area, and its activity appears to play a role in acquisition of memory functions [16], and long term potential (LTP) [17]. Recent studies further demonstrated a role for iPLA$_2$ in exacerbating antidepressant effects and nociceptive responses [18–20]. A recent study demonstrated the effects of iPLA$_2$ and DHA release to interaction with 15-lipoxygenase (Alox 15), responsible for conversion of DHA to the oxylipin intermediates such as resolvin D1 (RvD1) [21].

The preferential production of AA by cPLA2 and DHA by iPLA2 led to further interest in understanding the multiple and diverse roles of these PUFA in mediating brain cell functions [22]. In particular, interest has focused on the role of DHA in neuropsychiatric diseases, including schizophrenia, depression, autism and age-related diseases such as Alzheimer's disease [23]. DHA is particularly important in brain development as there is a "DHA accretion spurt" during the last gestational period [24]. With increasing age, over the life span from 20 to 100 years, there is a 30% increase in PS (high in 16:0/22:6 species) and a 25% decrease in mitochondrial PE with 18:0/20:4 species [25]. The age-related changes in phospholipids with 22:6- and 20:4-containing phospholipid species suggest the need for these phospholipids to maintain proper brain functions. Due to rapid neurogenesis during the brain developmental period, sufficient dietary sources of DHA and (n-3) fatty acids are needed for maintenance of neuronal functions [22]. This pertains especially to the synaptic membranes which contain high levels of 22:6 phospholipids [26]. Findings from animal and clinical studies support the role of n-3 fatty acids as essential nutrients and a life-long factor spanning from childhood to old age [27].

2. Source of DHA in brain and cautionary notes regarding studies with dietary DHA

The DHA found in the CNS is not produced de novo in mammals. Instead, it must be obtained from the diet or synthesized from the precursor fatty acid, alpha-linolenic acid (ALA, 18:3 n-3). From a pure nutrition perspective, ALA is the only omega-3 fatty acid that is defined as a dietary essential nutrient [28]. Since the conversion of ALA into DHA is quite inefficient, involving many desaturase and elongase enzymes, many researchers speculate that there could be benefits in providing pre-formed DHA in the diet rather than relying solely on ALA [29]. This is particularly problematic during fetal and neonatal

development when CNS demands for DHA cannot readily be met by ALA alone [30]. In fact, it has been argued that nutrition guidelines associated with consumption of omega-3 fatty acids, particularly to those related to maternal and perinatal periods for infants, should be reconsidered [31].

Over the past decade, the focus of DHA research has shifted from its role in CNS development to maintenance of CNS health and function, particularly during aging and/or diseases. Among the most pressing questions for researchers are whether supplementation of the diet with DHA and/or other long-chain omega-3s can alter the risk of development or progression of these diseases [32]. For studies with animal models, it is important to distinguish between those studies that compare DHA treatment throughout life vs. those that provide DHA treatment at later stages of the animal's life. Additionally, many animal studies use dosages of omega-3s that exceed what is achievable in humans. Therefore, caution should be taken when interpreting results from such studies.

Dietary supplementation of DHA is thought to offer neuroprotection against chronic and acute inflammation within the CNS [33,34]. However, these studies may need to consider factors such as dosage, duration and mode of diet. In one study, two-month old (i.e., young adult) rats were fed a diet supplemented either with 150–300 mg/kg/day or a high dose of 600 mg/kg/day of DHA for one month. The low dose group resulted in improved spatial learning performance (escape latency) as well as retention (probe trial) in the Morris water maze, but the high dose group actually showed impairment in performance [35]. As referenced by a recent review, excess DHA administration showed either no effects or harmful effects in neurodevelopment [36]. Many forms of stress are known to induce oxidative stress and inflammatory responses which subsequently lead to alterations of neuronal and glial cell functions [37]. Studies directed to investigating whether dietary intake of DHA mitigates stress-induced oxidative and inflammatory responses need to consider these factors [37].

3. DHA on aging and Alzheimer's disease

3.1. Studies with cell and animal models

The potential neuroprotective effects of DHA have drawn interest in the investigation of whether it may have a positive impact on age-related decline in cognition and in AD-related neuropathology. In a study with female young (3 months) and old (24 months) mice, total DHA levels in blood and brain were significantly lower in aged mice as compared with the young mice [38]. The decrease in DHA in the aged group could be partially compensated upon administration of fish oil (550 mg DHA/kg body weight/day via oral gavage for 21 days). In several studies with aged rodents, DHA and/or eicosapentaenoic acid (EPA) supplementation was shown to improve performance in cognitive tests and elicit protection against neuroinflammation and oxidative stress [39–41]. Studies with AD transgenic (Tg) animal models appear to provide a general consensus suggesting beneficial effects of dietary DHA on learning and memory. It is important to note that many studies used long-term DHA administration and DHA supplementation started before evident behavioral impairments in the Tg animals. Nevertheless, positive effects were observed in the Morris water maze test with the APPswe/PS1 mice [42], in the radial arm maze with 5 X FAD

mice [43], in the novel object recognition with the 3 X Tg-AD mice [44], and in the Y maze and fear conditioning for Tg2576 mice [45]. On the other hand, in a study with the AD transgenic mice (TgCRND8), diets supplemented with 0.246% DHA (~0.5%) or an equivalent amount of corn oil (control) for six months indicated poorer spatial memory and elevated levels of TNFα expression in the DHA treated mice [46].

