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N-3 (*OMEGA*-3) FATTY ACIDS: EFFECTS ON BRAIN DOPAMINE SYSTEMS AND POTENTIAL ROLE IN THE ETIOLOGY AND TREATMENT OF NEUROPSYCHIATRIC DISORDERS

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Abstract

A number of neuropsychiatric disorders, including Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder, and, to some extent, depression, involve dysregulation of the brain dopamine systems. The etiology of these diseases is multifactorial, involving genetic and environmental factors. Evidence suggests that inadequate levels of n-3 (*omega*-3) polyunsaturated fatty acids (PUFA) in the brain may represent a risk factor for these disorders. These fatty acids, which are derived from the diet, are a major component of neuronal membranes and are of particular importance in brain development and function. Low levels of n-3 PUFAs in the brain affect the brain dopamine systems and, when combined with appropriate genetic and other factors, increase the risk of developing these disorders and/or the severity of the disease. This article reviews the neurobiology of n-3 PUFAs and their effects on dopaminergic function. Clinical studies supporting their role in the etiologies of diseases involving the brain dopamine systems and the potential of n-3 PUFAs in the treatment of these disorders are discussed.

Keywords

dopamine; schizophrenia; attention deficit hyperactivity disorder; Parkinson's disease; depression; omega-3; docosahexaenoic acid

1. Introduction

A growing body of literature supports the importance of polyunsaturated fatty acids (PUFA) in brain function. PUFAs in the n-3 and n-6 (*omega*-3 and *omega*-6) families play a number of important physiological roles as components of cell membranes, as signaling mediators, and as precursors of signaling mediators. The role of PUFAs, particularly n-3 PUFAs, in brain development is well established [1]. There is also increasing evidence that suboptimal

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levels of n-3 PUFAs, as a result of inadequate diet or metabolic deficiencies, appear to interact with genetic and environmental factors in the etiologies of a variety of neuropsychiatric disorders. This article reviews the literature on the roles of n-3 PUFAs in the modulation of brain dopamine systems. Evidence for the involvement of these fatty acids in neuropsychiatric disorders involving dopamine systems, such as Parkinson's disease (PD), schizophrenia, and attention deficit hyperactivity disorder (ADHD) are discussed, as well the effects of n-3 PUFAs on dopaminergic alterations observed in depression. The potential of n-3 PUFAs, n-3 PUFA-derived mediators, or compounds that mimic their actions in the prevention and treatment of these disorders is also discussed.

2. N-3 PUFAs and t]he Brain

PUFAs are important dietary fats containing more than one double bond, and are named according to the number of carbons they contain, the number of double bonds, and the position of the first double bond from the methyl end. Long-chain PUFAs, which are at least 20 carbons in length, have important functional roles as components of membrane phospholipids and as signaling molecules in all tissues including the brain [2, 3]. Biologically important long-chain PUFAs include docosahexaenoic acid (DHA or 22:6n-3), a 22-carbon PUFA with six double bonds and the first double bond at the third carbon from the methyl end, is part of the n-3 class of PUFAs. DHA constitutes approximately 12–15% by weight of the total fatty acids in the human brain. The major species of n-6 PUFAs in brain is arachidonic acid (AA or 20:4n-6), which is 20 carbons in length, with four double bonds beginning with the sixth carbon from the methyl end, and which makes up 8–11% of the total fatty acids in the brain [4].

2.1. PUFA biosynthesis and brain accretion

Mammals cannot synthesize long-chain n-3 and n-6 PUFAs *de novo*. Instead, DHA and AA must be consumed in the diet, or their essential fatty acid precursors α-linolenic acid (ALA or 18:3n-3) and linoleic acid (LA or 18:2n-6) must be provided. ALA is metabolized by desaturases and elongases to form DHA (Fig. 1). The same enzymes convert LA to AA, and ultimately to docosapentaenoic acid (n-6 DPA or 22:5n-6) [5]. Accordingly, the relative abundance of ALA and LA influences the amounts of DHA and AA produced [6].

DHA plays an important role in brain growth and development. DHA is supplied from maternal sources to the fetus through the placenta, and to infants in breast milk. In humans, brain accumulation of DHA occurs primarily during late gestation and early childhood, with lifelong turnover [7, 8]. In rats, accumulation of DHA in the brain occurs in the last three days of gestation through weaning [9, 10]. Long-chain PUFAs are sometimes called "conditionally essential" because no gross deficiency disorders are known. However, visual and cognitive deficits in children fed a low n-3 diet, and conversely, benefits bestowed by supplementation with n-3 PUFAs during pregnancy have been reported [11–13].

2.2. Influence of diet and other factors on brain fatty acid composition

Inadequate brain accumulation of DHA during development, which can result from an n-3 PUFA-deficient diet or a metabolic deficit, causes the compensatory incorporation of n-6

DPA, an n-6 PUFA that is normally present in only trace amounts, thus qualitatively altering the composition of the fatty acids in the cell membranes [14, 15].

Diet can also affect tissue PUFA composition in adult animals. In mature animals, peripheral tissues are affected first, such that feeding adult rats an n-3-PUFA-deficient diet for 7 months decreased n-3 PUFA content of several organs, including liver, heart and testes, but not the brain [16]. However, in adult female rats or adult male mice, prolonged consumption of n-3 PUFA-deficient diets did decrease the percentage of DHA the brain [17, 18]. These observations suggest that regulation of brain fatty acid composition may differ between sexes and/or species.

Human dietary consumption of n-3 PUFAs varies widely. In contrast to some diets where the n-6:n-3 ratio can be as low as 2:1, Western diets are low in n-3 fatty acids, and have an n-6:n-3 ratio as high as 16.7:1 [19]. A high dietary n-6:n-3 ratio has been implicated in a variety of human diseases such as coronary artery disease, hypertension, diabetes, arthritis, osteoporosis, autoimmune disorders, cancer and psychiatric disorders, whereas low dietary n-6:n-3 or n-3 supplementation has beneficial effects [20–27]. Thus, there is high potential for individuals in Western countries to benefit from nutritional or pharmacological interventions targeting n-3 PUFAs or their derivatives.

Physiological states can also affect the PUFA status of the brain. For example, the demands of supplying DHA to offspring during pregnancy and lactation can deplete n-3 PUFAs in reproducing females. Although brain fatty acid composition after pregnancy has not been examined in humans, several studies found as much as a 50% decrease in maternal plasma DHA levels after pregnancy [28–30]. Studies in rats, where it is possible to exam the brain postpartum, indicate that if the diet contains inadequate n-3 PUFAs, the fatty acid compositions of both the brain and peripheral tissues are affected, and that gestating and nursing a single litter can result in a decrease in brain DHA content of as much as 25% [17, 31, 32].

