Role of omega-3 fatty acids in brain development and function: Potential implications for the pathogenesis and prevention of psychopathology

Robert K. McNamaraa,*, Susan E. Carlsons

aDepartment of Psychiatry, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0559, USA
bDietetics and Nutrition, Smith Mental Retardation Research Center, University of Kansas Medical Center, Kansas City, KS 66160, USA

Abstract

The principle omega-3 fatty acid in brain, docosahexaenoic acid (DHA), accumulates in the brain during perinatal cortical expansion and maturation. Animal studies have demonstrated that reductions in perinatal brain DHA accrual are associated with deficits in neuronal arborization, multiple indices of synaptic pathology including deficits in serotonin and mesocorticolimbic dopamine neurotransmission, neurocognitive deficits, and elevated behavioral indices of anxiety, aggression, and depression. In primates and humans, preterm delivery is associated with deficits in fetal cortical DHA accrual, and children/adolescents born preterm exhibit deficits in cortical gray matter maturation, neurocognitive deficits particularly in the realm of attention, and increased risk for attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. Individuals diagnosed with ADHD or schizophrenia exhibit deficits in cortical gray matter maturation, and medications found to be efficacious in the treatment of these disorders increase cortical and striatal dopamine neurotransmission. These associations in conjunction with intervention trials showing enhanced cortical visual acuity and cognitive outcomes in preterm and term infants fed DHA, suggest that perinatal deficits in brain DHA accrual may represent a preventable neurodevelopmental risk factor for the subsequent emergence of psychopathology.

1. Introduction

Because mammals lack the capacity to introduce double bonds at the omega or n-6 and omega or n-3 positions from the carbonyl end of oleic acid, they are dependent on dietary sources of linoleic acid (LA, 18:2n-6) and α-linolenic acid (ALA, 18:3n-3), respectively, to meet their physiological needs for these families of fatty acids. Good dietary sources of ALA include flaxseed, linseed, canola, soy, and perilla oils. The principle omega-3 fatty acid metabolites of ALA are eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). DHA synthesis from dietary ALA is limited in humans[1–4]. However, preformed DHA and EPA can be obtained directly from the diet, particularly fatty fish, e.g., salmon, trout, and tuna. Dietary DHA is significantly more effective than is dietary ALA as a source for DHA accrual in the developing human[5–7], primate[8], and rat brain[9], as well as in the adult rat brain[10].

Mammalian brain tissue is predominantly composed of lipids which are comprised of different saturated, monounsaturated, and polyunsaturated fatty acids (Fig. 1). The principle omega-3 fatty acid found in brain is DHA, comprising 10–20% of total fatty acids composition, whereas the omega-3 fatty acids ALA, EPA, and docosapentaenoic acid (22:5n-3) comprise <1% of total brain fatty acid composition. The ratio of saturated, monounsaturated, and polyunsaturated fatty acids observed in postmortem human frontal cortex is generally conserved among other mammals, including monkeys[11], rats[12], and mice[13]. For example, adult rodents/primates maintained on a diet containing...
2. Consequences of brain DHA deficiency

2.2.1. Brain fatty acid composition

Under our experimental conditions, maternal and offspring dietary ALA-deficiency led to a ∼70% reduction in frontal cortex DHA concentrations in first generation adult (P90) offspring, and second generation offspring exhibited greater reductions (∼80%) (Fig. 2). Postweaning (P21-P90) dietary ALA-deficiency led to a...
However, dietary ALA deficiency, these data would indicate that dietary metabolism or brain-regional specific susceptibilities to may represent differences in rat and mouse brain DHA concentrations in the frontal cortex and striatum (Fig. 3). Although the discrepancy between these findings and those of Bourre et al. [44] may represent differences in rat and mouse brain DHA metabolism or brain-regional specific susceptibilities to DHA loss, these data would indicate that dietary omega-3 fatty acid intake is necessary for the maintenance of regional brain DHA concentrations even following brain maturation. This receives further support from recent studies finding that adult female rats maintained on an omega-3 fatty acid-deficient diet exhibit significant reductions in brain DHA concentrations after one reproductive cycle that cannot be attributed to the effects of diet [45,46].

Different brain regions exhibit a differential loss of DHA accrual following perinatal omega-3 fatty acid deficiency. The greatest reductions are observed in the frontal cortex > hippocampus > cerebellum > striatum > hypothalamus > midbrain [13,15,17]. Moreover, brain DHA concentrations recuperate at different rates in different brain regions. The frontal cortex and hippocampus are among the last brain regions to fully recuperate normal DHA concentrations following dietary fortification [12,13,17]. Therefore, perinatal deficits in DHA accrual within the frontal cortex and hippocampus may be the most difficult to restore in the absence of specific postnatal dietary intervention.

