

Review Article

Omega 3 fatty acids and the brain: review of studies in depression

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The brain is a lipid-rich organ containing mostly complex polar phospholipids, sphingolipids, gangliosides and cholesterol. These lipids are involved in the structure and function of cell membranes in the brain. The glycerophospholipids in the brain contain a high proportion of polyunsaturated fatty acids (PUFA) derived from the essential fatty acids, linoleic acid and alpha-linolenic acid. The main PUFA in the brain are docosahexaenoic acid (DHA, all *cis* 4,7,10,13,16,19-22:6) derived from the omega 3 fatty acid, alpha-linolenic acid, and arachidonic acid (AA, all *cis* 5,8,11,14-20:4) and docosatetraenoic acid (all *cis* 7,10,13,16-22:4), both derived from the omega 6 fatty acid, linoleic acid. Experimental studies in animals have shown that diets lacking omega 3 PUFA lead to substantial disturbances in neural function, which in most circumstances can be restored by the inclusion of omega 3 PUFA in the diet. In the past 10 years there has been an emerging interest in treating neuropsychological disorders (depression and schizophrenia) with omega 3 PUFA. This paper discusses the clinical studies conducted in the area of depression and omega 3 PUFA and the possible mechanisms of action of these PUFA. It is clear from the literature that DHA is involved in a variety of processes in neural cells and that its role is far more complex than simply influencing cell membrane properties.

Key Words: docosahexaenoic acid, ethyl eicosapentaenoate, membrane function, depression, dopamine, BDNF, turnover of arachidonic acid

Introduction

Omega 3 fatty acids in the brain

The brain contains the second highest concentration of lipids in the body, after adipose tissue, with 36-60% of nervous tissue being lipids. The lipids in brain are complex lipids and include glycerophospholipids, sphingolipids (sphingomyelin and cerebrosides), gangliosides and cholesterol, with little or no triglycerides and cholesterol esters. Brain glycerophospholipids contain a high proportion of PUFA, derived from the two main essential fatty acids, mainly docosahexaenoic acid (DHA, 22:6 omega 3), arachidonic acid (AA, 20:4 omega 6) and docosatetraenoic acid (22:4 omega 6). The proportion of DHA in the glycerophospholipids of brain grey matter is higher than the white matter¹ and phosphatidylethanolamine and phosphatidylserine contain the most DHA amongst all the glycerophospholipids. The DHA content of the adult cerebral cortex is approximately 3% of the dry weight and 0.4% of the white matter.¹ The omega 6 fatty acid content (20:4 omega 6 plus 22:4 omega 6) of the cerebral cortex is similar to that of the DHA content. In white matter there is a higher proportion of omega 6 than omega 3 PUFA.¹

What is the role of DHA in the brain?

The classical way of studying the role of DHA in the brain has been to examine what happens in animals fed diets lacking omega 3 PUFA. These studies reveal that such

diets lead to significant reductions in the level of DHA in brain lipids. When there is a reduced level of DHA in the brain, many dramatic changes in brain function have been reported including changes in size of neurons, changes in learning & memory, changes in the auditory and olfactory responses to stimuli, and changes in nerve growth factor levels. A recent report described an increase in depression and aggression scores in rats deprived of dietary omega 3 fatty acids for 15 weeks after weaning.²

Various mechanisms have been suggested to account for these physiological changes in the brain. Mostly, the changes appear to be related to changes in membrane function, however recent studies have shown that DHA can also influence gene expression in the brain. In summary, in the brain DHA plays a crucial role in:

Membrane related events

[a] membrane order (membrane fluidity) which can influence the function of membrane receptors such as rhodopsin through effects on the membrane environment and on binding to the membrane protein,^{3,4} [b] regulation of dopa-

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minergic and serotonergic neurotransmission,⁵ [c] regulation of membrane-bound enzymes (Na/K-dependent ATPase),⁶ [d] signal transduction via effects on inositol phosphates, DAG and protein kinase C,⁷ and [e] regulation of glucose uptake,⁸ perhaps via effects on brain glucose transporters.⁹