Genetic variation in the ability to synthesize or use long-chain PUFAs may also affect brain PUFA status. Polymorphisms in genes such as the fatty acid desaturase (FADS) FADS1/FADS2 genes have been identified that cause reduced biosynthesis of long-chain PUFA [33, 34]. Other polymorphisms, such as the phospholipase A2G4A BanI polymorphism, and some SNPs of arachidonate 12-lipoxygenase (ALOX12), also affect utilization of long-chain PUFAs [35–38].

2.3. Roles of PUFAs in cell function

As elements of the cell membrane, long-chain PUFAs contribute to the membrane's physicochemical properties, and thus impact the function of lipid rafts and membrane-bound proteins, such as receptors, transporters, and ion channels [6, 39, 40]. Notably, manipulation of membrane PUFA composition *in vitro* has been shown to alter the function and/or signaling of a variety of receptors, including dopaminergic, cholinergic, and GABAergic receptors, as well as the Na^+/K^+ ATPase [41–45].

AA is distributed evenly among cell types within the brain, and is an important signaling molecule in inflammatory cascades [46, 47]. It is preferentially cleaved from phospholipids in the brain by both cytosolic phospholipase A_2 ($cPLA_2$) and secretory phospholipase A_2 ($sPLA_2$). A portion of the released AA can by metabolized by cyclooxygenases (COX) and lipoxygenases (LOX) to form a class of compounds known as the eicosanoids, which include a variety of mediators of cellular activity, including prostaglandins, leukotrienes and lipoxins. Most AA-derived metabolites have pro-inflammatory functions, although AA contributes to mediators with a broad range of functions in signaling, memory, and learning modulation [48, 49].

DHA is highly enriched in neuronal and synaptic membranes, suggesting an important role in neural cell signaling [46]. It is incorporated preferentially into phosphatidylethanolamine and phosphatidylserine on the inner membrane layer of synapses, and its steric incompatibility with cholesterol drives the formation of either DHA- or cholesterol-rich lipid rafts. These rafts serve as protected microdomains and function in compartmentalization of various cell signaling molecules [46]. DHA also affects membrane fatty acid chain fluidity, ion permeability, elasticity, protein function, phase behavior, and fusion [50–52]. In addition, it is cleaved from the phospholipids by the inducible DHA-selective calcium-independent phospholipase A_2 ($iPLA_2$) [53]. Once unesterified, DHA acts as a ligand for a variety of receptors, such as the peroxisome-proliferator-activated receptor (PPAR), the retinoid X receptor (RXR) and the toll-like receptors (TLR), as well as being metabolized by COX and LOX to form docosanoids such as the resolvins, protectins, maresins, neuroprotectin D1 (NPD1), and the recently discovered electrophile oxo-derivatives (EFOXs) [49, 54–58]. The resolvins are a class of anti-inflammatory compounds produced by the COX-2 pathway in the presence of aspirin [59, 60]. NPD1 is a peptide that is formed by PLA_2 lipoxygenase from free DHA, and has been shown to induce anti-apoptotic B-cell lymphoma-2 (Bcl-2) proteins, inhibit pro-apoptotic Bcl-2 proteins, and suppress inflammatory gene expression [61]. Like DHA, NPD1 affects membrane structure and stability, and alter the balance of n-3 to n-6 PUFAs in the membrane, which in turn influences the AA cascade by suppression of COX-2. Maresins, DHA-derived metabolic products with anti-inflammatory properties similar to the resolvins and NDP1, are produced by macrophages under inflammatory conditions [62]. COX-2 EFOX metabolites act as anti-apoptotic Nrf-2 activators, PPAR-γ agonists, and inhibitors of cytokine and nitric oxide (NO) production [56]. DHA also has the ability to inhibit TLR4, an important pro-inflammatory factor, and various nuclear receptor initiators of the nuclear factor kappa-light-chain-enhancer of activated B cells (Nf-κB)-mediated anti-inflammatory response [54, 63]. Accordingly, in clinical studies, n-3 fatty acid treatment decreased cytokine production, and COX-2 activity [54, 64]. Conversely, under oxidative stress, DHA is oxidized into neuroprostanes, a class of prostaglandin-like compounds formed without COX. These compounds trigger reactive oxygen species (ROS) formation at both sides of the phospholipid membrane [65]. DHA also activates syntaxin-3, a crucial factor in neuron growth and regeneration, which may contribute to DHA's role in optimal brain growth and development [4]. Stimulation of the Src-mediated calcium-induced growth and phosphatidylinositol$_3$ kinase (PI_3K)-Akt-protein kinase C (PKC) cascades are also implicated in the beneficial effects of n-3 PUFAs in brain [66].

Although not as well studied as DHA, eicosapentaenoic acid (EPA or 20:3n-3), the 20-carbon n-3 precursor to DHA. Although the EPA incorporated into brain phospholipids represents only about 1–2% of total brain fatty acids [67], the fatty acid has a number of important biological activities. Like DHA, EPA forms eicosanoids, most of which are less inflammatory than their AA-derived counterparts, as well as anti-inflammatory mediators such at the E-series resolvins [68]. EPA competes with AA for the same enzymes, so the n-6:n-3 ratio influences EPA metabolite production. Under conditions of cell membrane damage (such as oxidative stress), abundant intracellular calcium and inflammatory stimuli, PLA_2 and COX-2 transcription is upregulated, leading to increased production of AA metabolites [49]. It also inhibits COX-2 expression and also acts as an inhibitor of COX-2, activates the PI_3-K-Akt pathway, stimulates myelinogenesis, and is a PPAR ligand [69–73].

2.4. Mechanisms by which n-3 PUFAs may influence development and maintenance of dopaminergic neurons

DHA is one of a number of ligands for the nuclear receptor RXR [55], and as such, dietary DHA intake may play a role in RXR regulation. The RXR family consists of three main isotypes: RXR-α, RXR-β and RXR-γ. RXR-α is expressed in liver, kidney, spleen, placenta, epidermis, and visceral tissue; RXR-β is expressed in nearly every body tissue; and RXR-γ is mostly in muscle and brain tissue. The physiological roles of RXR are complex and not completely understood, but RXR isoforms are known to be involved in muscle metabolism, insulin resistance, atherosclerosis and cholesterol metabolism, apoptosis, and a variety of differentiation processes, including neuronal development [74].