Studies with DHA dietary interventions also provided evidence for beneficial effects on neuropathology such as amyloid-beta and tau pathology, inflammation, and changes in certain biomarkers [47–51]. DHA was able to reduce AD-like neuropathology even when given to older Tg mice [52]. Sex-specific effects of the DHA diet have also been described; DHA had a greater effect on reducing plaque load in female than in male APPswe/PS1 mice. DHA diet also resulted in an increase of cortical synaptotagmin levels in female Tg mice but not in males [53]. A recent review on DHA and EPA, and oxylipins in pre-clinical and animal models of AD revealed evidence for differences in action between EPA and DHA [54]. The underlying mechanisms responsible for these effects are unknown and should be investigated in the future.

Considering $iPLA_2$ being a major source of DHA, the deficiency of DHA in the AD brain can be attributed to a reduction of $iPLA_2$ and in turn the availability of lipid mediators responsible for memory function [55]. In support of this phenomenon, bromoenol lactone (BEL), a specific inhibitor for $iPLA_2$, was shown to cause impairment of long term potentiation in the cortico-straital brain region, and the impairment could be rescued by an acute injection of DHA [56].

The evidence for chronic inflammation in the pathogenesis of AD has raised the question regarding whether n-3 PUFA may suppress the inflammatory responses. One hypothesis for the increase in oxidative stress and inflammatory responses in AD brain is related to the production of toxic beta amyloid (Abeta) species from the amyloid precursor protein (APP). Studies with cultured neurons demonstrated ability for oligomeric Abeta to cause excitotoxicity, increase production of reactive oxygen species (ROS) and activation of $cPLA_2$ [57]. Although this study did not test the effects of DHA, botanical antioxidants could reverse the neurotoxic effects of oligomeric Abeta [58]. In a more recent study, oligomeric Abeta were observed in an extract from AD brain and their exposure caused impairment of synaptic proteins [59]. In fact, oligomeric Abeta could also alter PLA_2s in astrocytes and despite of unknown mechanism of action, these interactions resulted in mitochondrial dysfunction [60]. There is increasing evidence supporting the role of microglial cells in mediating the oxidative and inflammatory responses in the AD brain. A recent review demonstrated a role for DHA and its oxygenated derivatives to modulate these inflammatory responses in glial cells through interacting with the peroxisome proliferator-activated receptor-γ (PPARγ) [61]. Microglial cells are known to exhibit multi-functions with ability to show phenotypic changes depending on the micro-environment. In a study with human CHME3 microglial cells, treatment with DHA and EPA was shown to stimulate microglial phagocytosis of Abeta, decrease in secretion of cellular inflammation markers, and increase neurotrophin production [62].

3.2. Studies with human subjects

Over recent years, numerous studies have been carried out to investigate whether fish oil or omega-3 PUFA has a protective effect in AD in human subjects [54,63]. Although there are supports for beneficial effects of n-3 PUFA on mild cognitive impairment (MCI), especially during the very early phase [64,65], other studies have provided contradictory results instead [66]. In a Medline search for epidemiological evidence for n-3 PUFA on dementia, 17 studies provided beneficial effects but 3 showed negative effects [67]. With few exceptions, many randomized controlled trials of omega-3 fatty acids in AD have not yielded obvious benefits [68–70]. There is possibility that beneficial effects of n-3 PUFA are related to specific demographic factors, and subgroups of AD patients, e.g., subjects with apolipoprotein E epsilon 4 (APOE4) status [71]. Studies with mouse models demonstrated influence of DHA on APOE4 alleles [72,73]. Since APOE is linked to transport of lipids, there is strong rationale to further investigate effects of DHA on APOE4-related changes during aging and AD. A review by Cederholm (2017) concluded that healthy populations may have preventive benefits from fish and docosahexaenoic acid intake [74]. Taken together, there is general support for the notion that long term supplementation of n-3 PUFA may benefit older adults with memory complaints/mild cognitive impairment as well as subgroups of patients with mild/moderate AD [71]. Since n-3 PUFA can generate bioactive lipid mediators, whether these lipids may play a role in mitigating the chronic inflammatory responses and cognitive decline in AD brain are studies that need further investigation.

4. DHA and autism spectrum disorder (ASD)

The important role of DHA for brain development has generated extensive interest on whether this fatty acid may offer therapeutic effects on ASD. Similar to AD, this is again a highly controversial subject. A number of studies demonstrated differences in DHA/AA ratio in plasma of ASD patients [75–79]. However, studies with DHA supplementation on ASD children have not provided consistent results. In a recent pilot non-randomized study, ASD children ranging 7–18 years old were provided DHA for 12 weeks, and significant improvements were observed in all subscales including blood fatty acid profiles [80]. Positive response was also observed in another study, albeit with a single ASD patient [81]. However, in a randomized, placebo controlled study, DHA supplementation (1.5 g/day) was not able to significantly alter the behavioral deficits of young children with ASD [82]. A recent meta-analysis using Medline and EMBRASE data-bases [83] together with another study searching the Cochrane data-base also concluded no evidence of an effect of omega-3 supplements for the ASD spectrum [84]. One difficulty for these studies is the sampling of subjects from different geographical locations with different dietary backgrounds. Furthermore, once a child already has autism, DHA is not likely able to correct the deficits, suggesting involvement of other factors [82]. However, these studies do not exclude the possible presence of a subgroup of ASD who are “responders” to DHA [81].

