DHA Deficiency and Prefrontal Cortex Neuropathology in Recurrent Affective Disorders

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Abstract

Increasing evidence suggests that docosahexaenoic acid [DHA, 22:6(n-3)], the principal (n-3) fatty acid in brain gray matter, has neurotrophic and neuroprotective properties. Preliminary clinical evidence also suggests that the perinatal accrual, and the subsequent dietary maintenance of, cortical DHA is positively associated with cortical gray matter volumes. The pathophysiology of recurrent affective disorders, including unipolar and bipolar depression, is associated with (n-3) fatty acid deficiency, DHA deficits, impaired astrocyte mediated vascular coupling, neuronal shrinkage, and reductions in gray matter volume in the prefrontal cortex (PFC). Preclinical studies have also observed neuronal shrinkage and indices of astrocyte pathology in the DHA-deficient rat brain. Together, this body of evidence supports the proposition that DHA deficiency increases vulnerability to neuronal atrophy in the PFC of patients with affective disorders. Because projections from the PFC modulate multiple limbic structures involved in affective regulation, this represents one plausible mechanism by which (n-3) fatty acid deficiency may increase vulnerability to recurrent affective disorders. J. Nutr. 140: 864–868, 2010.

Introduction

The WHO identified major depressive disorder (MDD) as the 4th ranked cause of disability and premature death globally and excess mortality in MDD is primarily attributable to suicide and cardiovascular-related properties. It has been projected that by 2020, MDD and ischemic heart disease will be the 2 most important causes of disability worldwide. In the US, lifetime prevalence rates are currently estimated at 16% for MDD and 1.1% for bipolar disorders. Subtotal heritability estimates and monozygotic twin discordance rates indicate that nongenetic factors confer equal if not greater vulnerability for recurrent affective disorders, including MDD and bipolar disorder. Accordingly, efforts need to be made to identify environmental risk factors that confer vulnerability, particularly in view of their amenability to prevention.

A growing body of evidence from cross-national and cross-sectional epidemiological surveys and prospective longitudinal studies suggest that greater habitual dietary (n-3) fatty acid intake is associated with reduced risk for both MDD and bipolar disorder. This is further supported by independent meta-analyses of placebo-controlled trials finding that increasing dietary intake of (n-3) fatty acids, including docosahexaenoic acid [DHA, 22:6(n-3)] and/or eicosapentaenoic acid [EPA, 20:5(n-3)], is associated with a significant advantage over placebo for reducing depression symptom severity in adult patients with affective disorders. Subsequent trials have also found that increasing dietary (n-3) fatty acid intake is associated with significant reductions in depression and manic symptom severity in pediatric and adolescent patients. Dietary (n-3) fatty acid intake is reflected in erythrocyte membrane (n-3) fatty acid composition, and case-control studies have repeatedly observed significant erythrocyte (n-3) fatty acid deficits in patients with MDD and bipolar disorder. Although these data suggest that (n-3) fatty acid deficiency represents a reversible environmental risk factor for affective disorders, it remains unclear how (n-3) fatty acid deficiency increases vulnerability to affective dysregulation.

DHA [22:6(n-3)] is the principal (n-3) fatty acid in cortical gray matter, accounting for ~15% of total fatty acid composition in the adult human prefrontal cortex (PFC) and/or eicosapentaenoic acid [22:5(n-3)], comprise <1% of total brain fatty acid composition. Recent
postmortem studies have found significant DHA deficits in PFC gray matter of patients with affective disorders (19,20). Because preclinical studies have found that brain DHA and/or its bioactive metabolites are neuroprotective (21), DHA deficits in PFC gray matter may increase vulnerability to the neuropathology also observed in the PFC of patients with affective disorders (22). In this paper, evidence linking DHA deficiency and neuropathology in the PFC is summarized and evaluated as a potential mechanism by which (n-3) fatty acid deficiency may contribute vulnerability to affective dysregulation.

**DHA: neurotrophic and neuroprotective properties**

During perinatal development of the human brain, cortical concentrations of DHA increase sharply in association with active periods of neurogenesis, neuroblast migration, differentiation, and synaptogenesis (17,23). Preclinical studies have demonstrated that DHA positively regulates cortical neurogenesis (24), neuroblast migration (25), neuronal differentiation/ arborization (26), neurotrophic factor expression (27), and nerve growth factor-induced neurite outgrowth and synaptogenesis (28). These developmental studies suggest that DHA has important neurotrophic properties required for normal perinatal cortical maturation. Indeed, dietary (n-3) fatty acid insufficiency during perinatal rat brain development is associated with enduring alterations in dopamine and serotonin neurotransmission (29), cognitive deficits, and elevated behavioral indices of anxiety, aggression, and depression (30) in young adulthood.