In the dopaminergic system, RXR is a crucial developmental and survival factor, and acts in conjunction with its *NR4A1* partners nuclear receptor-related-1 protein (Nurr1) and nerve growth factor 1B (Nur77) [75]. RXR forms heterodimers with many other nuclear receptors, implicating it in multiple transcription pathways. In particular, RXR heterodimerizes with both Nurr1 and Nur77. Nurr1 is crucial to dopaminergic neuronal development, as well as regulation of the hypothalamic-pituitary-adrenal axis [76]. Nurr1 is expressed chiefly in the substantia nigra, ventral tegmental area, and limbic areas, where dopamine plays a vital role. Expression of these proteins peaks in the embryo, yet remains high in dopaminergic neurons throughout the lifespan, with Nurr1 expressed in 96% of adult substantia nigra neurons [77–79]. Nurr1 regulates the transcription of tyrosine hydroxylase and the dopamine transporter by binding to the nerve growth factor 1B response element (NBRE) sequence in the 5'-untranslated region, and binds to RXR. The resulting heterodimer plays an important role in the development of neurons [80, 81]. Dopaminergic terminal fields express both RXR-β and RXR-γ isoforms. Mice deficient in these receptors have impaired motor function, and decreased mRNA transcription of D_1 and D_2 receptors in the striatum [82]. Knockout RXR-γ animals have also been found to have abnormalities in synaptic plasticity and learning [74]. Although the specific role(s) of n-3 PUFAs in RXR-mediated effects on the dopaminergic systems remain to be elucidated, it is likely that these fatty acids influence dopaminergic neuronal development and survival through these mechanisms.

3. N-3 PUFAs and Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder affecting 0.1–0.2% of the general population and 2% of people over 65 years of age [83]. Major clinical signs of PD are bradykinesia, resting tremor, rigidity, postural instability, and "masked" facial expression [84]. The neuropathology of PD is histologically characterized by loss of melanin-pigmented neurons in dopaminergic regions of the brain, most notably the substantia nigra pars compacta, and the presence of Lewy bodies containing abnormal α-synuclein aggregations. The etiology of the majority of cases is unknown, but a minority, especially early-onset cases, are attributable to familial mutations in genes such as Park 1, which encodes α-synuclein [85–90]. The variability in clinical presentation, progression of disease, and age of onset of the disease suggest a multifactorial etiology likely occurring as "multiple hits" in which perinatal anomalies and insults, genetic polymorphisms, and postnatal environmental factors lead to a reduction in dopamine neuron numbers or function, thus making an individual more susceptible to subsequent stressors, and therefore more likely to develop PD [91–93]. Several environmental toxins, notably metals and agricultural agents may contribute to incidence of PD, as well as certain viral infections. A number of cases were also caused by exposure to the nigrostriatal-selective neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [94–99]. Current treatments for PD include pharmacological management, primarily with drugs that mimic or augment dopaminergic neurotransmission [83]. Surgical treatment, deep-brain stimulation, and physical therapy are also used; however, there is no cure, and all current treatments eventually become ineffective at managing symptoms [100, 101]. Therefore, understanding the foundations of PD, including the effects of diet on the etiology and treatment of PD, may prove crucial to developing treatments to minimize suffering of PD patients.

Oxidative stress appears to be central to the pathogenesis of PD. The oxidative metabolism of dopamine can yield hydrogen peroxide and other ROS, which contribute to lipid peroxidation [102]. Increased concentrations of the lipid peroxidation products malondialdehyde and hydroperoxide have been found in the substantia nigra of PD patients [103]. Another cell-damaging product of lipid peroxidation, 4-hydroxynonenal, has also been detected in PD dopaminergic neurons [104]. The substantia nigra, even under ideal conditions, is highly prone to oxidative stress, being rich in both reactive dopamine and in peroxidation-prone PUFAs, which can lead to the formation of dopamine adducts. Importantly, an AA-derived adduct, hexanoyl dopamine, was found to be notably cytotoxic in human SH-SY5Y neuroblastoma cells expressing monoamine transporters [105, 106], suggesting that it, and perhaps other PUFA-dopamine products, may play an important role in the pathogenesis of PD.

3.1. Clinical studies

A few studies have examined the involvement of PUFAs in PD patients. The prospective cohort Rotterdam study evaluated 5,289 subjects age 55 and older to examine the relationship between intake of PUFAs and the incidence of PD. In that study, a high intake of PUFAs was associated with lower risk of PD [107]. Likewise, a case-control study of n-3 PUFA consumption in individuals with and without occupational exposure to pesticides

found the incidence of PD to be inversely related to dietary n-3 PUFA content, and that higher consumption of n-3 PUFAs reduced the PD risk associated with pesticide exposure [108]. Another case-control study in a Japanese population, however, found that n-3 PUFA intake and dietary n-6:n-3 ratio did not affect risk of PD, although increased AA intake, interestingly, increased risk [109]. Finally, a randomized, double-blind, placebo-controlled clinical trial in PD patients found that treatment with flaxseed oil, a source of the n-3 PUFA ALA, plus vitamin E for 3 months improved the Unified Parkinson's disease rating state score, as well as increased total antioxidant capacity and glutathione concentrations, and decreased high-sensitivity C-reactive protein levels [110]. Accordingly, most of these studies suggest that increased consumption of n-3 PUFAs may be beneficial for both the prevention and treatment of PD.

3.2. Preclinical studies

Animal studies also generally indicate beneficial effects of n-3 PUFAs in PD and point towards underlying mechanisms. Of note, consumption of adequate n-3 PUFAs appears to be important for the survival and health of dopaminergic neurons. Rats raised from conception on an n-3 PUFA-deficient diet had 33% fewer neurons in the substantia nigra and ventral tegmental area expressing the dopamine marker tyrosine hydroxylase at adulthood compared to controls [111]. Similarly, a study of rats raised from conception on a diet that resulted in a 65% decrease in brain n-3 PUFA content found a 40% decrease in the number of dopamine neurons in the substantia nigra, as well as increased lipid peroxidation and decreased catalase activity in both the substantia nigra and striatum [112]. These decreases in the number of dopaminergic neurons, as well as increased indices of oxidative stress, may increase susceptibility to other insults, consistent with the "multiple hit" hypothesis.

Studies in experimental models of PD also suggest that n-3 PUFAs may mitigate the effects of dopaminergic neurotoxins. In rat studies using the unilateral 6-hydroxydopamine (6-OHDA) lesion model of PD, various treatments with n-3 PUFAs reduced the effects of 6-OHDA, resulting in decreased agonist-induced rotation. In addition, the lesioned striata of the n-3 PUFA-treated animals had higher levels of tyrosine hydroxylase, dopamine, and synapsin-1 expression, and lower lipid peroxidation, nitrite levels, density of inducible nitric oxide synthase (iNOS)-immunoreactive cells, microglia and astrocyte reactivity compared to controls [113–115]. Likewise, n-3 PUFA treatments in MPTP-treated rats or mice improved motor performance, showed smaller reductions in MPTP-induced dopamine cell loss, striatal dopamine content, COX-2 activity, Nurr1 and dopamine transporter mRNA levels, and modulated Akt and Bcl-2 pathways [116–119]. DHA supplementation in an MPTP model also increased glial cell-derived neurotrophic factor (GDNF) and neurturin, both important trophic factors involved in dopaminergic neuron health [120]. Likewise, in MPTP-treated cynomolgus monkeys, DHA administration reduced levodopa-induced dyskinesias when given either before or after MPTP administration [121]. Interestingly, in the MPTP-probenecid mouse model, pretreatment with an ethyl-EPA-enriched diet decreased the MPTP-induced hypokinesia, but did not reduce dopaminergic cell loss [122]. Finally, administration of the DHA-derived resolvin D_2 in rats treated with the dopaminergic neurotoxin lipopolysaccharide prevented the activation of the TLR4/Nf-κB pathway [123]. Similar neuroprotective effects have also been observed in primary mesencephalic primary

cultures [124]. Taken together, evidence from these animal studies points to the ability of n-3 PUFAs to modulate factors involved in neuroprotection in PD models, suggesting that increased n-3 PUFA intake could prevent or attenuate the progress of PD in humans.