2.2.2. Neuroanatomy

Perinatal omega-3 fatty acid deficiency is not associated with gross neuronal laminar abnormalities or neuronal loss in the rat hippocampus [47–49]. A neuroimaging study did not find gross alterations in brain gray or white volumes in omega-3 fatty acid-deficient aged (>15 months) rats relative to aged control rats [50], though aged rats maintained on omega-3 fatty acid fortification [12,13,17]. Therefore, perinatal deficits in DHA accrual within the frontal cortex and hippocampus may be the most difficult to restore in the absence of specific postnatal dietary intervention.
phosphatidylserine concentrations [57]. Because phosphatidylserine plays an important role in mediating the binding of several structural and signal transduction proteins with the plasma membrane (see below), reductions in synaptic membrane phosphatidylserine concentrations would be anticipated to lead to a dysregulation in synaptic second messenger cascades, deficits in growth cone motility, synaptogenesis, and synaptic function.

2.2.4. Synaptic signal transduction

Binding of the myristoylated alanine-rich C kinase substrate (MARCKS) protein to synaptic plasma membranes is mediated in part by electrostatic interactions between the highly basic phosphorylation site domain of the MARCKS protein and acidic phosphatidylserine [58]. Perinatal dietary omega-3 fatty acid deficiency (~70% DHA) was associated with a significant reduction (~30%) in mature neuronal membrane phosphatidylserine concentrations [55,56], and a significant reduction (~35%) in membrane-bound MARCKS expression [27]. Biochemical studies have demonstrated that binding of MARCKS to the plasma membrane plays an important role in regulating the phosphoinositide signal transduction pathway and intracellular calcium homeostasis [59–62]. These findings would suggest that even small reductions in MARCKS membrane binding would lead to elevations in receptor-generated phosphoinositide (IP$_3$) synthesis and intracellular free calcium concentrations. Perturbations in intracellular calcium homeostasis during neuronal development would be anticipated to induce premature growth cone collapse and deficits in synaptogenesis [63].

MARCKS membrane binding also plays an important role in modulating filamentous actin cytoskeletal plasticity to regulate neurotransmitter vesicle trafficking and neurotransmitter release efficacy (reviewed in [64]). Reductions in MARCKS binding to the plasma/vesicle membrane as a consequence of perinatal dietary omega-3 fatty acid deficiency could account for the observation that omega-3 fatty acid-deficient rats exhibit use-dependent reductions in neurotransmitter vesicle densities within presynaptic terminals [53] and reduced stimulated extracellular levels of several neurotransmitters, including serotonin [65], acetylcholine [66], and dopamine [67]. Deficits in filamentous actin cytoskeletal plasticity would also be anticipated to lead to a disruption of growth cone migration and motility, dendritic spine motility, and ultimately synaptogenesis [68–70].

Reductions in synaptic membrane phosphatidylserine concentrations also has implications for the protein kinase C (PKC) signal transduction pathway. Binding of PKC with phosphatidylserine is necessary for membrane binding and maximal kinase activity [71], and perinatal
omegα-3 fatty acid deficiency (−70% DHA) has been associated with significant reductions in membrane-associated PKC isozyme (ζ, ζ) expression [27]. Deficits in the PKC signaling transduction pathway within neuronal growth cones during development would be anticipated to impair neurite outgrowth and synaptogenesis [72,73]. Furthermore, PKC activation is associated with long-term elevations in neurotransmitter release efficacy via the phosphorylation of MARCKS (reviewed in [74]), and omega-3 fatty acid deficiency is associated with decrements in serotonergic and dopaminergic neurotransmitters [75] and release of dopamine [67,76–79], serotonin [65], and acetylcholine [66]. Alterations in PKC signaling activity would also have implications for the activity, trafficking and membrane localization of serotonin 5-HT2A receptors [80], dopamine D2 receptors [81], noradrenaline transporters [82], dopamine transporters [83] and the serotonin transporters [84]. Omega-3 fatty acid deficiency is associated with significant elevations in cortical serotonin 5-HT2A receptor binding density [76,85] and reductions in dopamine D2 receptor binding density [67,76,85]. Although alterations in dopamine transporter binding have not been observed in the DHA-deficient rat brain [86], amphetamine-induced dopamine release is impaired in DHA-deficient rats [79], suggesting deficits in dopamine transporter function. Similarly, fenfluramine-induced serotonin release is impaired in DHA-deficient rats [65], suggesting deficits in serotonin transporter function. Deficits in rat brain serotonin and dopamine neurotransmission resulting from prenatal omega-3 fatty acid deficiency can be normalized if dietary omega-3 fatty acid fortification is initiated early in postnatal development. Specifically, Kodas et al. [65] found that deficits in fenfluramine-induced serotonin release in the adult (P60) rat hippocampus could be normalized when dietary omega-3 fatty acid fortification was initiated on postnatal day 0, 7 or 14, but not when initiated on postnatal day 21 despite the normalization of hippocampal DHA concentrations. Similarly, deficits in tyramine-induced dopamine release in the adult (P60) rat medial prefrontal cortex and nucleus accumbens could be normalized when dietary omega-3 fatty acid fortification was initiated on postnatal day 0, 7 or 14, but not when initiated on postnatal day 21 despite the normalization of brain DHA concentrations in the prefrontal cortex [77]. These studies suggest that there is a critical developmental window of opportunity to normalize deficits in dopamine and serotonin neurotransmission following prenatal omega-3 fatty acid deficiency in rat brain.

