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MENTAL HEALTH BENEFITS OF OMEGA-3 FATTY ACIDS
MAY BE MEDIATED BY IMPROVEMENTS IN
CEREBRAL VASCULAR FUNCTION

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SUMMARY

Since the pivotal role of long chain omega-3 (n-3) polyunsaturated fatty acids (PUFA) in brain structure and development became apparent in the 1970s, they have been investigated in relation to a range of psychiatric disorders, with some positive and some conflicting evidence to support their use as a supplementary treatment for various symptoms. A number of mechanisms of action have been proposed to account for their potential benefits, largely based on their structural role in brain development and purported influences on central neurotransmission.

Theories on the pathogenesis of mental health and psychiatric illness have traditionally focused on the role of neurotransmitters, although there is also ample evidence that psychiatric disorders are associated with impaired cerebral blood flow (CBF) or impairments in blood-brain barrier (BBB) function. Associations between cardiovascular and psychiatric pathologies are further indicative of a possible underlying vascular component to psychiatric illness. We hypothesise that treatment with vasoactive nutrients that can improve cerebral perfusion may help to improve a variety of mental disorders.

In presenting our hypothesis, we provide an overview of cerebral vascular function, focusing specifically on the role of the endothelium in CBF and BBB integrity, and review evidence for associations between impaired CBF/endothelial function and psychiatric illness. Then, as an example of a potential treatment, we review the influence of n-3 PUFA on endothelial function, drawing on evidence of anti-inflammatory, anti-aggregatory and vasodilatory roles in blood flow and vascular permeability. We hypothesise that n-3 PUFA may act on the blood side of the BBB as well as on central neural pathways to influence cerebral functions. In the former case, they may act on endothelial cells to influence both vasodilation and selective permeability, thereby assisting in CBF and delivery of oxygen and glucose to brain tissue in response to requirements.
INTRODUCTION

Interest in the role of long chain (LC) omega-3 (n-3) polyunsaturated fatty acids (PUFA) in mental health has steadily increased since their pivotal role in brain structure and function became apparent in the 1970s [1, 2]. LC n-3 PUFA have now been investigated in epidemiological, prospective cohort, cross-sectional and clinical trials in bipolar disorder, schizophrenia, depression, dementia and Alzheimer’s Disease (AD) and developmental disorders including attention deficit hyperactivity disorder (ADHD), dyslexia, dyspraxia, and the autistic spectrum disorders [3-5], with some conflicting and some positive indications for their use as a supplementary treatment for symptoms. More clinical work is required to investigate and clarify effects of n-3 PUFA supplementation on symptoms of psychiatric illness across the lifespan and also on biological mechanisms for their effects on brain function and mental health.

A number of theories for biological mechanisms have been proposed and reviewed elsewhere [3, 4, 6-10]. Over half of the brain’s dry weight is composed of lipids. PUFA constitute significant structural components of cellular membrane phospholipids, and the largest concentration of the LC n-3 PUFA docosahexaenoic acid (DHA) in the body is found in the nervous system, particularly brain and retina [11]. As a precursor of DHA, eicosapentaenoic acid (EPA) is also thought to have important functions in the brain, possibly due to its role in synthesis of eicosanoids which have anti-inflammatory, anti-thrombotic and vasodilatory properties. DHA and EPA have been related to many functions important for neural activity including myelination, membrane fluidity, neurotransmission, ion channel and enzyme regulation and gene expression.

Although there has been a long-standing focus on the role of neurotransmitters in the pathogenesis of mental health and psychiatric illness, e.g. dopamine deficiency in Parkinson’s disease, there is also ample evidence that psychiatric disorders are associated with impaired cerebral blood flow (CBF). Associations between cardiovascular and psychiatric pathologies are further
indicative of a possible underlying vascular component to psychiatric illness. We will give an overview of cerebral perfusion addressing 1) the role of the endothelium in CBF and in blood brain barrier (BBB) integrity, 2) evidence for associations between CBF/endothelial integrity and psychiatric illness and 3) the potential influence of n-3 PUFA on endothelial function in cerebral vessels. We hypothesise that LC n-3 PUFA may influence cerebral functions by acting on the blood side of the BBB as well as on central neural pathways. In the former case, they may act on endothelial cells to influence both vasodilation and selective permeability, thereby assisting in CBF and substrate delivery to brain tissue in response to requirements.