Other studies, however, found effects of PUFAs that may be detrimental in PD. The double bonds in PUFAs make them susceptible to lipid peroxidation in pro-oxidative environments, and several studies have implicated high n-3 PUFA levels with increased oxidative damage in PD and PD models. For example, the DHA-derived lipid peroxidation products neuroprostanes were increased in the brains of advanced PD patients [65]. Also, dopamine can react *in vitro* with fatty acid peroxides to form 6-OHDA, providing a potential mechanism for endogenous production of 6-OHDA in the pathogenesis of PD [125]. In one 6-OHDA study in mice, intraperitoneal injection of a DHA ethyl ester resulted in increased levels of lipid peroxidation in the striatum [126]. In A53T α-synuclein mutant mice, accumulation of both soluble and insoluble α-synuclein, neuritic injury, and astrocytosis were increased after DHA supplementation, whereas these effects were attenuated by decreased dietary DHA content[127]. In addition, an *in vitro* experiment with oligodendrocytes transfected with A53T α-synuclein that were supplemented with DHA for 3 days before subjection to oxidative stress showed enhanced aggregation of α-synuclein [128]. Furthermore, PUFAs in the brain can form neurotoxic adducts with dopamine [105]. Since the most toxic of these adducts was formed from an n-6 PUFA, the n-6:n-3 ratio in the diet may have an effect on development of these adducts and the damage they can cause.

Some of the effects of n-3 PUFAs in PD may result in activation of RXR and/or Nurr1. The apparent complexity of the relationships among the nuclear receptors involved in nigral neurogenesis make it difficult to isolate the effects of each, but it is apparent that these developmental and survival factors may play an important role in the susceptibility of adult neurons under conditions of neurodegenerative disease. For example, stimulation of RXR by synthetic RXR ligand LG100268 and RXR-Nurr1 ligand XCT0139508 in rat dopaminergic cell cultures protected against oxidative stress induced by 6-OHDA and hypoxia; however, RXR expression alone could not protect the cells when treated with kainic acid and hydrogen peroxide; rather, neuroprotection against these was selective to Nurr1-expressing cells, still implicating RXR as its dimerization partner [129]. Notably, when administered to rats treated with 6-OHDA, IRX4204, a selective RXR agonist, and bexarotene, a cancer drug that binds to Nurr1-RXR heterodimers, attenuated the behavioral and neurochemical deficits in that PD model [130, 131]. Bexarotene also restored signaling by Ret, the canonical GDNF receptor, in mesencephalic mouse neurons overexpressing α-synuclein, suggesting that activation of RXR-Nurr1 may counteract the effect α-synuclein in PD [132, 133]. Nevertheless, the specific involvement of RXR in the effects of n-3 PUFAs in PD remain to be definitively determined.

3.3. Implications for prevention and treatment

The potential for n-3 PUFAs to contribute to the processes involved in neuroprotection and neuronal repair, or alternately to the increased lipid peroxidation found in PD, suggest the possibility for a role of these fatty acids in both the prevention and treatment of the disease. Furthermore, n-3 PUFAs appear to influence survival and function of dopaminergic neurons

during neurodevelopment as well as at adulthood, suggesting a variety of opportunities for intervention. However, while evidence for the role of n-3 PUFAs in PD remains promising, it is currently inconclusive, and additional clinical and preclinical studies are necessary to determine the effects of n-3 PUFAs in PD.

4. N-3 PUFAs and Schizophrenia

Schizophrenia is a complex disorder involving symptoms such as hallucinations, delusions, disorganized thought, blunted or inappropriate affect, social withdrawal, and cognitive dysfunction [134, 135]. The disease affects roughly 1% of the population worldwide. Its etiology is unclear but appears to involve the interaction of genetic and epigenetic factors that result in aberrant neurodevelopmental processes [136–139]. Several studies suggest the second trimester of gestation as the period during which incidents, such as maternal malnutrition or influenza infection, increase the risk of developing schizophrenia later in life [140–142]; however, events in later development may also contribute.

Although schizophrenia involves dysfunction of a variety of neurotransmitter systems, including the glutamatergic, serotonergic, and GABAergic systems, the brain dopamine systems play an important role [143, 144]. Of note, all clinically effective antipsychotic drugs are antagonists at the D_2 dopamine receptor, and their affinity for the D_2 receptor correlates with their clinical potency [145]. These, and other observations, led to the formulation of the “Dopamine Hypothesis of Schizophrenia”, which theorizes that the psychotic symptoms of schizophrenia result from hyperactivity of the mesolimbic dopamine pathway. Mesolimbic hyperactivity in schizophrenics has yet to be definitively demonstrated[143]; however, the assertion is supported by the effects of drugs, such as amphetamine, that can produce psychotic symptoms [146]. Likewise, increased density of striatal D_2 receptors has been repeatedly observed in schizophrenics and does not appear to be an artifact of antipsychotic drug treatment [147]. In addition, schizophrenics exhibit hypofunction of the prefrontal cortex, which appears to involve decreased activity of mesocortical dopamine neurons [147–149], in particular reduced activity of the cortico-striatal-thalamic loop circuit, which, in normal subjects, is activated by salient stimuli [150]. Decreased expression of Nur77 and Nurr1 have also been reported in the dorsal lateral prefrontal cortex of schizophrenics [151].

4.1. Clinical studies

A number of clinical studies suggest the contribution of n-3 PUFAs in schizophrenia. Studies of erythrocytes and other peripheral tissues of schizophrenics demonstrate alterations in the relative abundance of a variety of long-chain PUFAs, and meta-analyses support decreased levels of DHA and AA in erythrocyte membranes of schizophrenics compared to controls [152, 153]. Furthermore, levels of n-3 PUFAs were inversely correlated with the severity of schizophrenic symptoms, particularly negative symptoms [154–157]. Similarly, in individuals at ultra-high risk of psychosis, low peripheral tissues levels or low dietary consumption of n-3 PUFAs, which can lead to low tissue levels, were associated with electroencephalographic (EEG) alterations indicating poorer alertness and vigilance and increased risk conversion into psychosis [158, 159].