Maternal high fish intake during pregnancy does appear to have neuropsychological benefits for offspring [85]. One study revealed that mothers with the lowest 5% of intake of omega-3 during pregnancy had a significant increase in ASD risk in offspring [86]. Although not directly related to ASD, maternal diet enriched in n-3 PUFA was shown to enhance cell

proliferation in the dentate gyrus and subsequently alter the contents of neurotransmitters, including gama-aminobutyric acid and dopamine and its metabolites [87]. Omega-3 fatty acids have been shown to rescue the fragile X phenotype in Fmr1-KO mice [88], one genetic model relevant to autism. DHA has also been shown to rescue the ASD-related behaviors in prenatally stressed mice born to dams that are genetically susceptible to stress [89]. In a mouse model of maternal immune activation (MIA) induced by gestational exposure to the viral mimetic polyriboinosinic-polyribocytidilic acid (Poly I: C), dietary DHA was able to protect offspring of autism-associated behaviors [90]. In a rat model of autism induced by prenatal exposure to valproic acid (VPA), oral administration of DHA (300, but not 75 or 150, mg/kg/day) for 21 days from post-natal age of 14 days, rescued the VPA-induced reduction of DHA in plasma and hippocampus, increased levels of p-CaMKII and p-CREB, and inhibited caspase-3 activity [91]. Finally, a maternal diet with a relative deficiency in omega-3 was able to induce ASD-associated behaviors in mice [92]. Taken together, these studies with different animal models and feeding paradigms have provided evidence showing beneficial effects of DHA to ameliorate behavioral deficits due to MIA or other risk factors associated with autism.

The BTBR mice have been regarded as a model of idiopathic autism as they show many manifestations of autistic behaviors including impaired social interaction, communication, and increased repetitive behaviors [93,94]. Zilkha et al. showed that high-fat diet could aggravate autism-related behaviors in the BTBR mice but not in the C57 mice [95]. Apparently, despite that the effects of omega-3 fatty acids in established ASD are unclear, future studies may use different mouse models to test whether DHA supplementation may reduce behaviors and physiological abnormalities that mimic ASD.

5. N-3 fatty acids effects on schizophrenia (SZ) and other psychiatric disorders

Currently, only 40–50% of SZ patients respond favorably to pharmacological treatment [96] and those who do not respond to treatment often have prominent cognitive deficits and persistent negative symptoms. Recent studies have indicated a link between a low content of n-3 PUFAs in diet to an increased susceptibility to psychiatric disorders [97,98]. There are also data showing a deficiency in n-3 fatty acids in phospholipids in subjects with SZ [99–101], and supplementation of n-3 fatty acids has proved to provide a favorable treatment modality for SZ patients and women with psychotic-like symptoms [102,103]. In fact, a causative role has been proposed to link phospholipid and fatty acid metabolism deficits to the development of cognitive disorder in SZ [104,105]. Supplementation with n-3 fatty acids has shown promising results, not only for movement-related symptoms [106], but also for cognitive impairments [107]. Data from human subjects suffering with SZ showed a reduction in perseverative errors (performance on the Wisconsin Card Sort Test) at 3- and 6-months after initiating EPA supplementation (2 g/day in 4×500 mg ethyl-EPA capsules daily) and these changes paralleled the more than 2.5- and 3-fold increases in red blood cell (RBC) membrane levels of EPA [108,109]. In another randomized placebo-controlled study, subjects with first-episode schizophrenia were given either 2.2 g/day of concentrated fish oil (containing EPA and DHA) or olive oil as placebo for 26 weeks, and results of clinical

evaluation of schizophrenia symptom severity change analyzed by the Positive and Negative Syndrome Scale (PANSS) indicated ability for the fish oil diet to reduce the severity of schizophrenia symptoms [110].

There is evidence linking n-3 PUFA with mood disorders, including depression [111,112]. Analysis of erythrocyte EPA and DHA composition indicated lower n-3 PUFA in patients with major depressive disorder (MDD). In a systematic review and meta-analysis of 31 studies on fish oil consumption and depression, results support the consensus that dietary n-3 PUFA intake are associated with lower risk of depression [113]. Studies with rodents suggest that n-3 PUFA deficiency during perinatal development exhibit neuropathological, neurochemical, and behavioral features reflecting mood disorders, and n-3 PUFA supplementation can correct these deficits [114]. Since serotonin is known to regulate a wide variety of brain functions and behaviors, alleviation of the depressant effects upon n-3 PUFA supplementation was attributed to a link to serotonergic neurotransmission in the hippocampus [114]. There is evidence that supplementation with EPA and DHA together with vitamin D, could increase serotonin release from presynaptic neurons [115]. Obviously, more studies are needed to further establish the mechanism linking n-3 PUFA and neurotransmitter release.