Metabolic events

[a] regulation of the synthesis of eicosanoids derived from AA,¹⁰ [b] DHA can serve as a precursor of docosatrienes¹¹ and 17S resolvins, novel anti-inflammatory mediators.¹² The docosatrienes (17S-hydroxy-containing docosanoids) and 17S series resolvins are biosynthesised via enzymatic oxygenation and are potent regulators of both leukocytes (reducing infiltration *in vivo*) and glial cells (blocking their cytokine production).¹² It is not known whether these bioactive mediators derived from DHA are responsible for some of the beneficial actions reported following dietary supplementation with DHA. Bazan¹¹ has also described a 10,17S-docosatriene called neuroprotectin D1 (NPD1) which he proposes protects the brain and retina from oxidative stress-induced apoptosis. NPD1 is formed through enzyme-mediated steps involving phospholipase A₂ followed by a 15-lipoxygenase-like activity.¹¹

DHA can also undergo non-enzymatic free-radical catalysed oxidation in the brain to form F₂-isoprostane-like compounds that are known as F₄-neuroprostanes and highly reactive A/J-ring neuroprostanes which may provide a marker of oxidative injury in the brain. These results suggest that oxidative stress is ongoing in the central nervous system. Preliminary studies show significantly increased levels of neuroprostanes in brain regions in Alzheimer's patients.¹³

Gene expression

Regulation of gene expression of many different genes in rat brain (for review see, Kitajka et al¹⁴) and other tissues (for review, see Decklebaum et al¹⁵). Rats fed throughout life with either a vegetable oil (rich in ALA) or a fish oil-rich diet (containing eicosapentaenoic acid (EPA) plus DHA) showed highly significant alterations in the expression of more than 100 genes in the brain (approx equal number over- and under-expressed). Of interest was the fact that the ATP-generating machinery of the brain responded to the dietary omega 3 PUFA most intensively. The brain is known to exhibit a high metabolic rate and a high proportion of this is used to maintain Na/K ATP-ase activity, which regulates ion flow resulting from nerve transmission. Genes involved in signal transduction were also over-expressed, almost to same extent, by both the ALA-rich and EPA plus DHA-rich diet. Also of interest is that genes encoding for alpha- and gamma-synuclein were over-expressed in young rats fed fish oil for one month.¹⁶ Synucleins are associated with synaptosomes and play a role in neural plasticity and learning. Alpha-synuclein has also been implicated in the pathophysiology of Parkinson's disease possibly via effects on dopaminergic neurotransmission.¹⁷

Cellular events

[a] regulation of phosphatidyl serine levels which is involved in the protection of neural cells from apoptotic death, via effects on phosphatidylinositol 3-kinase/Akt signaling,¹⁸ [b] stimulation of neurite growth in hippocampal cells,¹⁹ [c] selective accumulation of DHA by synaptic growth cones during neuronal development,²⁰ [d] regulation of neuron size,²¹ [e] regulation of nerve growth factor,²² and [f] stimulation of cell membrane expansion by action on syntaxin 3.²³ AA also demonstrated this effect. Taken together, these data provide strong support for the role of DHA in the growth of neuronal cells and the protection of cells from apoptosis.

What is the role of omega 3 fatty acids in neuropsychiatric disorders?

Manic-depressive illness (bipolar disorder), depression and schizophrenia are common neuropsychiatric disorders. The incidence of depression has increased markedly in the past decades in western countries.²⁴ Epidemiological evidence suggests that the condition has both genetic and environmental components. In 1995, it was hypothesized that a low omega 3 PUFA status could predispose subjects to an increased risk of suicide and depression.²⁵ Shortly after this, several studies reported that low omega 3 PUFA levels in serum phospholipids, cholesteryl esters and erythrocyte membranes were positively associated with depression.^{26,27}

The exact mechanisms involved in the pathogenesis of depression are not known, however there are many effective treatments such as various antidepressant medications or electroconvulsive treatment.²⁸ The main drugs of choice were discovered by chance in the middle of last century and are known as tricyclic agents or monoamine oxidase inhibitors. These inhibit re-uptake transporters of serotonin and norepinephrine or inhibit the oxidation of monoamine neurotransmitters (stopping the catabolism). The treatments are not effective in all cases, with estimates that only about half of all patients demonstrate a complete remission although about 80% show some benefit.²⁸

There are a number of parallels between the neural systems affected in depression and those affected in dietary deficiency of omega 3 PUFA (Table 1). This paper discusses these and the results of research trials of omega 3 PUFA in treating depression.