In addition to the differences in the relative abundance of various fatty acids observed in peripheral tissues of individuals with schizophrenia, several alterations in PUFAs and PUFA-related mediators have been found in the brain. Notably, lower concentrations of fatty acids including DHA and AA were found in the orbitofrontal cortex of schizophrenics relative to controls [160, 161], although no differences in these fatty acids were found in the prefrontal cortex or the amygdala [162, 163]. Post-mortem brains of schizophrenics also exhibited higher levels of $iPLA_2$, which cleaves DHA from the membrane, and Δ6 desaturase, an enzyme involved in PUFA biosynthesis [164–166]. Schizophrenia or schizophrenia-related behaviors were also associated with several PUFA-related genes such as Acyl-CoA synthetase medium-chain family member 1 (ASCM1), fatty acid binding protein 7 (Fabp7), the phospholipase A2G4A BanI polymorphism, and certain single nucleotide polymorphisms (SNP) of arachidonate 12-lipoxygenase (ALOX12) [35–38]. In addition, RXR, along with its dimerization partner Nur77, has been implicated in modulating a number of motor side effects of antipsychotic drugs, and decreased Nur77 has observed in post-mortem brains from schizophrenic patients [75], suggesting another potential mechanism by which n-3 PUFAs could play a role in schizophrenia.

A relatively small number of clinical trials have examined the efficacy of n-3 PUFA preparations in schizophrenia. Although one review of these clinical trials was unable to draw firm conclusions regarding the therapeutic utility of n-3 PUFA supplements in this disease [167], several studies, as well as a meta-analysis, indicate that while n-3 PUFA supplements may enhance the effects of antipsychotic drugs, the n-3 PUFA treatments were not sufficiently effective for use as monotherapy [168–172]. Another meta-analysis found that n-3 PUFAs appeared to be more efficacious during the prodrome and first episode, rather than in chronic patients or for preventing relapse [173]. Finally, a trial in individuals with subthreshold psychotic states found that n-3 PUFAs prevented progression to a psychotic disorder [174].

4.2. Preclinical studies

Depending on the specific manipulation and the point in development when it is made, changes in brain phospholipid fatty acid composition produce neurobiological effects that may be relevant schizophrenia [175], as well as other conditions such as ADHD (see below). In particular, feeding an n-3 PUFA-deficient diet for two generations, which produced adult rats with a 70% reduction of brain DHA content, produced a number of effects on the dopamine systems, many of which were similar to those observed in schizophrenics [176]. Dopaminergic alterations in the frontal cortices of these animals included reduced levels of dopamine-immunoreactive vesicles, the vesicular monoamine transporter $VMAT_2$, and the D_2 dopamine receptor [177–179], suggesting decreased activity of the mesocortical projection. Conversely, the treatment also resulted in an apparent net increase in activity of the mesolimbic projection as indicated by increased basal dopamine release and D_2 dopamine receptors density in the nucleus accumbens, and increased tyrosine hydroxylase activity in the ventral tegmental area [180, 181]. In contrast, the nigrostriatal system of these rats did not appear to be affected [177, 182]. In another multigenerational rat model that reduced the concentration of DHA in brain phospholipids by about 80%, the decrease in brain DHA content resulted in different effects at adolescence and adulthood, with

adolescent rats exhibiting increased expression of tyrosine hydroxylase in the dorsal striatum, and adults exhibiting decreased tyrosine hydroxylase levels and increased levels of $VAMT_2$ [183]. Other studies used a model in which an n-3 PUFA-deficient diet was fed during prenatal and early postnatal development in a single generation, which increased the ratio of n-6 DPA:DHA in brain tissue phosphatidylcholine by 6.8-fold compared to controls. These studies found dopaminergic alterations such as decreased levels of tyrosine hydroxylase and $VMAT_2$ in the hippocampus, and increased expression D_1 and D_2 receptors in the striatum and cortex [184, 185]. However, a pre- and postnatal diet-induced decrease in brain DHA of about 20%, resulted in no alterations in either the concentration of dopamine or the densities of D_1 or D_2 receptors in the nucleus accumbens, the frontal cortex, or the striatum [186]. These observations suggest that effects of variation in the availability of n-3 PUFAs on the brain dopaminergic systems varies depending on the magnitude and timing of the change in brain DHA status, and may thus, along with an individual's genotype, influence that individual's susceptibility to a particular neuropsychiatric disorder.

Similar to the variety of effects of n-3 PUFA manipulations on dopaminergic neurochemistry, the behavioral changes resulting from such treatments also differ between studies. Several investigations reported increased locomotor activity in rats raised on n-3 PUFA-deficient diets [183, 186–189], although the effects varied depending on magnitude of the decrease in brain DHA and the age of the rats [186, 187]. Likewise, compared to those fed a control diet, rhesus monkeys with long-term deficiency of n-3 PUFAs showed a higher level locomotor activity, as well as more stereotyped behavior [190]. However, another study of adult rats found that those with a 70% decrease in brain DHA displayed less exploratory behavior in a novel environment than controls [191]. Accordingly, changes in n-3 PUFA status affect the dopaminergic systems involved in motor function; however, the specific effects appear to differ depending on the specific treatment. Furthermore, a study in which brain DHA was restored by feeding a rats a DHA-supplemented diet at adulthood found that the developmental deficits in brain DHA content were fully reversible; however, only some of the effects of the dopamine-related behavioral effects of inadequate DHA accumulation during early development were reversed [188]. Thus, taken together, these observations suggest that developmental processes and brain DHA status interact to produce at least some of the observed effects.

N-3 PUFAs also affect behavior in several animal models of schizophrenia. In a study of amphetamine-induced behavioral impairment as a rat model of schizophrenia, treatment with DHA and EPA reduced the amphetamine-induced deficits in several behavioral tests and also decreased lipid peroxidation and cytokine release. In that study, the n-3 PUFAs were most effective when co-administered with the antipsychotic drug risperidone, thus supporting the use of n-3 PUFAs as an adjunct treatment [192]. In addition to motor function, sensorimotor gating, which is altered in schizophrenia [193], is affected after experimental manipulation of brain DHA in animal models. For example, in rats raised from conception on diets varying in n-3 PUFA content to produce varying concentrations of brain DHA, those with lowest brain DHA levels exhibited deficits in prepulse inhibition compared with those with the highest brain concentrations of DHA [194]. Likewise, in the ketamine model of schizophrenia, behaviors such as impaired social interactions, inhibition of startle

response, and ketamine-induced increases in acetylcholinesterase were decreased by n-3 PUFAs [195–197]

In addition to their effects of dopaminergic function, n-3 PUFAs modulate glutamatergic neurotransmission, which is also aberrant in schizophrenia [198]. Most notably, in mice with reduced levels of NMDA receptors, n-3 PUFAs failed to attenuate any of the behavioral deficits resulting from NMDA receptor hypofunction; however, the NMDA receptor knock-down mice had elevated brain concentrations of n-6 PUFAs regardless of the n-3 PUFA content of their diet, and an n-3 PUFA-deficient diet increased their deficits in executive function [199]. Likewise, in an *in vitro* study, addition of free, but not membrane-bound, DHA to cultured rat astrocytes or rat brain membrane preparations, decreased glutamate uptake [200].