### 2.2.5. Behavior

The net effect of perinatal deficits in brain DHA accrual on behavioral and neurocognitive processes in omega-3 fatty acid deficient rats has been reviewed elsewhere [87]. Briefly, rodent perinatal omega-3 fatty acid deficiency is associated with deficits in hippocampus-dependent spatial learning [88,89], deficits in frontal cortex-dependent working memory [90], deficits in olfactory discrimination learning [91], and elevated behavioral indices of anxiety [92], aggression and depression [93]. Deficits in hippocampus-dependent spatial learning [89], but not elevated indices in anxiety [92], are corrected following dietary omega-3 fatty acid fortification.

### 3. Nonhuman primates

#### 3.1. Brain DHA accrual during perinatal brain development

In the developing primate (monkey) brain, frontal cortex DHA concentrations at birth represent ~15% of total fatty acids, and between birth and 22 months of age, increase to comprise ~22% of total fatty acids [11,97]. Primates (baboon) born preterm (gestation week 22 vs. term—gestation week 26) exhibit significantly lower (22–35%) postmortem brain DHA concentrations relative to term-born primates [98,99]. These findings indicate that in primates, the majority of brain DHA accrual occurs during the later phase of gestation.

#### 3.2. Consequences of brain DHA deficiency

##### 3.2.1. Brain fatty acid composition

A maternal diet low in ALA from 2 months prior to conception reduced neonatal monkey prefrontal cortex DHA concentrations by ~75% at birth relative to neonates whose mothers were maintained on a diet containing ALA [11,97]. Dietary omega-3 fatty acid fortification leads to a progressive increase in DHA concentrations in the DHA-deficient primate (monkey) cortex, reaching control levels after approximately 10–12 weeks [97,100]. By comparison, retinal DHA deficiency, and associated electroretinogram abnormal-
ities, were not restored to control levels following 3 years of dietary omega-3 fatty acid fortification [97]. Moreover, deficits in cortical DHA concentrations in preterm baboons were not restored to control (term, breastfed) levels following feeding with either human infant formula not fortified with DHA/EPA (−35%) or DHA/EPA-fortified formula (−10%) at 4 weeks [98]. These findings indicate that deficits in primate prenatal brain DHA accrual requires long-term (>4 weeks) daily dietary DHA intervention.

3.3. Behavior

Relative to rodents, little is known about the effects of perinatal omega-3 fatty acid deficiency on primate brain neurochemistry or behavior. Perinatal omega-3 fatty acid deficiency in primates is associated with deficits in visual acuity and electroretinogram abnormalities [11,97,101], visual attention processes [102], polydipsia (excessive thirst) [103], and increased home cage stereotypy and locomotion bouts [104]. Electroretinogram abnormalities have also been documented in neonatal baboons born preterm [105].

4. Humans

4.1. Brain DHA accrual during perinatal brain development

DHA accumulates in human brain tissue at a rapid rate (~14.5 mg/week) during the third trimester (gestational weeks 26–40) [106,107]. At term birth, DHA represents approximately 9% of total cortical fatty acid composition, and increases by an additional ~6% between birth and age 20 to compose ~15% total cortical fatty acid composition in postmortem brain tissue from subjects residing in the US at time of death [108]. Infants born preterm (<33 weeks of gestation) exhibit lower (~40%) postmortem cortical DHA concentrations relative to term infants when fed the same ALA-fortified formula postnatally [6,7,36,106,107]. These findings indicate that the majority of DHA accumulation occurs in the human brain during the last trimester of normal gestation, and that DHA continues to accumulate throughout postnatal brain maturation. As in rodents and primates, the linear increase in DHA accumulation in human frontal cortex between birth and 20 years of age corresponds with linear increases in frontal cortex white matter during this period, and additionally corresponds with the initial frontal gray matter expansion which continues until ~12 years of age and then declines thereafter [109,110] (Fig. 4).

4.2. Consequences of brain DHA deficiency

4.2.1. Prenatal deficiency

4.2.1.1. Brain fatty acid composition. Preterm infants fed formulas without DHA have lower red blood cell phospholipid DHA concentrations relative to those fed human milk [111] and DHA accumulates rapidly in the human fetal brain during the third trimester [36,106]. A number of randomized studies have measured and observed effects of DHA supplementation of infant
formula on visual acuity and other aspects of infant development following premature birth (for reviews see [112–114]). Infants born preterm (<36 weeks of gestation) and fed formulas without DHA after birth exhibit lower (~40%) postmortem cerebral cortex DHA concentrations relative to term, human milk-fed, infants [6,7,107]. These findings are consistent with those obtained from primates born preterm [98,99].