Besides mood disorders [116], studies have also demonstrated effects of n-3 PUFA on psychosis. In a clinical trial, supplementation of n-3 fatty acids (2 g ethyl-EPA/day) has shown promising results in first-episode psychosis patients with better clinical response, requiring lower doses of antipsychotic drugs, and fewer extrapyramidal side effects [106]. Another double-blind, random-assignment clinical trial of n-3 fatty acids supplementation (700 mg EPA and 480 mg DHA/day) involving individuals at familial risk for psychotic disorders also showed a reduction of the rate of progression to psychosis together with an improvement in functioning and symptomatology in the treatment group as compared with the placebo group [117]. Subsequently, a longer-term follow-up of the above clinical trial at a median of 6.7 years further demonstrated that the majority of individuals from the n-3 PUFA treated group did not show severe functional impairment and no longer experienced psychotic symptoms at follow-up [118]. On the other hand, not all studies show positive outcomes as another double-blind, placebo controlled randomized multi-center clinical trial conducted with young males at ultra-high risk for psychotic disorders – the NEURAPRO, indicated no significant difference in transition rates comparing the n-3 PUFA group with the placebo groups [119]. Taken together, n-3 PUFAs supplementation appears to be more suitable for early intervention in high-risk subjects.

In general, n-3 PUFA supplement is well tolerated, even when used in relatively high doses (10 g EPA/day) [120]. However, although a dose of up to 3 g EPA/DHA per day is considered safe by the US FDA [121], it is recommended that clinicians be aware of possible increases in bleeding time, as well as changes in body weight and lipid metabolism [122,123]. Obviously, it deems prudent to regularly monitor these variables in this type of clinical study [120,124,125].

Altered membrane PUFAs have been linked to the severity of a variety of clinical symptoms including development of tardive dyskinesia, cognitive impairments, as well as physiological

responses, such as reduced niacin-induced cutaneous flushing [126,127]. Previously, it has been suggested that molecular changes in membrane phospholipids may contribute to the clinical and biological manifestations of SZ [128]. In this regard, it is possible to analyze RBC PUFA as a potential biomarker for assessing treatment response in SZ patients [129]. In studies with a rat model, chronic deficiency in n-3 PUFAs was shown to influence dopamine function in the frontal cortex [130] as well as in the ventral striatum [131]. It appears that changes in behavior due to supplementation of n-3 PUFAs are in part associated with changes in monoamine neurotransmission [132–134]. There is also evidence of abnormal fatty acid metabolism in plasma, RBC, platelets, skin fibroblasts and in post-mortem brain tissues from SZ patients [100,101,124]. Two separate meta-analyses of RBC-PUFA composition concluded that levels of both DHA and AA are lower in SZ patients than in healthy control subjects [135,136]. On the other hand, a recent study reported that both DHA and AA were significantly higher in patients with psychosis and their unaffected siblings than in healthy controls [137]. It should be noted, however, that not all SZ patients demonstrate low levels of PUFAs in RBC membranes and that a bimodal distribution of DHA and AA can occur in SZ patients and not in healthy control subjects [138,139]. Obviously, further studies are needed to evaluate possible presence of two genetically distinct subgroups within these subjects.

6. DHA alters membrane physical properties and cell functions

As discussed in the previous paragraph, PUFA in membrane phospholipids may affect membrane physical properties and alter activities of transmembrane enzymes and binding of receptor proteins [140]. Although the mechanism(s) remains elusive, there is evidence for interactions of DHA with adenosine A2A and dopamine D2 receptors which causes an increase in the rate of receptor oligomerization, and subsequently neuropsychiatric conditions [141]. In a recent study, rat brain DHA levels were enhanced by administering micro-emulsions of linseed oil (gavage for 60 days); this regimen was shown to change n-6/n-3 fatty acid ratios in synaptic membranes and alter synaptic membrane fluidity and enzymes, including Na^+-K^+ ATPase, acetylcholine esterase, Ca^{2+}-Mg^{2+} ATPase, monoamine oxidases, and subsequently increased dopamine and serotonin levels [142]. In another study, DHA treatment could ameliorate the avoidance learning deficit observed in rats after infusion with amyloid beta (1–40) (a toxic peptide), and the beneficial effects were attributed to alterations in synaptic plasma membrane fluidity [143]. In another study using atomic force microscopy measurements, DHA was shown to cause an increase in membrane fluidity and protected membranes from damage due to effects with Aβ(25–35) peptide aggregates [144]. Other studies also showed effects of DHA to increase neuronal membrane fluidity and alter non-amyloidogenic processing of amyloid precursor protein (APP), leading to enhanced secretion of the neurotrophic and neuroprotective α-secretase-cleaved soluble APP (sAPPα) [145,146]. Besides altering membrane fluidity, DHA and EPA treatment also alters activities of G-protein-coupled receptors, namely, GPR40 and GPR120. Using an immortalized cell model derived from rat hypothalamus (rHypoE-7), DHA treatment was shown to inhibit activation of GPR120 by TNFα and the signaling pathways associated with activation of AKT and ERK [147].