Finally, some antipsychotic drugs appear to affect n-3 PUFA homeostasis. Administration of risperidone to rats for 30 days resulted in higher erythrocyte and brain DHA concentrations compared to controls [201]. However, brain DHA status was not altered by treatment with haloperidol or clozapine for 21 days [67], suggesting either differential effects of these drugs or an inadequate treatment period or dose in the latter study.

4.3 Implications for prevention and treatment

Taken together, these clinical and preclinical studies suggest that inadequate availability of n-3 PUFAs during key periods of early brain development may lead to altered dopaminergic function consistent with at least some of the abnormalities observed in schizophrenia. Combined with observations of reduced n-3 PUFAs in the brains and other tissues of schizophrenics, this observation supports the need for adequate nutrition during fetal and neonatal life, which is already acknowledged as being important for optimal brain development. The potential for n-3 PUFAs or n-3 PUFA-derived mediators as treatments for schizophrenia is less clear. The few studies done to date suggest that at least some dopamine-related behavior deficits of developmental n-3 PUFA deficiency are not reversible. The relative lack of efficacy of n-3 PUFA treatments in patients with symptomatic schizophrenia also suggests that n-3 PUFAs may prove more useful as a preventative intervention, though use as a an adjunct to antipsychotic medications, particularly early in treatment appears to have some promise.

5. N-3 PUFAs and ADHD

ADHD is a clinically heterogeneous disorder characterized by inattention, hyperactivity, and impulsivity that affects 2–5% of the general population [202, 203]. It is five-times more prevalent in boys than girls [204]. Although initially described as a childhood disorder, attention deficits can continue into adulthood [205]. The heritability of ADHD is about 80%, indicating a strong genetic component; however, other causative factors are likely involved [202].

Although the underlying pathology of ADHD is not fully understood, it appears to involve dysregulation of the brain dopaminergic and/or noradrenergic systems [206]. Neuropsychological and neuroimaging studies in patients with ADHD indicate frontolimbic

dysfunction involving brain regions such as the cortico-striato-thalamo-cortical loop [207–212]. The behavioral symptoms of ADHD are typically treated with psychostimulants, such as methylphenidate or amphetamine, which improve attention and decrease motor activity. These drugs increase synaptic availability of dopamine and norepinephrine and have been shown to enhance the inhibitory effects of frontal cortical activity on subcortical structures [213]. Taken together, these clinical observations and experimental results suggest that ADHD involves decreased activity of dopaminergic and/or noradrenergic projections from the ventral tegmental area, substantia nigra, and locus coeruleus that innervate the frontosubcortical brain regions. A role for dopamine in the pathogenesis of ADHD is further supported by animal and genetic studies. Rats with neonatal 6-OHDA lesions exhibit hyperactivity [214]. Mutant mice lacking the dopamine transporter also exhibit increased activity and are considered an animal model of the disease [215]. Genetic association studies in ADHD implicate polymorphisms of the D_2 and D_4 dopamine receptors, dopamine transporter, and dopamine β-hydroxylase genes [216–218]. These studies also implicate the D_4 receptor gene in novelty seeking, which could contribute to the impulsivity observed in ADHD [219, 220].. Furthermore, a recent systematic review of brain imaging-genetics studies identified 62 candidate genes, most of which were dopamine-related [221]. A single nucleotide polymorphism FADS2, a desaturase enzyme involved in the biosynthesis of long-chain PUFAs, has also been associated with ADHD [222].

5.1. Clinical studies

At least a subset of children and adults with ADHD exhibited altered fatty acid compositions of plasma or erythrocytes compared to normal controls, including lower levels of DHA [223–226]. These findings were supported by meta-analyses that found either low n-3 PUFA levels or increased ratio of n-6:n-3 PUFAs in ADHD [227, 228]. Erythrocyte DHA levels, which appear to correlate with brain levels [229], were reduced to 70–85% of normal controls [223, 224, 230]. Moreover, patients with low plasma or erythrocyte levels of DHA and other long-chain PUFAs had significantly more ADHD-related behavioral symptoms than those with higher DHA levels [230]. In the studies that also examined dietary n-3 PUFA content, consumption by individuals with ADHD was considered adequate [231, 232]; however, another study found that children with ADHD had higher than normal exhalant levels of ethane, suggesting increased oxidative metabolism of n-3 PUFAs [233], which could necessitate increased dietary consumption of these fatty acids.

Clinical trials of fatty acid preparations in ADHD have yielded varying results. Treatment with n-3 PUFA preparations increased serum and/or erythrocyte EPA and DHA in adults and children with ADHD [228, 234, 235]. Furthermore, in children treated with n-3 or n-3/n-6 PUFA preparations, the resulting increases in plasma or erythrocyte EPA and n-6 DPA correlated with decreased ADHD symptoms [236, 237]. Although studies varied with respect to the PUFA preparations used, dose, and duration of treatment, a number of randomized, controlled trials with various n-3 or n-3/n-6 preparations in children with ADHD also reported improvement in symptoms [235, 238–244]. However, other randomized, controlled trials failed to find a beneficial effect of these treatments on ADHD symptoms in children [245–249], even in subjects in whom the treatment resulted in increased erythrocyte EPA and DHA concentrations [250]. Meta-analyses of the effects of

n-3 PUFA treatments in ADHD have yielded varying results ranging from a small beneficial effect [227, 251, 252] to effective only on some symptoms in a subpopulation of patients [253], to negative [254, 255], to inconclusive [256]. Concomitant treatment with methylphenidate and either an n-3 or n-3/n-6 PUFA preparation was not superior to methylphenidate alone [257, 258].

5.2. Preclinical studies

As discussed above for schizophrenia, inadequate availability of n-3 PUFAs during development can result in neurochemical alterations consistent with frontocortical dopaminergic hypoactivity, as well increased locomotor and stereotyped activity (see 4.2). In addition, rats with reduced amounts of brain DHA during development exhibited impaired performance compared to controls on delayed matching-to-place in a water maze, in an active avoidance test, and in acquisition of olfactory discrimination [259–262]. Initiation of a diet low in ALA as late as one month of age, also decreased performance of rats in the Morris water maze [261]. Moreover, the spontaneously hypertensive rat (SHR), a putative model of ADHD [263], has lower brain DHA content than its less active progenitor strain, the Wystar Kyoto rat [264]. In the SHR rat model, locomotor activity was inversely related to the dietary n-3 PUFA content [265]. Lower n-3 PUFA consumption also resulted in higher brain total creatine levels which where correlated hyperactivity in a familiar environment [266]. In addition, feeding a diet enriched in n-3 PUFAs increased striatal turnover of dopamine and serotonin, increased attention, and decreased hyperactivity and impulsiveness of male, though not female, SHR rats [267]. Thus, lower brain DHA content during development appears to result in animals that exhibit increased activity, inattention, and impaired cognitive function similar to that associated with ADHD, as well as the frontocortical dopaminergic hypofunction associated with the disorder.