Cerebellar DHA concentrations were also significantly lower when the diet did not contain DHA, however, there was no difference in cerebellar DHA concentrations between infants born preterm and term who had been fed the same infant formula [115], suggesting that cerebellar cortex DHA accrual may precede that of cerebral cortex during gestation. It is not known for how long low brain DHA concentrations persist following preterm delivery or whether dietary DHA intake would reverse low DHA concentrations in brain. Based on a primate recuperation study [97], complete brain DHA recuperation would require intensive (daily) and chronic (months) dietary DHA-fortification.

4.2.2. Postnatal deficiency

4.2.2.1. Brain fatty acid composition. After birth infants are reliant on maternal breast milk (or formula) as the sole source of DHA. Human breast milk DHA concentrations are highly correlated with maternal dietary DHA intake [139], and diets fortified with only ALA do not increase breast milk DHA concentrations [140]. Breast milk DHA concentrations vary widely across different countries in accordance with dietary seafood consumption rates, e.g., ~0.17% of total milk fatty acids in the US and 1.1% of total milk fatty acids in Japan [141]. The recognition that human breastmilk DHA represents an important source for postnatal infant brain DHA accrual has led to the recent (2002) commercial availability of DHA-fortified infant formula in the US. Prior to this time, infants in the US that were not breastfed were maintained on formulas that did not contain DHA. Term infants fed formulas without DHA consistently exhibit significantly lower RBC and/or postmortem brain cortex DHA concentrations relative to breastfed infants or infants fed formula containing DHA [5,7,114,115,142–144]. Consistent with primate studies [98,99], infant frontal cortex accumulates DHA faster over the course of postnatal development in breast-fed infants relative to formula-fed infants [114].

4.2.2.2. Neurocognition. The effect of postnatal omega-3 fatty acid deficiency on neurocognitive development of term infants has been reviewed in detail previously [112–145]. Published studies have not always yielded consistent results, and interpretation of these findings must be made with caution in view of variability in fetal brain DHA accrual during gestation, variability in maternal breast milk DHA concentrations, and variability in dietary DHA intake following weaning from formula/breast milk. Nevertheless, studies have found that infants fed formulas without DHA exhibit several neurological and neurocognitive ‘soft signs’ in infancy and childhood relative to infants fed formulas with DHA or maternal breast milk, including lower visual acuity, slower processing speed on tests of visual recognition memory, more mature motor movement, problem-solving, psychomotor function, and lower IQs [129–131,146–155].
4.2.2.3. Childhood deficiency. The first documented case of human omega-3 fatty acid deficiency was reported in 1982 [156]. This case report describes a 6-year-old female patient maintained for 5 months on an ALA-deficient parenteral nutritional preparation following intestinal surgery. The patient exhibited a 17% reduction in plasma DHA concentrations relative to age-matched controls, presented with dermatitis and neurological symptoms, including neuropathy, blurred vision, and ‘psychological disturbances’. When the parenteral nutritional preparation was replaced with an ALA-fortified preparation, plasma omega-3 fatty acid levels normalized and neurological symptoms abated [156,157]. No standardized neurocognitive or psychiatric scales were administered to this subject.

4.2.3. Psychopathogenesis

A growing body of evidence suggests that deficits in attention and memory processes during childhood may precede and predict the subsequent emergence of psychopathology in high-risk populations [125,158–161]. The neurocognitive differences observed in children exposed to lower DHA in utero, born preterm or fed a diet without DHA postnatally suggest a link between perinatal brain DHA accrual and deficits that have been associated with risk of psychopathology in young adulthood. Furthermore, rodent studies have demonstrated that perinatal deficits in brain DHA accrual are associated with impaired mesocorticolimbic dopamine neurotransmission, which has been implicated in the pathophysiology and treatment of ADHD and schizophrenia.

In the following section, we will explore the potential role of perinatal deficits in brain DHA accrual in the pathogenesis of ADHD and schizophrenia, two psychiatric disorders that have been associated with familial transmission, a neurodevelopmental aetiology, abnormalities in mesocorticolimbic dopamine neurotransmission, and omega-3 fatty acid deficiency. It should be noted that bipolar disorder and major depressive disorder have also been associated with familial transmission, a neurodevelopmental etiology, abnormalities in mesocorticolimbic dopamine neurotransmission, and omega-3 fatty acid deficiency. However, discussion of these disorders is beyond the scope of the present review.