[1] Altered neurotransmission in major depression In omega 3 PUFA deficient rats, the expression of the dopamine receptor (D2R) is decreased in the frontal cortex and increased in the nucleus accumbens.²⁹ In these studies, the release of dopamine was significantly reduced however the picture is complex revealing a more active mesolimbic dopamine pathway compared with a less active mesocortical pathway in the omega 3 PUFA deficient rats. In contrast to this, supplementing the diet of rats with omega 3 PUFA (EPA and DHA) led to a 40% increase in dopamine levels in the frontal cortex as well as an increase in the binding to the dopamine D2 receptor.³⁰

Table 1. Comparison of effects of depression and omega 3 PUFA on various neural parameters

Item	Depression	Deficiency of omega 3 PUFA	Addition of omega 3 PUFA
Neurotransmission	Treatment maintains levels of neurotransmitters	Decreased levels of dopamine and D2 receptor	Increased levels of dopamine and increased binding to D2 receptor
Glucose metabolism in brain	Reduced metabolism. Increased by treatment with lithium.	Reduced uptake of glucose via glucose transporter	
AA metabolism in brain	Treatment reduces AA turnover & metabolism	Increases AA turnover & metabolism	
Pro-inflammatory cytokine levels	Increased		Reduced
Neuronal atrophy	Increased		DHA promotes neural cell growth and reduces apoptosis
BDNF levels in brain	Decreased (restored by antidepressant treatment)	Decreased by deficiency, diets high in saturated fat & sucrose and COX inhibitor	Increased by omega 3 PUFA, exercise, vitamin E, and prostaglandins

[2] In major depression there are reports of decreased cerebral blood flow³¹ and reduced glucose metabolism.³² As noted above, omega 3 PUFA deficiency decreases glucose uptake of brain cells and cytochrome oxidase activity by at least 30%; both are measures of functional neuronal activity.^{7,8}

[3] Depression is associated with excessive production of pro-inflammatory cytokines, including interleukin (IL)-1beta, IL-12, IL-6, interferon-gamma and tumour necrosis factor-alpha.^{33,34} Some anti-depressant medications can inhibit the release of these cytokines.³⁵

Omega 3 PUFA are well known to inhibit the production of pro-inflammatory cytokines, via effects in reducing the production of pro-inflammatory prostaglandins (PGE₂) and leukotrienes (LTB₄).³⁶

[4] Major depression is associated with neuronal atrophy (decrease in density and size of neurones) in the hippocampus & prefrontal cortex.^{37,38}

As noted above, the literature provides strong support for the role of DHA in the growth of neuronal cells and the protection of cells from apoptosis.¹⁸

[5] There is evidence of a link between brain-derived neurotrophic factor (BDNF) and depression. BDNF is a widely distributed trophic factor in the brain, and it is involved in neuronal growth, maintenance and neural plasticity.³⁹ Chronic administration of antidepressants is associated with an increased (normalized) serum level of BDNF.⁴⁰ BDNF expression can be altered by both exercise and components of the diet. Its expression is inhibited by a diet high in saturated fat and sucrose,⁴¹ however high levels of vitamin E or exercise can restore the level of BDNF.^{42,43} It has been shown recently that omega 3 PUFA can normalize BDNF levels and counteract the learning disability after traumatic brain injury in rats.⁴³ Rao et al⁴⁴ have reported that omega 3 PUFA deficiency in rats leads to a reduced expression of BDNF in the frontal cortex, and that addition of DHA to cultured rat cortical astrocytes induced BDNF protein expression. Another report in murine astrocyte cultures showed that prostaglandins D₂ and E₂, derived from membrane AA, are

powerful inducers of nerve growth factors and BDNF.⁴⁵ Consistent with this, Shaw et al⁴⁶ reported that the broad spectrum cyclooxygenase inhibitor, ibuprofen, reduced exercise-induced increases in BDNF and PGE₂ levels, and blocked long-term potentiation and spatial learning in rats.

