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Deciphering the role of docosahexaenoic acid in brain maturation and pathology with magnetic resonance imaging

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ABSTRACT

Animal studies have found that deficits in brain docosahexaenoic acid (DHA, 22:6n-3) accrual during perinatal development leads to transient and enduring abnormalities in brain development and function. Determining the relevance of this evidence to brain disorders in humans has been hampered by an inability to determine antimortem brain DHA levels and limitations associated with a postmortem approach. Accordingly, there is a need for alternate or complementary approaches to better understand the role of DHA in cortical function and pathology, and conventional magnetic resonance imaging (MRI) techniques may be ideally suited for this application. A major advantage of neuroimaging is that it permits prospective evaluation of the effects of manipulating DHA status on both clinical and neuroimaging variables. Emerging evidence from MRI studies suggest that greater DHA status is associated with cortical structural and functional integrity, and suggest that reduced DHA status and abnormalities in cortical function observed in psychiatric disorders may be interrelated phenomenon. Preliminary evidence from animal MRI studies support a critical role of DHA in normal brain development. Neuroimaging research in both human and animals therefore holds tremendous promise for developing a better understanding of the role of DHA status in cortical function, as well as for elucidating the impact of DHA deficiency on neuropathological processes implicated in the etiology and progression of neurodevelopmental and psychiatric disorders.

1. Introduction

Mammalian brain tissue is predominantly composed of lipids (60–65% of brain dry weight) which are comprised of saturated, monounsaturated, and polyunsaturated fatty acids. The principle omega-3 polyunsaturated fatty acid in mammalian brain is docosahexaenoic acid (DHA, 22:6n-3), which comprises approximately 10–20% of gray matter, and approximately 2% of white matter, fatty acid composition depending on brain region, age, and habitual dietary omega-3 fatty acid intake [1–6]. Although omega-3 fatty acid precursors of DHA, including α-linolenic acid (ALA, 18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3), and docosapentaenoic acid (22:5n-3), cross the blood–brain barrier, they are rapidly β-oxidized [7,8] and consequently comprise $<1\%$ of total brain fatty acid composition [1–6]. Mammals require a dietary source of omega-3 fatty acids to procure and maintain adequate concentrations of DHA in peripheral and central tissues, and healthy adult humans exhibit limited ALA→EPA, and negligible ALA→DHA and EPA→DHA, biosynthesis [9]. However, preformed DHA can be obtained directly from the diet, particularly from fatty cold water fish or fish oil supplements [10], and preformed DHA is significantly more effective than ALA for increasing DHA levels in erythrocytes [11], breast milk [12,13], and brain gray matter [14].

Unesterified DHA rapidly diffuses from plasma to brain [15], and at a rate that is equilibrated with brain DHA consumption [16]. DHA preferentially accumulates in gray matter [16,17], and is enriched in synaptic and mitochondrial membranes [18]. DHA is acetylated into the *sn*-2 position of membrane phospholipids phosphatidylethanolamine and phosphatidylserine [19], and is mobilized preferentially by the calcium-independent phospholipase A2 ($iPLA_2$) isoform [20]. It has been estimated that approximately 2–8% of rat brain DHA is replaced daily due to metabolism, and has a loss half-life in total rat brain phospholipids of 33 day under steady state ALA intake [21,22]. Dietary ALA insufficiency resulting in deficits in rat brain DHA composition are associated with a reduction in $iPLA_2$ expression and activity [23], and an increase in the brain DHA half-life [21]. Preliminary estimates of the DHA half-life in human brain phospholipids are 2.5 years [17].

During perinatal rat brain development, cortical DHA concentrations increase sharply in parallel with active periods of neurogenesis, neuroblast migration, differentiation and synaptogenesis [1]. In human brain, DHA accumulates at a rapid rate initiating at approximately the third trimester in utero, and increases to approximately 9% of total cortical fatty acid composition in

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term-birth infants [24,25]. Infants born preterm exhibit lower postmortem cortical DHA concentrations relative to term infants maintained on the same ALA-fortified formula [25–28]. Non-human primates born preterm similarly exhibit lower postmortem brain DHA concentrations relative to term-born primates [29,30]. During human childhood and adolescence, there is a linear increase in postmortem frontal cortex DHA composition, which stabilizes at ~15% of total cortical fatty acid composition by ~20 years of age [4].

Preclinical studies have provided evidence that brain DHA accrual during perinatal maturation is required for normal neurotrophic factor expression, neurite outgrowth, neurogenesis and migration, neuronal differentiation and dendritic arborization, embryonic cortical plate expansion, nerve growth cone membrane signaling dynamics, and synaptogenesis and plasticity [31–42]. Moreover, early cortical DHA accrual during perinatal development is required for the normal functional maturation of multiple neurotransmitter systems, including dopamine, serotonin, and acetylcholine [43–45]. Behavioral studies have demonstrated that deficits in cortical DHA accrual during perinatal development are associated with enduring impairments in different cognitive tasks [46], and elevated indices of depression and aggression [47]. In addition to the demonstrated neurotrophic effects of DHA, emerging evidence suggests that DHA is protective against neuronal degenerative processes in response to a variety of excitotoxic insults [48–54], and increases resilience of axons and white matter in experimental injury and inflammation models [55–57].