5.3. Implications for prevention and treatment

As with schizophrenia, the ADHD-like effects of inadequate availability of n-3 PUFAs during early brain development on behavior and dopaminergic function combined with the clinical observations of reduced levels of n-3 PUFAs in individuals with ADHD support a potential role for n-3 PUFAs or n-3 PUFA-derived mediators in the disorder. Again, this observation supports the need for adequate nutrition during fetal and neonatal life, which is already acknowledged as being important for brain development. Although the clinical trials with n-3 PUFAs in ADHD have been somewhat more promising than those in schizophrenia, the potential for n-3 PUFAs or n-3 PUFA-derived mediators as treatments for ADHD remains to be determined, and again likely depends to a great on extent on the reversibility of n-3 PUFA deficiency-induced effects that contribute to the disorder.

6. N-3 PUFAs and Dopaminergic Aspects of Depression

Depression is characterized by symptoms such as depressed mood, lack of interest, anhedonia, feelings of worthlessness or guilt, and suicidality [268]. It has a lifetime prevalence of about 20% and occurs roughly twice as often in women, with the postpartum period representing a time notable vulnerability for women [269–271]. Although the pathophysiological basis of the disease remains to be fully understood, genetic and

environmental factors are involved [272, 273]. Extensive clinical and animal evidence implicates the serotonin system, brain-derived neurotrophic factor (BDNF) in the hippocampus, and the hypothalamic-pituitary-adrenal axis as key systems affected in disorder [273–278]. A number of studies have examined the potential role of altered brain n-3 PUFA status, particularly decreased DHA, in depressive illnesses. These studies show that brain n-3 PUFA status affects these mediators in a manner consistent with an etiologic role in the disease. Furthermore, clinical trials indicate the potential therapeutic benefit of n-3 PUFA supplements in major depression (for extensive review of effects on the serotonin system, brain-derived neurotrophic factor (BDNF) in the hippocampus, and the hypothalamic-pituitary-adrenal axis, and clinical trials see: [279–281]). In view of the focus of this review on the effects of PUFAs on the dopaminergic systems, only the effects of PUFAs specifically on dopaminergic alterations relevant to depression are discussed here.

Altered dopaminergic function appears to contribute to the pathogenesis of depression, particularly the symptoms of anhedonia and decreased motivation [282, 283]. Notably, decreased engagement in reward-oriented behaviors is observed in animals with decreased activity of the mesolimbic dopamine projection [282, 283]. Consistent with these behavioral observations, levels of D_2 dopamine receptors or D_2 receptor mRNA were found the ventral striata not only of depressed women, but in several rat depression models including the Wystar-Kyoto rat, the socially-isolated Flinders sensitive line rat, and chronic mild stress-induced anhedonia [284–288]. The density of striatal dopamine transporters was also lower in depressed patients as assessed by single-photon emission computed tomography (SPECT) [289]. In addition, cerebrospinal fluid concentrations of the dopamine metabolite homovanillic acid (HVA) were lower in depressed patients and suicide victims, and were associated with depressed mood and psychomotor retardation [290–292]. Depression is also common in Parkinson's disease, often developing prior to the onset of motor symptoms [293–296], and depression-related behaviors, such as anhedonia and increased immobility in the forced swim test, have been observed in rodent models of the disease [297]. Furthermore, inhibition of dopamine re-uptake is a major mechanism of the antidepressant drug bupropion [298]. Taken together, these observations suggest a contributory role of altered dopaminergic function in at least a subset of depressed individuals.

6.1. Clinical studies

Although the effects of higher tissue and/or dietary levels of n-3 PUFAs have been studied in numerous human and animal studies relevant to depression including many clinical trials (for review see: [281]), only a few studies examined dopaminergic parameters. One clinical study examined serum concentrations of prolactin, an anterior pituitary hormone whose release is inhibited by dopamine and can thus serves as a marker of dopaminergic function. In depressed patients, plasma prolactin concentrations were inversely related to DHA levels, suggesting the association of decreased dopaminergic function with low DHA status [299].

6.2. Preclinical studies

Consistent with the clinical finding on dopamine in depression, adult rats fed diets that increased brain DHA content had higher dopamine concentrations [300]. In another study, postpartum female rats that were fed an n-3 PUFA-deficient diet during pregnancy and

lactation, had a 25% decrease in brain DHA and lower expression of D_2 dopamine receptors in the nucleus accumbens, similar to the decrease in D_2 receptor density observed in depressed females and rat models of depression [301]. In that study, virgin female rats with decreased brain DHA levels also exhibited a smaller, nearly significant decrease in accumbal D_2 receptors, suggesting that pregnancy and nursing augment the effects of DHA status on D_2 receptor regulation. Likewise, the density of D_2 receptors in the nucleus accumbens were lower in mutant mice lacking RXR-γ, a mediator of DHA signaling, which also exhibited the depressive behaviors of despair and anhedonia, along with changes in serotonin signaling [302].

6.3. Implications for prevention and treatment

The preponderance of the literature on the role of n-3 PUFAs in depression indicates that low dietary and tissue levels of n-3 PUFAs are consistently observed in the disorder, and that some experimental treatments that reduce n-3 PUFA levels cause a number of neurobiological effects similar to those observed in depression. Both the dopaminergic and non-dopaminergic effects (i.e., effects on the serotonin system, brain-derived neurotrophic factor (BDNF) in the hippocampus, and the hypothalamic-pituitary-adrenal axis) of n-3 PUFA deficiency support a role for n-3 PUFAs in depression in at least a subset of patients. The positive clinical trials of n-3 PUFA preparations in major depression support the involvement of brain n-3 PUFA status in the disorder, and suggest the benefit of these or related treatments in symptomatic patients. Interestingly, in contrast the effects of inadequate n-3 PUFAs during early brain development that resulted in dopaminergic alterations similar to those observed in schizophrenia, ADHD, or PD, depression-like neurobiological changes were observed most notable when n-3 PUFA status was altered in adult animals. This suggests that with respect to preventing depression, maintaining adequate n-3 PUFA levels throughout the lifespan may be critical. Thus, the potential of n-3 PUFA administration for prevention appears plausible, but must be tested in clinical trials. Furthermore, the preclinical data suggests that low levels of n-3 PUFAs may be contributory to anhedonic symptoms through effects on dopamine receptor expression, suggesting that n-3 PUFA treatment may prove useful in ameliorating depressive anhedonia and may thus be of particularly benefit to anhedonic patients. Future study must confirm this observation in depressed patients.