Trials of omega 3 PUFA in mood disorders

The observations linking the omega 3 PUFA to neural function and perhaps depression have led to a number of intervention studies in patients with depression. Results from case-control studies, clinical trials and case studies have shown that oils rich in omega 3 PUFA play a beneficial role in these conditions. Readers might also wish to consult a recent review of the evidence and method critique on omega 3 PUFA and depression.⁴⁷ Various omega 3 fatty acids have been considered in relation to mood disorders, including the ethyl ester of EPA (ethyl-EPA), DHA or mixtures of EPA and DHA as found in fish oil.

One of the first intervention studies was a 4-month double-blind, placebo-controlled trial in 30 patients on standard medication, aged 18 to 65 years, with bipolar disorder.⁴⁸ This study showed that episodes of severe mania and depression were significantly reduced in the omega 3 PUFA (EPA plus DHA) supplementation group (n=14) (9.6g/day) compared with the placebo group (n=16). Peet and Horrobin⁴⁹ studied 70 patients with persistent depression, despite treatment with standard antidepressants. The patients were randomized to receive 1, 2 or 4 g of pure ethyl-EPA per day or placebo for 12 weeks in addition to their usual medication. Interestingly, only those patients treated with 1 g/day (n=17) showed a significant improvement (reduction in the depression rating); in this group, 69% of patients showed a reduction of at least 50% of the symptoms rated on a standard depression rating scale compared with 25% of patients so improving in the placebo group. Another study in 20 patients with recurrent unipolar depression on their standard antidepressant medication, showed that there were highly significant benefits from ethyl-EPA (2 g/day), compared with

placebo after 3 weeks of treatment.⁵⁰ In a double-blind study, subjects with major depressive disorder were randomized to receive either 3.3 g/day of EPA plus DHA (from fish oil) or placebo for 8 weeks in addition to usual treatment.⁵¹ Patients in the omega 3 PUFA treated group had a significantly decreased score on the Hamilton Rating Score for depression compared with the placebo group ($P < 0.001$). However, a double-blind study in 36 depressed patients who received 2 g/day of DHA for 6 weeks as monotherapy showed no significant effect compared with the placebo treatment.⁵²

An open-label study in 12 bipolar patients treated with 1.5 to 2.0 g of EPA/day for up to 6 months showed beneficial effects in 8 out of 10 patients who completed 1 month of the treatment.⁵³ In contrast, Silvers et al⁵⁴ reported that 8 g of fish oil per day for 12 weeks in addition to usual medication in a randomized double-blind study showed no significant improvement in mood, over the placebo of olive oil, in 77 participants being treated for depression. Frangou et al⁵⁵ conducted a 12-week double blind study in 75 individuals with bipolar depression with 1 g/day or 2 g/day of ethyl-EPA as adjunctive therapy. There was a significant improvement with the ethyl-EPA (no dose response effect) based on the Hamilton rating scale and the clinical global impression scale. However, Keck et al⁵⁶ reported no significant effect of ethyl-EPA in individuals with bipolar depression and rapid cycling bipolar disorder. The study was conducted using 6 g/day of ethyl-EPA as adjunctive therapy for 4 months in a randomized, placebo-controlled study.

A single case report has found that ethyl-EPA given to a treatment-resistant, severely depressed and suicidal male patient, resulted in dramatic and sustained clinical improvement in all symptoms of depression within one month.⁵⁷ The EPA treatment was accompanied by a reduction in the lateral ventricular volume in the brain.