4.2.4. Attention-deficit/hyperactivity disorder (ADHD)

Children as well as adults with ADHD exhibit significantly lower RBC or plasma DHA concentrations relative to age- and sex-matched controls [162–166]. Several trials have used DHA and EPA supplements as primary treatment for ADHD [167–170] and several others have used DHA and EPA supplements as adjunctive treatment [169,171,172]. Some intervention trials [167,172,173], but not others [168,171], have observed significant symptomatic improvement in ADHD patients following dietary DHA and EPA supplementation. A report for the US Department of Health and Human Services [145] concluded there was little evidence for benefits of DHA or EPA for ADHD. Although there have been no prospective intervention treatment trials conducted to evaluate whether low prenatal or perinatal accrual of brain DHA accrual could contribute to the pathogenesis of ADHD, larger studies of pre- and postnatal DHA supplementation appear to be warranted.

Patients with ADHD exhibit significant deficits in frontal cortical dopamine synthesis and metabolism [174,175], and first-line medications (methylphenidate & atomoxetine) which reduce symptom severity in the majority of ADHD patients, increase extracellular dopamine levels in rat frontal cortex [176,177]. These data suggest that deficits in frontal cortex dopamine neurotransmission may be central to the underlying disease pathophysiology in ADHD. Rat studies have demonstrated that perinatal deficits in brain DHA accrual during the development and maturation of dopaminergic projections to the frontal cortex (E16-P60; [178]) lead to significant deficits in basal and stimulated extracellular dopamine concentrations in this region in young adulthood [54,77,79]. These deficits are reversible with early (P0-P14), but not late (P21), postnatal omega-3 fatty acid supplementation [77], and rodent maternal dietary fish oil supplementation throughout gestation and lactation significantly increases dopamine (+40%) concentrations in the frontal cortex of adult offspring [57]. Behaviors associated with altered dopaminergic function (reduced haloperidol-induced catalepsy, increased basal and amphetamine-stimulated locomotor activity, increased stereotyped behavior) have been observed in rodents and nonhuman primates with lower brain DHA [94,104]. In adult rodents, the effects of early DHA deficiency on haloperidol-induced catalepsy, but not the effects on amphetamine-induced locomotor activity, were normalized by restoring brain DHA concentration initiated at 21 days of age [94]. These findings suggest that perinatal brain DHA accrual plays an important role in the functional development of the mesocortical dopamine pathway.

Patients with ADHD also exhibit deficits in mesostriatal dopamine neurotransmission which is augmented by methylphenidate treatment [179,180]. Rats subjected to perinatal deficits in brain DHA accrual also exhibit deficits in mesostriatal dopamine neurotransmission [67,79] which is reversible with early (P0-P14), but not late (P21), postnatal omega-3 fatty acid supplementation [77]. Perinatal brain DHA accrual therefore also plays an important role in the functional development of the mesostriatal dopamine pathway.
The development and maturation of dopaminergic projections in the human frontal cortex occurs predominantly between midgestation and birth [181,182], suggesting that deficits in brain DHA accrual during the third trimester may contribute to deficits in attention in preterm children. Preterm delivery, which results in lower third trimester cortical DHA accrual [6], is associated with elevated rates of ADHD [120,124], and preterm infants provided with dietary DHA supplementation postnatally exhibited significant improvements in visual attention processes consistent with increased processing speed [129,130].

In addition to early delivery, brain DHA accrual may be modified both in utero and postnatally by the DHA intake and other factors that influence DHA status of the mother and infant, including individual variability in DHA synthesis [1–4]. Term infants, the majority of whom received formula without DHA postnatally, exhibited differences in focused attention in infancy and distractibility in toddlerhood relative to the amount of DHA in their mother’s blood (a putative surrogate for prenatal DHA accrual). Specifically, infants/toddlers whose mothers had red blood cell DHA concentrations below the median at delivery demonstrated less mature attention, slower processing, and higher distractibility relative to those whose contents were above the median [134]. As well, a retrospective study found that children with ADHD had significantly shorter breastfeeding durations (a putative surrogate for postnatal DHA accrual) relative to children without ADHD [183]. These findings suggest that perinatal deficits in brain DHA accrual may contribute to deficits in attentional processing and ADHD, and that postnatal DHA supplementation may represent a safe and efficacious strategy to mitigate these deficits.

Neuroimaging studies suggest that ADHD is associated with perinatal deficits of cortical maturation. As with children born preterm, ADHD children exhibit cortical gray and white matter volume reductions, though the magnitude of these volume reductions are greater in preterm children (cf. [117,184]). Specifically, ADHD children exhibit significantly smaller (3–5%) frontal and temporal cortex gray and white matter volumes [184,185], reduced corpus callosum (splenium) volumes [186,187], and enlarged cerebral ventricles [187]. Nine independent studies have observed significant reductions in prefrontal cortical volumes in ADHD patients (reviewed in [188]).