A study with microglial cells showed that excess DHA was incorporated into dynamic organelles named lipid bodies, and their accumulation may result in disruption of mitochondrial integrity as well as alteration of cellular responses to lipopolysaccharide (LPS) [148]. In all, these studies provide evidence for DHA interacting with cell membranes through a number of mechanisms and eliciting changes in neuronal membrane protein activities and functions. However, caution should be given to interpretation of results from studies that elucidate effects of DHA on brain cell cultures because cells in the culture medium do not reflect the true environment as in the brain.

7. Conversion of DHA to lipid mediators

DHA and AA are substrates for metabolism by a number of enzymes. While AA is metabolized by COXs and LOXs and is converted to prostanoids and leukotrienes, DHA appears to be metabolized mainly by the 15-LOX and is converted to oxylipins, such as resolvin (RvD1) and neuroprotectin D1 (NPD1) (Fig. 1.). Biosynthesis and structure of RvD1 and NPD1 had been extensively studied and were verified by Serhan's group [149]. These metabolites are active lipid mediators with specific effects on resolving neuroinflammation in different body systems including the brain [150,151]. Besides DHA, EPA (precursor of DHA) can also produce resolving metabolites, namely, resolvin E1 (RvE1). In fact, differences in mechanisms of action were observed between DHA-derived RvD1 and EPA-derived RvE1 in microglial cells. While RvD1 is targeted towards activating the nuclear factor kappa-light-chain-enhancer (NF-κB) pathways, RvE1 appears to be regulated by miRNAs instead [150].

Studies by Bazan's group have demonstrated ability for NPD1 to protect injury to the brain and retina [152,153]. Interestingly, NPD1 can be further activated by aspirin which converts it to the AT-NPD1 form [154,155]. In a brain ischemia model induced by occlusion of middle cerebral artery (MCAo), administration of NPD1 was shown to protect and ameliorate the acute and long-term tissue damage as early as 3 h after onset of ischemia [156]. In another study with aged NMR1 mice, fish oil supplementation for 21 days improved mitochondrial function in these mice, and this effect was attributed to the increase in synthesis of a NPD1-like compound [38].

In a study by Hashimoto et al. [157], the effects of EPA versus TAK-085 (a prescription drug containing both EPA and DHA) on eicosanoids and docosanoids production as well as learning ability of aged rats were compared. Animals administered TAK-085 for 17 weeks showed reduced reference memory errors. Furthermore, while both TAK-085 and EPA showed increase in DHA and decrease in AA in plasma and brain, differences in the EPA- versus TAK-085-derived mediators (PD1, RvD1 and RvE1) were observed [157]. This study suggests better effects with a regimen containing both EPA and DHA.

8. DHA enhances expression of brain-derived neurotrophic factor (BDNF)

Together with the cAMP responsive element-binding protein (CREB), BDNF is an important neurotropic factor for regulation of synaptic transmission. In a study in which rats were subjected to traumatic brain injury (TBI), the increase in oxidative stress and

learning impairment was marked by a decrease in BDNF, and supplementation of DHA counteracted the effects of TBI and normalized levels of BDNF, synapsin as well as CREB [158]. In another study, dietary deprivation of n-3 PUFA for 15 weeks in rats resulted in an increase in depression and aggression scores, and a decrease in BDNF and CREB expression [159]. Study with primary astrocytes showed ability for DHA to induce BDNF expression through a pathway involving p38MAPK. In another study, aged Kunming-line mice given DHA orally for 7 weeks showed improvement in age-related decline in cognitive function and a positive relationship with the protein level of BDNF [39]. In fact, BDNF is becoming a useful biomarker for assessing neurologic disorders.

9. Oxidative AA and DHA metabolites are substrates of the Nrf2 antioxidant pathway

Recent studies have placed emphasis on the antioxidant pathway involving the Kelch-like ECH-associated protein 1 (Keap1) and Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2, Nrf2) [160,161]. Upregulation of this pathway is linked to transcriptional activation of a large number of genes encoding the Antioxidant Response Elements (AREs) in their promoters [162]. These genes are responsible for production of a number of Phase II proteins such as GSH, and gamma-GCS, which are involved in detoxification and maintenance of cell redox homeostasis (Fig. 3). Under normal conditions, Nrf2 is kept at a low level due to constant degradation by the Keap1/cul3 protein through the ubiquination process. Since Keap1 has a number of cysteine residues, compounds that interact with these residues can perturb the ubiquination process leading to stabilization of Nrf2. Indeed, a large number of structurally diverse compounds, both from within the cell as well as from exogenous sources (including botanical polyphenols and lipids), can perturb the Keap1-mediated repression of Nrf2, leading to its stabilization and subsequently translocation to the nuclei and interaction with the AREs [163]. Transcriptional synthesis of these antioxidant genes is known to play a central role in both intrinsic resistance and cellular adaptation to ROS and consequently regulation of neuroinflammation [164]. Much interest has been focused on induction of heme oxygenase-1 (HO-1), a potent antioxidant enzyme responsible for catabolizing heme to biliverdin, carbon monoxide and free iron [165]. Serini and Calviello (2016) provided a recent review with supporting evidence that n-3 PUFA may modulate the oxidative – antioxidative balance in brain through regulating the Nrf2 anti-oxidant pathway and expression of heme oxygenase −1 (HO-1) [64].