**CEREBROVASCULAR FUNCTION**

The brain is critically dependent on a stable supply of glucose and oxygen for the maintenance of cellular integrity and for information processing [12, 13]. Glucose is the principal energy source for the brain, which requires as much glucose as a skeletal muscle during vigorous exercise. However, the brain’s energy storage capacity is very limited and it therefore depends on a continuous supply of glucose from the blood [14]. In addition to high requirements for glucose and oxygen, metabolic activities and chemical transmission in the brain rely on a range of nutrients [15] which also need to be delivered via the blood and absorbed through the BBB. Hence cerebral blood flow and substrate transport across the BBB are primary determinants of brain function [16].

Although the brain is more dependent on the circulation than any other part of the body, it has no autonomic regulation of blood flow and is therefore entirely reliant on autoregulation of local blood flow. CBF increases in response to local activity in specific brain regions (referred to as functional hyperaemia) enabling the delivery of substrates to neurons and removal of metabolic byproducts. Emerging evidence suggests that the distribution of CBF in response to regional increases of neural activity is coordinated by neurons, glia and cerebral blood vessels working together to induce the release of vasoactive agents [12]. Autoregulation of CBF can be accomplished by a number of myogenic, metabolic and neural mechanisms and activation of potassium channels,
as well as flow-mediated dilatation (FMD) [17]. FMD occurs when blood flow increases in the vessel and causes an increase in shear stress on the endothelial lining of the blood vessels. This in turn prompts the endothelium to release vasodilatory substances. It has been proposed that this method of vasodilation is particularly important in large cerebral arteries which play a major role in regulating vascular resistance in the brain [18].

The endothelium is comprised of a layer of metabolically active cells lining all blood vessels; its main roles include maintenance of blood circulation and fluidity, vascular tone and blood vessel integrity. It releases vasoactive compounds in response to metabolic conditions (e.g. hypoxia, hypercapnia) and chemical agonists (e.g. acetylcholine) as well as shear stress. It also releases factors which inhibit platelet aggregation, cell adhesion, macrophage infiltration and smooth muscle cell proliferation. Hence impairment of endothelial function may ultimately result in vascular remodeling including increased arterial stiffness, decreased permeability, resistance to flow, and capillary rarefaction that can chronically impede blood flow and tissue perfusion. Risk factors for endothelial impairment include smoking, hypercholesterolemia, hyperhomocysteinemia, hypertension and diabetes mellitus [19] as well as obesity.

Endothelium-derived vasoactive factors have received in-depth review by Faraci and Heistad [17]. Major vasoconstrictor compounds released by the endothelium include prostaglandin H2, thromboxane A2 and endothelin 1; vasodilators include endothelium-derived hyperpolarising factor, prostacyclin and endothelium-derived relaxing factor. The latter has been identified as nitric oxide (NO), which is synthesised from L-arginine by endothelial NO-synthase. NO is regarded as the most important vasodilator released by the endothelium and reductions in NO have been associated with impaired endothelial function and impairments in CBF autoregulation [20]. However, hydrogen peroxide may also have a contributory role in cerebral vasodilation [21]. As well as producing vasoactive substances, the endothelium is responsible for the regulation of amyloid β (Aβ) peptide levels, which if accumulated in the brain can produce vasoconstrictor effects. Aβ is a risk factor for
AD and is associated with vasoconstriction, inflammation and potential alteration of BBB integrity [16].

The BBB is comprised of tightly interconnected cerebral endothelial cells lining the inner blood vessel walls and are in fact its most important structural components. The brain is highly sensitive to and reliant on substances transported across the BBB. The permeability and chemical properties of the endothelium are critical to the maintenance of homeostasis and the selective transportation of glucose, oxygen and nutrients from the blood to neural tissue as well as the protection of brain tissue from potentially toxic substances such as heavy metals which, without the protection of the BBB, may accumulate in the brain [20]. It is thought that NO, released by the endothelium, also plays a key role in regulating transport of substances across the BBB, as well as linking extracellular signaling, via ion exchange (i.e., receptor activation), to BBB function [22].

Therefore the cerebral endothelium plays a fundamental role, both structurally and functionally, in CBF autoregulation, delivering glucose, oxygen and nutrients to brain regions as required, maintaining homeostasis, and selectively transporting nutrients and eliminating potentially damaging molecules, activities that are all critical for healthy neural function.