Dietary (n-3) fatty acid supplementation resulting in elevations in brain DHA content has been found to be neuroprotective against a variety of insults associated with the generation of reactive oxygen species and oxidative stress, including focal and global ischemia (31), glutamate excitotoxicity (32,33), and traumatic head injury (34). Furthermore, (n-3) fatty acid supplementation prevents or significantly attenuates age-related neuropathological features in a transgenic mouse model (APPswe) of Alzheimer’s disease, including amyloid-β deposition, caspase activity, presenilin expression, dendritic pathology, plaque burden, and neuronal apoptosis (35,36). Emerging data also suggest that increasing brain DHA content during perinatal rodent development increases neuronal resilience to oxidative stress and indices of lipid peroxidation (37,38), and perinatal (n-3) fatty acid insufficiency resulting in significant cortical DHA deficits is associated with region-specific reductions in neuron size (39). The mechanisms mediating the neuroprotective effects of DHA and its lipoxigenase metabolite, Neuroprotectin D1, may involve several complementary pathways, including reductions in proinflammatory signaling [prostaglandin E2 synthesis], upregulating antiapoptotic genes (Bcl-2, Bcl-xl, Bfl-1), and decreasing proapoptotic genes (Bax, Bad) (40). Importantly, elevated markers of excitotoxicity and inflammation are observed in the postmortem PFC of patients with bipolar disorder (41). Moreover, mood stabilizers including lithium also converge on these signaling pathways and, like DHA, have neurotrophic (42) and neuroprotective (43) properties. Mood stabilizer medications as a class also have antiinflammatory properties mediated in part by decreasing arachidonic acid [20:4(n-6)] generated proinflammatory signaling cascades (44).

Preliminary clinical data also suggest that (n-3) fatty acids promote neuronal resilience in humans. First, human and primate infants born preterm exhibit significant deficits in cortical DHA composition (45–48) and neuroimaging studies have found that children and adolescents born preterm exhibit significant reductions in regional cortical gray matter volumes (49,50). Second, a voxel-based morphometry study found that habitual dietary (n-3) fatty acid intake was positively correlated with anterior cingulate and amygdala gray matter volumes among 55 healthy adult participants residing in the US (51). Third, a preliminary double-blind, placebo-controlled neuroimaging (proton MRI) trial found that chronic (12 wk) EPA [20:5(n-3)] treatment significantly increased cortical concentrations of N-acetyl aspartate, a putative measure of neuronal integrity, in the anterior cingulate (single voxel) of adult bipolar patients (52). Fourth, the orbitofrontal cortex (OFC) subregion of the PFC exhibits significant reductions in gray matter volume with increasing age (53) and DHA composition exhibits a significant age-related decline in the postmortem OFC (18). These clinical findings suggest that the perinatal accrual of cortical DHA, and the subsequent maintenance of cortical DHA through the diet, is positively associated with PFC gray matter volume over the human lifespan.

**Neuropathology in affective disorders**

Evidence from neuroimaging and postmortem histology studies indicate that adult patients with affective disorders have significant neuropathology in the PFC. Among the different PFC subregions, the OFC (Brodman Areas 10,11,47) has emerged as a region that is particularly vulnerable to gray matter volume deficits in young adult and geriatric patients with affective disorders (54–60). Postmortem histological studies suggest that deficits in PFC gray matter volume in young adult and elderly patients with affective disorders are attributable in part to pyramidal neuron atrophy (i.e. reductions in neuronal size and density) (61–64). In addition to deficits in gray matter density, bipolar patients also have significant frontal white matter tract pathology (61). Importantly, glutamatergic pyramidal neurons within the human OFC have reciprocal connections with limbic structures, including the amygdala, hippocampus, hypothalamus, and striatum (65) (Fig. 1), and evidence from lesion and imaging studies suggest that the OFC modulates hedonic and emotional processes that characterize affective disorders, including euphoria, depression, irritability, impulsivity, recklessness, and socially inappropriate behavior (66). The pathophysiological relevance of OFC gray matter volume deficits in affective disorders is further supported by emerging evidence linking changes in OFC volume to functional connectivity abnormalities in mood disorders.

**FIGURE 1** Diagram illustrating the connections between the prefrontal cortex (Brodman Areas 10, 11, 47) and subcortical structures implicated in affective regulation. Potential consequences of abnormal functional connectivity between the prefrontal cortex and these regions are presented, including dysregulation in hypothalamic-pituitary-adrenal axis (cortisol) and mesolimbic dopamine activity. A dysregulation in these processes are major features associated with the pathophysiology of mood symptoms in recurrent affective disorders.