7. Conclusion

The clinical and preclinical studies reviewed here indicate that n-3 PUFAs, when combined with genetic and other environmental factors, likely contribute to the development and maintenance of brain dopamine systems and the etiologies of neuropsychiatric disorders involving those systems. The differing effects in conditions such as Parkinson’s disease, schizophrenia, ADHD, and depression likely result from the interaction of n-3 PUFA status with genetic and other factors to result in specific neurobiological alterations and symptoms. Furthermore, these studies suggest these disorders may be amenable to prevention and/or treatment with n-3 PUFAs, n-3 PUFA-derived mediators, or drugs that mimic their effects.

Future studies must fully elucidate the roles of long-chain PUFAs in the etiology of each of the neuropsychiatric disorders affecting the brain dopamine systems. In particular, how n-3 PUFA status interacts with genetic and environmental factors must be determined, as well as the interaction with developmental processes. In addition, the critical biological functions of the long-chain PUFAs, such as their role in membrane phospholipids, actions of long-chain PUFA-derived mediators, etc., in each of these disorders must be established. It is likely that these may differ between dopaminergic disorders. Furthermore, n-3 PUFAs may have both beneficial and detrimental actions in these conditions. Ultimately, the net effect in each disease must be determined as the definitive assessment of therapeutic potential and utility. In addition, although studies have shown that a DHA-enriched diet can restore brain DHA content in animals that have experienced a diet-induced loss of DHA from the brain [188, 303], the reversibility of each of neurobiological consequences of inadequate accumulation or a loss of n-3 PUFAs from brain must be determined, and may likely differ depending on the point in lifespan the deficit occurred. If such effects prove not to be fully reversible, this would indicate the critical importance of ensuring adequate DHA accumulation during development, as well as preventing a loss of brain DHA under physiological demands such as pregnancy. In contrast, effects that prove to be reversible would be anticipated to respond to treatments initiated after symptoms arise. Finally, should the data indicate the viability of using n-3 PUFAs, n-3 PUFA-derived mediators, or drugs that mimic their effects for the prevention or treatment of neuropsychiatric disorders involving the brain dopamine systems, the optimal agent, formulation, dose, and treatment duration must also to be determined.

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Abbreviations

AA	arachidonic acid
ALA	α-linolenic acid
ADHD	attention deficit hyperactivity disorder
ALOX12	arachidonate 12-lipoxygenase
ASCM1	Acyl-CoA synthetase medium-chain family member 1
Bcl-2	B-cell lymphoma-2
BDNF	brain-derived neurotrophic factor
cPLA$_2$	cytosolic phospholipase A$_2$
COX	cyclooxygenase
DHA	docosahexaenoic acid

n-6 DPA	docosapentaenoic acid
EEG	electroecephalograph
EFOX	electrophile oxo-derivatives
EPA	eicosapentaenoic acid
Fabp7	fatty acid binding protein 7
FADS	fatty acid desaturase
GDNF	glial cell-derived neurotrophic factor
iPLA$_2$	calcium-independent phospholipase A$_2$
LA	linoleic acid
LOX	lipoxygenase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Nf-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NBRE	nerve growth factor 1B response element
NMDA	n-methyl-d-aspartate
NO	nitric oxide
iNOS	inducible nitric oxide synthase
NPD1	neuroprotectin D1
NURR1	nuclear receptor-related-1 protein
NURR77	nerve growth factor 1B
6-OHDA	6-hyrdoxydopamine
PD	Parkinson’s disease
PI$_3$K	phosphatidylinositol-3 kinase
PKC	protein kinase C
PPAR	peroxisome-proliferator-activated receptor
PUFA	polyunsaturated fatty acid
ROS	reactive oxygen species
SHR	spontaneously hypertensive rat
SNP	single nucleotide polymorphism
SPECT	Single-photon emission computed tomography

RXR	retinoid X receptor
sPLA$_2$	secretory phospholipase A$_2$
TLR	toll-like receptor

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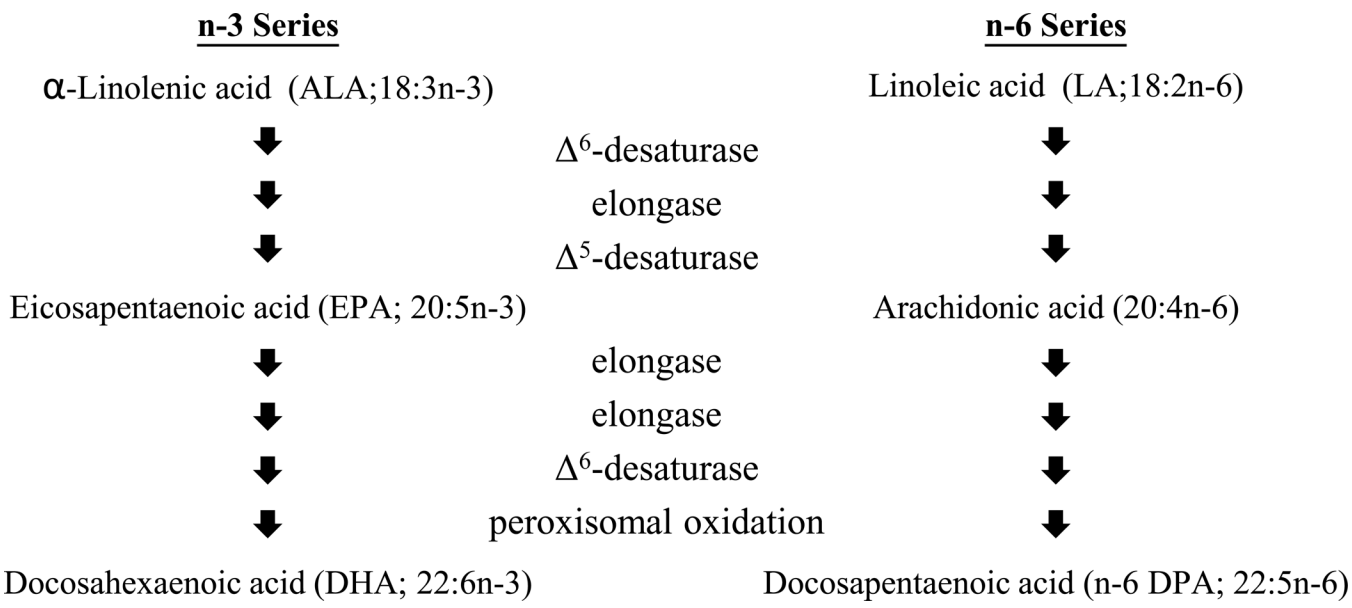

Fig. 1.
Biosynthesis of n-3 and n-6 PUFA.