**CBF AND CEREBRAL PATHOPHYSIOLOGY**

The neurotransmitter theory of psychiatric illness does not account for the large number of people who do not respond to pharmaceutical drugs that act on neurotransmitter mechanisms [e.g. 23-25]. Supporting evidence for a primary role of CBF in mental health is suggested by the pathophysiology of neurological disorders. Impaired cerebral blood flow has been implicated in mild cognitive impairment [26], dementias including AD [27-29], ADHD [30], depression [31], and schizophrenia [32, 33]. BBB dysfunction has also been associated with several central nervous system (CNS) pathologies and in many of these cases cooperation between astrocytes and endothelium is implicated. They have been reviewed by Abbott [20], and include stroke, multiple sclerosis, HIV, Alzheimer’s disease, Parkinson’s disease, and epilepsy.
Additionally, lower levels of NO have been found in patients with AD, leading to suggestions that resulting impairment in CBF may contribute to its development [34]. Reduced glucose uptake has also been found in patients with AD and it has been proposed that this may play a role in some forms of cognitive decline [35]. This may be attributable to reduced blood flow in addition to reduced glucose transportation across the BBB, which will be discussed later.

There are also a number of associations between cardiovascular risk factors and psychopathology, indicative of a possible common vascular component impacting on both cardiovascular and cerebral blood vessels. Hypertension has been identified as a risk factor for stroke and dementia, as well as cognitive decline. Recently in healthy aging people, markers of arterial stiffness were prospectively associated with cognitive decline [36]. A study with geriatric patients with low cardiac output found that they performed more poorly than controls on cognitive tests of executive function, indicating a link between hypoperfusion and brain function which may be mediated by slowed cerebral perfusion [37]. This link was more directly assessed in another study with hypotensive individuals, which found that attentional response directly improved with pharmacologically-induced increase in blood-flow, measured via transcranial Doppler sonography [38]. Importantly, a direct effect on central nervous system activity was ruled out as the pharmacological agent was chosen due to its inability to cross the blood-brain barrier. This provided evidence that the link between chronic hypotension and cognitive symptoms may be mediated by poor CBF. Depression is also highly prevalent in people with cardiovascular morbidity, and has in fact been identified as the strongest psychological predictor of having a myocardial infarct [39]. n-3 PUFA have been proposed as a possible mediator for this relationship. In support it was recently reported that serum levels of n-3 PUFA in patients recovering from an acute coronary syndrome were lower in those suffering major depression than those without depression [40].

**OMEGA-3 AND ENDOTHELIAL FUNCTION**
Lipids play a pivotal role in the integrity of the vascular and nervous system [1]. In the brain, 60% of nervous tissue is composed of lipids with relatively high concentrations of n-3 PUFA. Hence proposed mechanistic actions of n-3 PUFA in the brain have predominantly focused on their role in neural transmission. However, studies with fish oil, containing LC PUFA EPA and DHA, in animals and humans have also demonstrated a number of protective actions of n-3 PUFA on vascular structure and function including favourable effects on elevated blood pressure, exacerbated contractility, impaired endothelial relaxation and thromboxane induced vasoconstriction following NO inhibition [41]. As we have described, the endothelium also plays primary roles in neural function at the blood side of the BBB and produces vasodilator and vasoconstrictor compounds which are critical for achieving optimal perfusion of brain regions. There is evidence that n-3 PUFA can improve endothelial-dependent vasodilation [19, 42] and this has been proposed as a mechanism for their preventative role in cardiovascular disease. Endothelial function is typically assessed by the FMD technique which employs two-dimensional B-mode ultrasound to measure blood flow mediated changes in brachial artery diameter following 5 minutes of blood flow occlusion in the forearm (reactive hyperaemia). Assessment of FMD gives an indication of the health and function of the endothelial cells in the peripheral vasculature. Recent research conducted by our Centre has shown that n-3 PUFA supplementation can enhance FMD in the brachial artery [43], supporting results of previous studies [44, 45]. This may have implications for the role of the endothelium in CBF autoregulation. A link between bodily and cerebral endothelial function is supported by findings that low blood pressure was associated to lower blood flow velocity in the brain [38].

n-3 PUFA may influence vasodilation and blood flow primarily via effects on eicosanoids and NO synthesis. Eicosanoids are derivatives of the 20-carbon PUFAs AA, dihomogamma linolenic acid (DGLA) and EPA, released as required from phospholipid membranes. They are signaling hormones with complex roles in a number of body systems including the immune system, inflammation and central nervous system signaling, acting locally then rapidly inactivated.
Specifically, n-3s reduce the synthesis of series-2 prostanoids and series-4 leukotrienes from n-6 PUFA arachidonic acid (AA) with inflammatory, vasoconstrictor and aggregatory properties. Furthermore, n-3s increase synthesis of the anti-inflammatory, vasodilatory series-3 prostanoids (including prostacyclin PGI3) and series-5 leukotrienes synthesised from EPA. Most notably, it has been demonstrated that 1) although dietary intake of fish oil with EPA and DHA increases levels of PGI3, it does not decrease AA-derived vasodilatory prostacyclin PGI2, and 2) fish oil ingestion reduces production of thromboxane derived from AA (TxA2), a powerful platelet aggregator and vasoconstrictor [46]. Additionally, EPA appears to displace AA in tissues, decreasing its availability for synthesis of inflammatory and vasoconstrictor eicosanoids [47]. There is also evidence that both EPA and DHA contribute to increased NO production [19, 44, 48] and DHA may be particularly effective in reducing expression of substances that increase adhesion to the endothelium [19, 42].