9.1. Action of 4-HNE and 4-HHE on the Nrf2/HO-1 antioxidant pathway

Polyunsaturated fatty acids in membrane phospholipids are targets of lipid peroxidation by free radicals resulting in the release of hydroxyl-alkenals such as 4-hydroxyhexenal (4-HHE) from DHA and 4-hydroxynonenal (4-HNE) from AA (Fig. 2). Both metabolites are readily detected in human and rodent plasma [166]. Initially, 4-HNE and 4-HHE are regarded as cytotoxic molecules, especially when added to cultured cells at high non-physiological concentrations [167]. However, there is evidence that at sublethal concentrations, these compounds exhibit adaptive responses and can actually protect neurons (such as PC12 cells) against oxidative stress induced by H_2O_2 and 6-hydroxydopamine (a neural toxin) through activation of the Nrf2 pathway [168,169]. More recent studies further demonstrated

that these compounds can induce the production of heme oxygenase-1 (HO-1), a potent antioxidant enzyme downstream of Nrf2/ARE activation [165,170,171]. Mice fed a fish oil diet for 3 weeks showed changes in n-3 fatty acid levels together with an increase in 4-HHE and a decrease in 4-HNE levels in plasma [170]. In fact, DHA-induced HO-1 has been shown to occur in multiple organs, including liver, kidney, brain, heart and skeletal muscle [170]. In a study using 3T3-L1 adipocytes, treatment with (n-3) PUFA (DHA and EPA) could cause an increase in HO-1, and this effect was attributed to increased synthesis of 4-HHE which in turn, caused an up-regulation of the Nrf2 pathway [165]. Obviously, ability of these alkenal products to interact with the Nrf2 pathway and production of HO-1 may differ depending on cell types and oxidative conditions [172,173]. Using Nrf2 deficient mice, DHA, but not EPA, was shown to provide protective effects and increased synthesis of HO-1 in endothelial cells through generation of 4-HHE [174]. Besides the increase in HO-1 production, the endogenous nature of these n-3 PUFAs derivatives can also activate other cytoprotective pathways and enhance expression of other phase II detoxification genes [175]. Taken together, these studies demonstrated pleiotropic properties of these peroxidation products; besides interacting with macromolecules, they also can serve as second messengers for regulation of oxidative/electrophilic stress through activation of the antioxidant defense system [176,177]. It is important to recognize that although 4-HHE and 4-HNE are both oxidative products of PUFA, there are subtle differences between their ability to form adducts (with DNA, proteins, GSH and PE) and their involvement in the Nrf2 detoxification pathways [178]. Obviously, more studies are needed to explore the physiologic mechanisms whereby these DHA metabolites may affect the brain under normal and pathologic conditions. Understanding the endogenous nature of these PUFA-derived electrophiles and their ability to activate multiple signaling pathways is important for development of new drugs for treatment of inflammatory diseases [175,179].

9.2. Regulation of the NF-κB and Nrf2 pathways by DHA and metabolites

Recent studies with microglial cells demonstrated ability for botanical polyphenols such as quercetin and herbal extracts such as Aswhagandha, to mitigate LPS-induced inflammatory responses (such as induction of NO) and enhance the Nrf2/ARE antioxidant pathway [180,181] (Fig. 3.). Our study with an immortalized astrocyte cell line (DITNC1) transfected with NF-κB and ARE promoters also support the ying-yang mechanism for these phytochemicals, i.e., compounds that are potent in inhibiting LPS-induced NO are also active in increasing Nrf2-mediated HO-1 [182]. In a study with macrophages, NO production due to stimulation with 10 ng/mL LPS was significantly decreased upon incubation with 500 nM of 4-HNE [183]. In the same study, the decrease in LPS-induced NO was also marked by an increase in HO-1, NQ01 and GCLC, products of the Nrf2/ARE pathways. The mechanism for 4-HNE to inhibit LPS-induced NO production and increase the Nrf2 phase II products remains to be an interesting area for investigation.

Besides the brain, there is also evidence that DHA and EPA supplementation can protect against cardiac ischemia-reperfusion injury through inhibition of NF-κB and induction of Nrf2 pathway [184]. In macrophages, DHA could be oxidized to form α,β-unsaturated ketone derivatives, which are potent anti-inflammatory signaling mediators [179]. In another study, neutrophils were isolated from healthy human subjects who were supplemented with

EPA and DHA for 4 month, and increased formation of 7-oxo-DHA and 5-oxo-EPA was observed [185]. These results support the precept that DHA can form oxygenate metabolites with electrophilic properties and that these metabolites can transduce anti-inflammatory actions through activation of the Nrf2/ARE pathway. With advance technology for sensitive detection, more studies are needed to discover these metabolites and elucidate their mode of action under physiological and pathological conditions.