Collectively, these findings provide support for the proposition that reduced perinatal DHA accrual in brain may represent a risk factor for ADHD. In view of the high prevalence rate of ADHD in preterm children, and rat data demonstrating the limited reversibility of deficits in mesocorticolimbic dopamine with later omega-3 fatty acid intervention, gestational or early postnatal DHA supplementation would be anticipated to have greatest therapeutic efficacy in human subjects. This perinatal time window may also account for the limited efficacy of chronic DHA + EPA treatment in children (6–12 years) with ADHD [168,171–173].

4.3. Schizophrenia

Several lines of evidence suggest that low brain DHA accumulation may be associated with the pathophysiology of schizophrenia. For example, cross-national and sectional epidemiological surveys link low seafood consumption with increased symptom severity in schizophrenia [189,190]. RBC or plasma DHA concentrations are significantly lower in male and female patients with first-episode psychosis [191–193] or schizophrenia [194–196]. DHA concentrations are significantly lower in the postmortem prefrontal cortex of adult schizophrenic patients [197] but not in the postmortem temporal cortex [198], cingulate gyrus [199], caudate nucleus [200] or cerebellum [201] of adult schizophrenic patients.

Intervention trials have observed significant symptomatic improvement in medicated-schizophrenic patients following chronic treatment with DHA + EPA or EPA alone [202–206]. Although it is not currently known whether DHA deficiency during perinatal brain development contributes to the pathogenesis of schizophrenia, preterm delivery which is associated in part with deficits in cortical DHA accrual (above), increases risk for schizophrenia [207–211].

Abnormalities in the development and maturation of mesocorticolimbic dopamine pathways implicated in the pathophysiology of ADHD have also been implicated in the pathophysiology of schizophrenia [212–214], and attentional impairments are a core negative feature of schizophrenia. Atypical antipsychotic medications that are efficacious in the treatment of psychosis in the majority of patients have in common the ability to increase extracellular dopamine concentrations in rat frontal cortex and ventral striatum [215,216]. Furthermore, chronic treatment with atypical antipsychotic medications at therapeutically relevant concentrations decrease (−50%) serotonin 5-HT2A receptor density [217] and increase (+30%) dopamine D2 receptor density [218] in adult rat frontal cortex. Conversely, rat studies have demonstrated that perinatal deficits in brain DHA accrual is associated with significant deficits in tyramine-stimulated extracellular dopamine concentrations in prefrontal cortex and ventral striatum [67,77–79], elevations in (+50%) in serotonin 5-HT2A receptor density, and significant reductions (−25%) in dopamine D2 receptor density, in the adult rat frontal cortex [76,85]. These findings demonstrate that perinatal deficits in brain DHA accrual lead to changes in dopamine and serotonin neurotransmission and receptor binding in the adult rat brain that are opposite to...
those produced by clinically efficacious atypical antipsychotic medications.

Epidemiological surveys have found that the duration of postnatal breastfeeding (a putative surrogate for postnatal DHA intake) is inversely correlated with age at onset of schizophrenia [219,220], and infants with no or short-term (<2 weeks) breast feeding have a 1.7-fold higher risk of developing schizophrenia relative to infants breast fed for ≥2 weeks [221]. Notwithstanding the methodological limitations associated with this type of retrospective epidemiological analysis, including variability in maternal breast milk DHA concentrations, and the failure of other studies to demonstrate excess risk in infants breastfed <1 month [222,223], these findings remain intriguing because they suggest that very early postnatal DHA deficiency may be associated with increased risk for schizophrenia.

As observed in children and adolescents born preterm, children, adolescents, and adults with schizophrenia exhibit neuroanatomical abnormalities indicative of deficits in cortical maturation. Specifically, children with schizophrenia (early-onset) [224–228], first-episode psychotic patients [229–238], and adult patients with schizophrenia (reviewed in [239]) exhibit significant reductions in cortical gray and white matter volumes, reductions in amygdala and hippocampal volumes, reductions in corpus callosum volumes, and enlargements in ventricular volumes. Postmortem histological studies indicate that the cortical and hippocampal gray matter volume reductions observed in schizophrenic patients are attributable to deficits in synaptic and dendritic spine density and reductions in cell body size rather than neuronal loss [240–246]. This histological pattern is therefore consistent with perinatal deficits in brain DHA accrual, which is associated with deficits in neuronal arborization [39] and neuronal shrinkage [47,48] but not neuronal loss [50].

Regarding genetic liability, monozygotic twin studies suggest that schizophrenic twins in monozygotic twin pairs exhibit significant volume reductions in dorsolateral prefrontal cortex, hippocampus, whole brain gray matter, as well as ventricular enlargement, relative to unaffected twins [247–250]. These findings indicate that gray matter deficits are not related to genotype and are therefore attributable to environmental factors. A case study found that a schizophrenic twin in a discordant monozygotic twin pair exhibited significantly lower birth weight relative to the unaffected monozygotic twin as well as deficits in gray matter volume [251]. It is of interest, therefore, that lower umbilical plasma polyunsaturated fatty acid concentrations are associated with smaller birth weights among twins [252], and schizophrenic twins exhibit significantly lower plasma DHA concentrations relative to their unaffected monozygotic twins [253]. Differential brain DHA accrual among monozygotic twins may therefore represent an

uterine environmental risk factor for impaired gray matter maturation and schizophrenia.