While the importance of cortical DHA accrual in human brain development and function is poorly understood and controversial, a body of evidence suggests that higher maternal DHA status during and following pregnancy is associated with improved infant cognitive development, particularly in the realm of attention [58–65]. Moreover, a growing body of evidence suggests that deficits in attention during childhood frequently precede and predict the subsequent emergence of psychopathology in high-risk populations [66–70]. Importantly, the initial onset of psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, and major depressive disorder (MDD), most frequently occurs during childhood and adolescence [71–73]. It is relevant, therefore, that cross-sectional studies have repeatedly found that patients with ADHD [74–77], schizophrenia [78–80], bipolar disorder [81–83], and MDD [83–89] exhibit peripheral (plasma, erythrocyte) DHA deficits compared with healthy controls. Together, these data suggest that low DHA status may contribute to impaired development of brain circuits that mediate attention.

While the contribution of DHA deficiency to the progressive abnormalities in cortical structure and function observed in psychiatric patients is not known, investigations of the relationship between cortical DHA status and psychopathology have relied on case-control studies of postmortem brain tissue. Some postmortem brain studies have observed significant cortical DHA deficits in patients with psychiatric disorders [90–93] whereas others have not [94–97]. The discrepancy in these findings may be attributable in part to methodological challenges and limitations associated with this approach [98]. Nevertheless, evidence from primary and secondary intervention studies suggest that elevating DHA status through dietary supplementation is efficacious for preventing and/or treating psychopathology in adolescent [99–102] and adult [103–105] patients, and prospective longitudinal studies have found that lower baseline DHA status is a significant predictor of future suicidal attempts in medication-free MDD patients [106] and cytokine-induced MDD [107]. However, it is currently not known if central mechanisms mediate the psychopathogenic effects of low DHA status, and new approaches are required to more definitively elucidate such mechanisms.

2. Clinical MRI studies

Conventional magnetic resonance imaging (MRI) techniques may be well-suited to elucidate the role of DHA in human cortical function and pathology. Modern MRI techniques permit investigation of dynamic changes in cortical structure, chemistry, and functional activity, as well as associated changes in clinical symptoms and DHA status. Because cortical DHA status cannot be determined in living human subjects, peripheral indices (i.e., erythrocyte membrane DHA composition) may serve as a surrogate measure of DHA status. In human subjects, erythrocyte DHA levels provide a valid and reliable index of habitual DHA intake [108–111]. Additionally, non-human primate and human postmortem studies suggest that cortical and erythrocyte DHA levels are positively correlated under steady state dietary conditions [4,5], though erythrocyte DHA levels change more rapidly than brain cortex levels in response to changes in dietary omega-3 fatty acid intake.

Potential neuroimaging techniques available to evaluate the role of DHA status in psychopathology include: (1) structural MRI, which determines cortical and subcortical gray and white matter volumes, (2) diffusion tension imaging (DTI), which determines white matter structural integrity, (3) MRI T_2 relaxometery which determines membrane water content as an index of fluidity, (4) functional magnetic resonance imaging (fMRI), which determines resting and task-elicited changes in cortical activation patterns, (5) proton magnetic resonance spectroscopy (^{1}H MRS), which determines concentrations of different chemical markers associated with cortical metabolic integrity, and (6) phosphorous magnetic resonance spectroscopy (^{31}P MRS), which determines chemical indices of phospholipid membrane turnover. Additionally, positron emission tomography (PET) can determine changes in multiple metabolic processes including cortical fatty acid incorporation and turnover rates and glucose metabolism. While these different imaging techniques have been used extensively in clinical and animal research, only recently have they been employed to investigate the role of DHA status on cortical structural and functional integrity.

The present review will focus on MRI studies investigating the role of DHA in neurodevelopmental and psychiatric disorders, and readers are referred to a separate review in this issue that is focused on the role of DHA in age-related neurodegenerative processes [112]. In the following sections, evidence for abnormalities in cortical structural and functional integrity in psychiatric disorders associated with DHA deficiency is briefly reviewed, and evidence from MRI studies investigating relationships with peripheral indices of DHA status and/or the effects of long-chain omega-3 fatty acid supplementation on MRI outcomes are presented.

2.1. Structural magnetic resonance imaging

Longitudinal and cross-sectional structural MRI studies have begun to characterize gray and white matter maturational patterns in typically developing youth [113]. The childhood and adolescent period is associated with dynamic changes in both regressive (synaptic pruning) and progressive (i.e., myelination) cellular events. Longitudinal structural MRI studies have found that the period between childhood and early adolescence (7–12 years) is associated with a rapid expansion of cortical gray matter density, whereas the period between adolescence (13–18 years) and young adulthood ($\geq$18 years) is associated with a progressive loss of cortical gray matter density, which stabilizes in the third decade of life [114]. These age-related changes in cortical volume are sexually dimorphic, peaking later in males than females