10. Influence of DHA metabolites in stroke and traumatic brain injury

Cerebral ischemia/reperfusion is associated with depletion in energy supply, increase in oxidative stress, and activation of proteases and PLA_2 that trigger protein degradation and release free fatty acids (Fig. 1). Considering the increases in oxidative stress and inflammation in cerebral ischemia, there is increasing interest to test whether supplementation of n-3 fish oil could provide beneficial effects and mitigate the progress of cerebral injury [186]. Similar therapies have been suggested to target lipid peroxidation in traumatic brain injury (TBI) [187]. In a mouse model of injury due to Controlled Cortical Impact (CCI), DHA was able to protect against hippocampal neuronal loss and to reduce white matter injury, pro-inflammatory response, ER stress, aberrant protein accumulation, and neurological deficits [188,189]. Furthermore, treatment with DHA in mice after spinal cord injury could significantly reduce the degree of tissue injury and spinal cord inflammation, pro-inflammatory cytokine TNF-α expression, nitrotyrosine formation, and apoptosis [190]. DHA treatment also improved recovery of limb function, and ameliorated the effects of oxidative stress on neurite length and branching in dorsal root ganglion (DRG) cells in this type of injury [190,191]. Besides increased synthesis of NPD1 [153], there is evidence that n-3 PUFAs attenuate brain injury (including cerebral ischemia and traumatic brain injury) through activation of the Nrf2/ARE pathway and production of HO-1 [186]. Under these conditions, reduction of cellular inflammatory responses is attributed in part to the increased release of 4-HHE [192,193]. In a mouse model of hypoxic/ischemia (H/I), mice fed a diet with n-3 PUFA supplement (from day 2 of pregnancy to 14 days after parturition) showed amelioration in blood brain barrier (BBB) leakage and decrease in the elevation of matrix metalloproteinase (MMP) activity [194]. In a mouse model of compression spinal cord injury, the transgenic fat-1 mice enriched in omega-3 PUFA showed better outcomes as compared to mice on a high omega-6 diet or a normal diet [195,196]. In another study in which TBI in rats was induced by cortical contusion, intraperitoneal injection of DHA (16 mg/kg) at 5 min after TBI and followed by a daily dose for 3–21 days, was shown to shift microglial morphology from the activated, amoeboid-like state into the surveilling state [197]. Finally, in a randomized, placebo-controlled trial study, supplementation with n-3 PUFA (3 g/day) for 6 months resulted in lower levels of plasma lipids, gelatinases (MMP-2/-9), and inflammatory parameters [198]. Taken together, although the mechanism for DHA to confer neuroprotective effects remains to be elucidated, there is strong evidence for DHA to serve as a nutraceutical and provide positive effects against tissue damage associated with brain injury.

11. Conclusion and future directions

The high content of DHA in brain phospholipids has generated great interest to search for its role in regulating brain cell functions and in maintaining brain health throughout the life spectrum. More interest is focused on DHA as a nutraceutical for prevention and treatment of neurological diseases. DHA is regarded an essential fatty acid and its limited de novo synthesis in the brain has led to question as to whether supplementation of n-3 PUFA can ameliorate age-related decline in cognitive function. Due to the immense information in this area, coverage in this review is limited to studies on neurological disorders associated with autistic spectrum disorder, Alzheimer's disease, schizophrenia, stroke and TBI. In general, many studies with animal models appear to support protective effects of n-3 PUFA supplementation under different conditions. However, studies to demonstrate clear benefits on human subjects towards a particular disease have not been conclusive, probably due to heterogeneous dietary habits and population in different demographic conditions. A recent review by Pusceddu et al. also supports the difficulties and challenges to arrive a clear cut answer for clinical use of n-3 PUFA for prevention and treatment of psychopathologies [199]. In many instances, positive effects appear to better relate to subjects at early stage of the disease process or to a specific subgroup of the population.

This review provides a strong evidence for the role of $iPLA_2$ in mediating DHA release. Studies also show ability for DHA to undergo a number of enzymatic and non-enzymatic reactions, leading to synthesis of potent lipid mediators, such as resolvin (RvD1) and neuroprotectin D1 (NPD1). Future studies are needed to determine the cell types responsible for their synthesis and elucidate their mechanism(s) of action. DHA also undergoes lipid peroxidation and produces oxylipin metabolites including 4-HHE. There is evidence that these metabolites may play a role in modulating oxidative homeostasis in cells through the NF-κB and the Nrf2/ARE pathway. Since many botanical polyphenols can also up- and down-regulate the same pathways [180], future studies may need to include testing for combination effects of DHA and these polyphenols. In addition, unique formulations may be used to develop new nutraceutical products [200,201]. Lastly, future studies should employ new technologies such as involving DHA in nanotechnology in order to enhance bioavailability, and using advanced proteomics, lipidomics and bioinformatics approach to examine how DHA and metabolites alter proteins and lipids in brain cells under physiologic and pathologic conditions.