It is of additional interest that individuals at high-risk for developing schizophrenia (e.g., having a first-degree relative with schizophrenia) have a significantly higher frequency of birth complications [254], and exhibit significant reductions in whole brain volumes, reductions in amygdala-hippocampal volumes, and increased third ventricle volumes, relative to healthy controls during the prodromal phase of the illness (pre-psychosis) [255–257]. Moreover, children at high-risk for developing schizophrenia exhibit deficits in attention and verbal memory during the prodromal phase which were found to be strong predictors for the subsequent emergence of psychosis in young adulthood [159,258]. Furthermore, ADHD is more prevalent in high-risk children (31%) relative to the general population 4–12% and is associated with a poorer psychiatric prognosis [160,161,259]. These findings suggest that high-risk children exhibit neurocognitive and neuroanatomical deficits that are also observed in children and adolescence born preterm and may indicate a common pathoaetiology.

Maternal dietary DHA intake has important implications for the developing fetal/infant brain. Maternal DHA stores in plasma and breast milk are largely determined by maternal dietary DHA intake [260–263], and DHA is preferentially transferred from maternal plasma to the fetus in utero in a concentration-dependent manner [264–267]. DHA transfer from mother to the neonate continues if infants are fed human milk postnatally and this transfer is also dependent upon maternal milk DHA concentrations [268]. Female and male schizophrenic patients exhibit significantly lower RBC or plasma DHA concentrations (~25%) relative to normal controls [194,195]. Tobacco smoking has been associated with reduced RBC DHA levels in schizophrenic women, but not in schizophrenic men [269], and schizophrenic women have been reported to smoke tobacco at a significantly higher rate prior to and during pregnancy than non-schizophrenic women [270,271]. As well, lower maternal RBC/plasma DHA content is associated with shorter gestation length [272–277], and women with schizophrenia exhibit higher rates of preterm delivery than non-schizophrenic women [271,278,279]. Based on primate studies, maternal deficits in RBC/plasma DHA concentrations of 25% would be anticipated to be associated with significant (~70%) deficits in fetal frontal cortex DHA accrual [97,101]. Based on these various lines of evidence, the risk of perinatal deficits in brain DHA accrual would be anticipated to be greater in the offspring of schizophrenic women, and may represent a nongenetic mode of risk transmission.

Collectively, these findings support the idea that perinatal deficits in brain DHA accrual may represent...
a potential neurodevelopmental insult that increases susceptibility to deficits in cortical DHA accrual, cortical maturation, prodromal neurocognitive deficits in attention and memory, and increased risk for schizophrenia. Definitive support for this hypothesis will require prospective follow-up with neuroimaging studies to determine whether treatment of schizophrenic mothers with DHA during and following pregnancy can prevent or mitigate gray matter and neurocognitive deficits during childhood/adolescence.

4.3.1. Preventative strategies

The evidence reviewed in the previous sections outline neurobiological evidence which supports the hypothesis that deficits in perinatal brain DHA accrual contribute to the pathogenesis of ADHD and schizophrenia. These deficits could be due to low exposure or intake as well as to an impaired ability to synthesize DHA. Regardless, the hypothesis predicts that risk for neurochemical, neuroanatomical, and neurocognitive features associated with DHA deficiency in ADHD and schizophrenia would be reduced if maternal DHA intake were initiated during gestation. Direct evaluation of this hypothesis will require randomized, double blind, placebo-controlled, prospective, longitudinal trials in which high-risk women (e.g., women with schizophrenia) would be randomly assigned to receive either DHA+EPA supplements or placebo beginning in the second trimester. The DHA+EPA dose would be based on doses previously found to be safe for the mother and fetus and to significantly reduce recurrence risk of preterm delivery (∼2–3 g/d of DHA + EPA from fish oil) [274,276,280]. Neuroimaging, neurocognitive, electroretinogram, and maternal and offspring RBC omega-3 fatty acid composition analyses could be conducted at intervals over the course of postnatal maturation.

Previous studies have demonstrated that women supplemented with DHA+EPA during pregnancy exhibit significantly greater DHA concentrations in RBC/plasma [281–284] and breast milk relative to controls [285,286]. Accordingly, fetal/infant RBC/plasma DHA concentrations are also increased at birth when women receive DHA+EPA supplementation during gestation [274,282,286,287]. Although there are currently no published data available regarding fetal/infant brain DHA accrual following maternal DHA+EPA supplementation during pregnancy, rat studies have demonstrated that maternal dietary fortification with fish oil significantly increases regional brain DHA concentrations (+15%) in offspring [57], and infant brain DHA concentrations are higher when human milk is consumed postnatally compared to formula without DHA [5–7,14,114,115]. Collectively, these studies, and the variability found in intrauterine brain DHA accumulation over the course of gestation [106], support the idea that higher maternal DHA intakes during pregnancy could result in higher fetal brain DHA accrual.