Noaghuil and Hibbeln⁵⁸ investigated cross-national prevalence rates of bipolar disorders and showed that there was a very strong relationship between greater seafood consumption and lower prevalence rates. Regular consumption of fish has also been associated with reduced suicidal ideation⁵⁹ and better self-reported mental health status.⁶⁰

In a cross-national study of prevalence rates of post-partum depression and breast milk EPA, DHA and AA levels and seafood consumption, Hibbeln⁶¹ found that higher concentrations of DHA in milk and greater seafood consumption both predicted lower prevalence rates of post-partum depression. However, two studies in post-partum depression have failed to demonstrate an effect of omega 3 PUFA. A small pilot open-label study in seven pregnant females with a past history of post-partum depression, who were provided 2.96 g of EPA plus DHA (provided as fish oil) for 2 weeks prior to birth, failed to show promising results.⁶² Llorente et al⁶³ reported that 2 g/day of DHA provided to breast-feeding mothers in the first four months after birth led to no changes in self-rating or diagnostic measures of depression compared with the placebo group.

In summary, seven of the ten studies in adults with depression or bipolar disorder (excluding post-partum depression) have reported positive effects of either fish

oil containing EPA and DHA (3.3 and 9.6 g/day) or ethyl-EPA (1-2 g/day). The three negative studies were with DHA alone (2g/day), fish oil (8g/day) and ethyl-EPA at 4-6 g/day. This leaves some questions for which we do not have adequate answers at this stage.

Question 1: which omega 3 PUFA is best to treat mood disorders (EPA or a mixture of EPA plus DHA)?

Question 2: what is the most effective dose?

Question 3: what is the most effective length of treatment?

Question 4: does the use of omega 3 PUFA give the most benefit in patients on usual medication?

Question 5: what is the mechanism of action of EPA? It should be noted that there is a lack of studies in animals that have examined the role of EPA in neural function and also that brain grey matter contains negligible levels of EPA.⁶⁴

It is of considerable interest that there is a relationship between depression and heart disease. For example, patients with an episode of major depression have a 3-fold risk of cardiac mortality later in life.⁶⁵ It is possible that the link between these conditions is that both have been associated with low intakes of omega 3 PUFA.

Mechanisms

Biophysical properties of synaptic membranes directly affect neurotransmitter biosynthesis, signal transduction, uptake of serotonin, binding of α -adrenergic and serotonergic receptors, and monoamine oxidase activity. The proposed mechanisms of action of the omega 3 PUFA in mood disorders include effects on neurotransmitter receptors and G-proteins via effects on biophysical properties of the membrane, effects on secondary messengers and on protein kinases, and effects on the inflammatory response of eicosanoids derived from AA.

Recent data in rats reveal that the drugs commonly used to treat bipolar disorder, lithium, carbamazepine and valproic acid, significantly decrease the turnover of AA and metabolism to eicosanoids in the brain (see below). This new information reveals the possibility of a link between omega 3 PUFA and mood disorders, given that deficiency of omega 3 PUFA leads to an increased metabolism of AA to eicosanoids, via specific phospholipase A₂ and cyclooxygenase enzymes (COX-2) in rat frontal cortex.¹⁰

Rats treated with lithium and carbamazepine demonstrated a reduced turnover of AA, but not DHA, in brain phospholipids and decreased mRNA, protein levels and enzyme activity of a cytosolic phospholipase A₂, which is AA-specific.^{66,67} This treatment also reduced the brain concentration of prostaglandin E₂, a product of the COX pathway, presumably due to reduced release of AA from the phospholipids. It is possible that EPA is effective in depression through its ability to inhibit COX activity, although the levels of EPA in the brain phospholipids are very low.

The same group showed that another drug used in treating bipolar disorder, valproic acid, also reduced AA turnover in the brain but by a different mechanism, namely the inhibition of the formation of arachidonoyl CoA.⁶⁸ It is of interest that two further papers from this group demonstrate effects of chronic lithium on the elevation of brain glucose metabolism⁶⁹ and on dopamine D2

receptor-initiated signalling, via effects on AA turnover in the brain.⁷⁰

Conclusions

DHA plays an important role in the structure and function of brain cellular membranes. There is biologically plausible evidence to suggest that omega 3 PUFA might play a role as adjunctive therapy for adult depression, though much research is required to determine the most effective omega 3 PUFA (EPA, DHA or a mixture of both) and the most effective dose.

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