Structural and functional roles of n-3 PUFA in membrane phospholipids are likely to be particularly critical for the highly selective permeability of endothelial cells forming the BBB. For instance, anti-inflammatory properties of EPA-derived eicosanoids may protect the endothelium from inflammation, which can open the BBB’s tight junctions [20]. It has also been demonstrated that n-3 PUFA may directly modulate glucose transportation across the BBB by favourably altering phospholipid composition of neural membranes in n-3 deficient rats. Following n-3 supplementation, EPA and DHA substantially increased basal glucose transport by GLUT1, while AA had no effect [49, 50]. Therefore n-3 PUFA may be inextricably involved in mediating endothelial transportation of glucose to supply neurons with the fuel required for metabolic processes and neural signaling.

This hypothesis provides a sound biological rationale as well as a plausible explanation for differential benefits of n-3 PUFA for mental health throughout the life-span and in different neurological conditions; i.e. by modulating the function of cerebral endothelial cells n-3 PUFA may facilitate cerebral perfusion and delivery of oxygen, glucose and nutrients more effectively to regions
where and when they are most needed for optimal neural performance, particularly neurotransmission.

**TESTING THE HYPOTHESIS**

The significance of an adequate intake of LC n-3 PUFA, particularly DHA, for brain development and function is well recognised. However, relatively little attention has been given to the possibility that the influence of n-3 PUFA supplementation in brain function may be mediated primarily via direct influences on CBF and BBB. In rats, dietary n-3 PUFA supplementation has been shown to improve cerebral perfusion [51] and BBB function [52] in rats with experimentally-induced chronic cerebral hypoperfusion. Improvements were also found in spatial memory performance on the Morris water maze in the n-3 supplemented groups, which had performed poorly when hypoperfusion was induced. This hypothesis can be examined in humans by adding pre- and post-measures of CBF to clinical randomised controlled trials investigating effects of n-3 PUFA on symptoms of psychiatric illness and neurological disorders, then correlating any changes in CBF with changes in symptoms after n-3 supplementation and, if blood samples are taken, with changes in erythrocyte levels of n-3 PUFA.

CBF can be assessed using MRI if resources are available. Simpler assessments can be undertaken using transcranial Doppler (tcD) ultrasound to measure blood flow velocity in the middle cerebral artery. The latter is particularly sensitive to chemoregulation; thus tcD can be used to assess the endothelium-dependent vasodilator responsiveness of the cerebral blood vessels to acute inhalation of 5% CO₂. This response to hypercapnia is analogous to the FMD response to sheer stress, except it is reflecting the activation of vasodilator mechanisms in cerebral vessels which may differ in their nature from those of peripheral arteries. Importantly, research has shown that the CBF responsiveness to CO₂, which is impaired in individuals with endothelial dysfunction [53], may be enhanced by nutrient supplementation [54].
L-arginine, asymmetric dimethylarginine (ADMA) and NO metabolites such as nitrosoglutathione could also be measured in blood to examine changes in endothelial function and blood flow resulting from n-3 PUFA supplementation. Guanidine substituted analogs of L-arginine such as ADMA, which is elevated in patients with endothelial dysfunction, selectively inhibit NO-mediated endothelial vasodilation [55]. The ratio of plasma L-arginine:ADMA has been proposed as a determinant of endothelium-dependent dilation; improvements of endothelial function assessed by FMD correlate directly with decreased ADMA [55]. Furthermore, initial rodent studies have shown that ADMA is reduced with increased n-3 consumption [56]. Elevated ADMA has also been correlated with lower levels of NO and impaired cognitive function among adults with AD [34].

In summary, impaired cerebral perfusion is associated with poorer cognitive function as well as various neurological disorders. It is plausible, given the role of n-3 PUFA in improved cardiovascular health and endothelial function, that the primary role of these lipids in mental health may be directly via their actions to improve endothelial function in the brain, resulting in optimised autoregulation of cerebral perfusion and BBB integrity, and thereby delivering oxygen and nutrients to brain regions as required for healthy brain function. It is recommended that this possibility be explored by including indices of CBF in future intervention studies investigating effects of n-3 PUFA on mental health and cognitive function.
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