Maternal DHA+EPA supplementation during pregnancy may also offer additional advantages for schizophrenic mothers and their offspring. For example, maternal DHA+EPA supplementation has been found to be protective against obstetric complications more common in women with schizophrenia, including preterm delivery [272–277,280] and preeclampsia [207,288]. Moreover, because DHA+EPA supplementation has previously been demonstrated to significantly reduce positive and negative symptom severity in medicated male and female schizophrenic patients [202–206], DHA+EPA treatment during pregnancy may have prophylactic efficacy in pregnant schizophrenic patients when antipsychotic/mood stabilizer/antidepressant medications are discontinued to avoid potential teratogenesis [289]. Indeed, DHA (2 g/d)+EPA (4 g/d) monotherapy was previously found to reduce positive and negative symptom severity in a pregnant schizophrenic women following medication discontinuation [290].

5. Summary and conclusions

There is now good evidence suggesting that DHA is accrued in rodent, primate, and human brain during active periods of perinatal cortical maturation, and that DHA plays an important role in neuronal differentiation, synaptogenesis, and synaptic function. In animal studies, prenatal deficits in brain DHA accrual that are not corrected via postnatal dietary fortification are associated with enduring deficits in neuronal arborization, multiple indices of synaptic pathology, deficits in mesocorticolimbic dopamine neurotransmission, deficits in hippocampal serotonin and acetylcholine neurotransmission, neurocognitive deficits on hippocampus- and frontal cortex-dependent learning tasks, and elevated behavioral indices of anxiety, aggression, and depression. Human and primate infants born preterm or fed diets without DHA postnatally exhibit lower cortical DHA accrual compared to infants born at term or fed human milk postnatally. Children/adolescents born preterm exhibit deficits in cortical gray matter expansion, neurocognitive deficits, and are at increased risk for attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. Individuals diagnosed with ADHD or schizophrenia exhibit peripheral indices of lower DHA status and exhibit deficits in cortical gray matter expansion and deficits in cortical dopamine neurotransmission. Based on this body of evidence, it is hypothesized that perinatal deficits in brain DHA accrual represents a modifiable neurodevelopmental risk factor for the emergence of neurocognitive deficits and...
subsequent psychopathology. Evaluation of this hypothesis is currently feasible.

In view of the potential contribution of perinatal deficits in brain DHA accrual to the pathogenesis of ADHD and schizophrenia, increasing awareness of the importance of maternal DHA status during pregnancy, particularly in high-risk groups, represents an important future challenge for mental health researchers and practitioners. This is particularly relevant in the US where dietary consumption of DHA has declined [291–295], resulting in breast milk DHA concentrations that are among the lowest in the world [141]. Furthermore, the recent (2004) US advisory issued jointly by the Food and Drug Administration and Environmental Protection Agency recommends that pregnant women, women who might become pregnant, young children, and nursing mothers modify their fish intake due to the threat of mercury contamination. These recommendations may have inadvertently led to further reductions in maternal and fetal/infant DHA accrual during critical stages of brain development [296]. The IOM Committee on Nutrient Relationships in Seafood: Selections to Balance Benefits and Risks, has undertaken the task to provide guidance that may be used for consumers to safely choose seafood sources of DHA [297], and DHA+EPA supplements are widely available which do not pose a risk for mercury contamination (Consumer Reports, Vol. 68, p. 30).

Acknowledgements

This work was supported in part by NIH/NIMH grants MH073704 and MH074858 (R.K.M.).

References


B. Calabrese, S. Halpain, Essential role for the PKC target MARCKS in maintaining dendritic spine morphology, Neuron 48 (2005) 77–90.


R.K. McNamara, B. Levant, N.M. Richtand, Omega-3 fatty acid deficiency decreases dopamine D2 receptor binding and increases serotonin 5-HT2A receptor binding in the adult rat prefrontal cortex, Biol. Psychiatry 59 (2006) S146.


Please cite this article as: Robert K. McNamara, S.E. Carlson, Role of omega-3 fatty acids in brain development and function: Potential implications for the pathogenesis and... Prostaglandins, Leukotrienes and Essential Fatty Acids (2006), doi:10.1016/j.plefa.2006.07.010.
Please cite this article as: Robert K. McNamara, Susan E. Carlson, Role of omega-3 fatty acids in brain development and function: Potential implications for the pathogenesis and..., Prostaglandins, Leukotrienes and Essential Fatty Acids (2006), doi:10.1016/j.plefa.2006.07.010.