DHA deficiency and neuropathology in mood disorders
disorders is further supported by associations with depression symptom severity (67). For example, chronic (4 wk) treatment with lithium was associated with a significant increase in PFC gray matter volume only in bipolar patients exhibiting a significant decrease in depression severity (68).

Although the etiological factors contributing to PFC neuropathology in affective disorders are not known, the absence of reactive gliosis is consistent with a developmental etiology rather than neurodegenerative processes (68). Indeed, longitudinal and cross-sectional structural imaging studies have found that affective disorders are associated with excessive gray matter loss in the OFC initiating during adolescence, when the first onset of affective disorders typically occurs (70,71). Specifically, OFC gray matter deficits are commonly observed in young adult and elderly patients with affective disorders (54–60) but not in first-episode (72) or adolescent patients with affective disorders (73,74). A recent 2-y longitudinal study found that OFC gray matter volume reductions during adolescence were accelerated in bipolar patients compared with healthy subjects (75). In this study, the relative OFC gray matter volume loss in typical adolescents (0.33%/y) was increased 5-fold in bipolar patients (1.8%/y). It is relevant, therefore, that the normal age-related increase in PFC DHA composition occurring between adolescence and young adulthood in healthy subjects (17) was not observed in the OFC of suicide victims with or without a history of affective disorders (76,77). Together, these data suggest that deficits in OFC DHA accrual during adolescence may contribute to accelerated and excessive gray matter loss in affective disorders.

Glial pathology in affective disorders

In addition to neuronal atrophy, several studies have observed reductions in glial size and density in the postmortem PFC of patients with MDD or bipolar disorder (69). Subsequent studies have found reductions in the expression of astrocyte-specific marker glial fibrillary acidic protein in the PFC of young, but not older, patients with MDD (78,79). Additionally, an immunohistochemical study found a significant paucity of astrocytes adjacent to blood vessels in the PFC of MDD patients (80). These findings are important, because astrocytes play a critical role in the vascular uptake and metabolism of glucose (81,82). Furthermore, the expression of the astrocyte-specific glucose transporter (45-kDa GLUT1) (83) and glucose uptake (84) are significantly reduced in the PFC of DHA-deficient rats. Moreover, we found a significant reduction in myo-inositol, a metabolite of glucose concentrated in astrocytes, in the PFC of DHA-deficient rats by magnetic resonance imaging (85), and significantly lower myo-inositol concentrations are also observed in the PFC of patients with unipolar or bipolar depression (86,87). In contrast, increasing dietary (n-3) fatty acid intake was found to significantly improve age-related deficits in cerebrovascular coupling in nonhuman primates (88) and we found that 8-wk DHA supplementation significantly increased PFC activation during sustained attention in healthy pediatric human participants (89). Lastly, plasma DHA levels were found to be associated with regional brain glucose metabolism in patients with MDD (90). Together, these data suggest that DHA deficiency impairs astrocyte-mediated neuron-vascular coupling, which may in turn contribute to neuronal atrophy in the PFC of patients with affective disorders.

Summary and conclusions

There is now considerable evidence that DHA and/or its bioactive metabolites have neurotrophic and neuroprotective properties and that DHA increases neuronal resilience to oxidative stress during perinatal development and in adulthood. Preclinical findings also indicate that dietary-induced DHA deficits in rat brain are sufficient to produce neuropathological features, including neuronal shrinkage and astrocyte pathology, also observed in the PFC of patients with affective disorders. Clinical evidence also suggests that cortical DHA accrual is positively associated with gray matter volumes and that affective disorders are associated with deficits in PFC DHA composition, gray matter volume, and neuronal pathology. This body of evidence supports the proposal that cortical DHA deficits in patients with affective disorders reduce neuronal resilience in the PFC to oxidative stress. Because projections from the PFC modulate multiple limbic structures involved in affective regulation, including the amygdala, this represents one plausible mechanism by which (n-3) fatty acid deficiency may increase vulnerability to affective disorders. However, direct support for this pathoetiologic mechanism will require evidence that (n-3) fatty acid supplementation during the prodromal phase of illness prevents the emergence of PFC gray matter volume deficits and affective dysregulation in asymptomatic adolescents with a familial risk for developing affective disorders.

Acknowledgment

R.K.M. wrote the paper and had primary responsibility for the final content.

Literature Cited


868 Symposium