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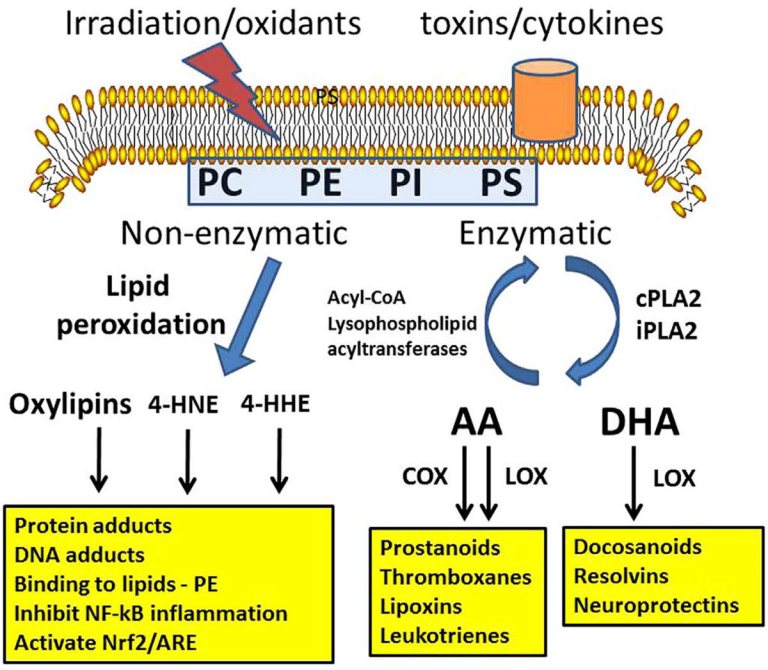

Fig. 1.

Enzymatic and non-enzymatic pathways for metabolism of PUFAs (AA and DHA) in membrane phospholipids.

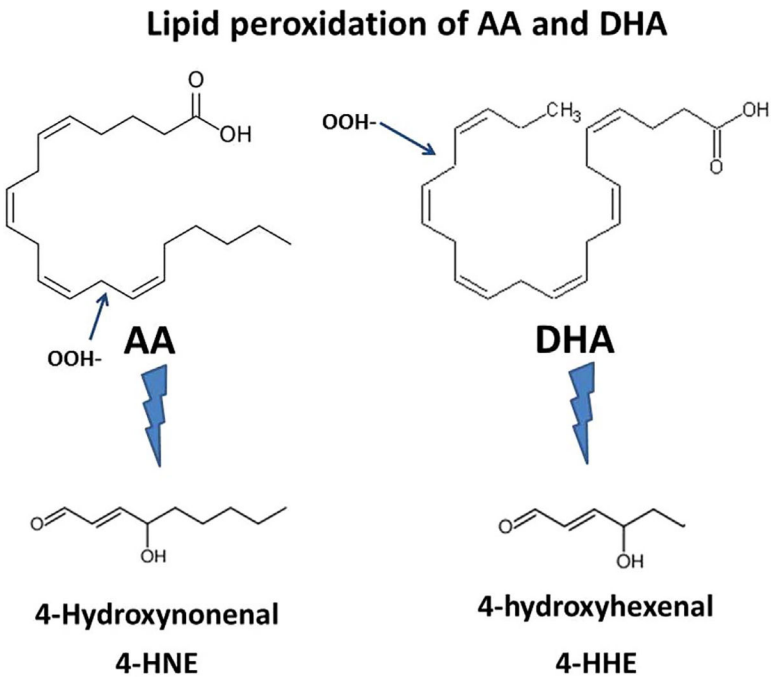

Fig. 2.

Free radical oxygen induces lipid peroxidation and conversion of AA and DHA to 4-HNE and 4-HHE, respectively.

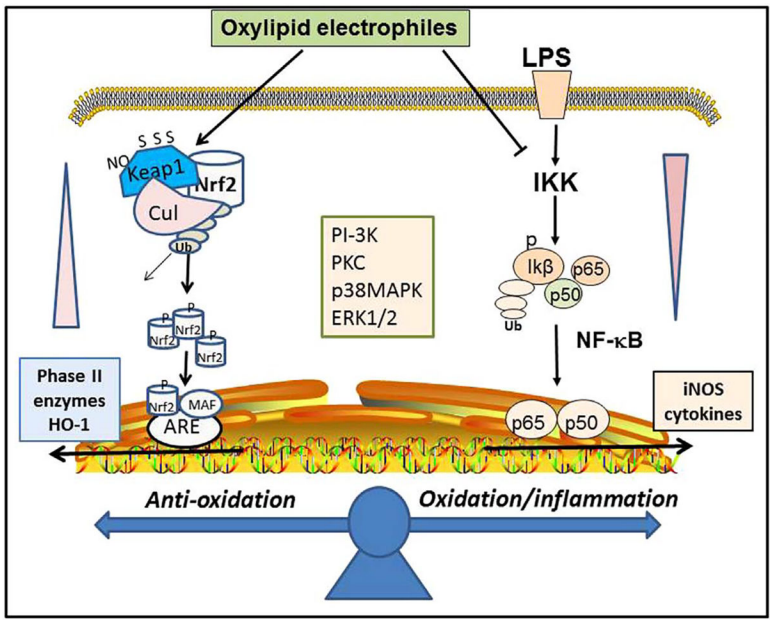

Fig. 3.

Oxylipid electrophiles inhibit LPS-induced NF-κB inflammatory pathway and enhance Nrf2/ARE anti-oxidant pathway in microglial cells. Possible cross-talk mediated by protein kinases.