

Neurobehavioral Aspects of Omega-3 Fatty Acids: Possible Mechanisms and Therapeutic Value in Major Depression

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Abstract

Omega-3 fatty acids have been the subject of volumes of international research, the results of which indicate these substances may have therapeutic value in a number of medical conditions. An emerging area of research is examining the neurobehavioral aspects of omega-3 fatty acids (alpha-linolenic, eicosapentaenoic, docosahexaenoic) and the critical role of these essential fats in the functioning of the central nervous system. Investigations have linked omega-3 fatty acids to a number of neuropsychiatric disorders, including depression. The purpose of this article is to examine the possible mechanisms of action and potential clinical value of omega-3 fatty acids in major depression. A novel mechanism involving omega-3 modulation of cAMP response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF) is proposed.

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Introduction

Omega-3 fatty acids are long chain, polyunsaturated fatty acids (PUFA) of plant and marine origin. Because these essential fatty acids (EFAs) cannot be synthesized in the human body, they must be derived from dietary sources. Flaxseed, hemp, canola, and walnuts are generally rich sources of the omega-3 PUFA alpha-linolenic acid (ALA). Fish provide varying amounts of omega-3 fatty acids in the form of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). ALA can

be metabolized into the longer chain EPA and DHA (Figure 1).¹ The role played by EFAs in the human body has been the subject of volumes of international research, particularly in recent years. The results indicate that omega-3 fatty acids may be of value in the treatment of various medical conditions.²

The brain contains a high concentration of PUFA (approximately 20 percent of dry weight) and, in the nervous system, one out of every three fatty acids (FAs) belong to the PUFA group.^{3,4} Given the high concentration of EFAs in the nervous system, it is not surprising that investigators have focused on the role of omega-3 fatty acids in brain function. Recent research underscores the important role of these fatty acids in central nervous system (CNS) function, and the potential EFAs have in the treatment of various neuropsychiatric disorders. While beneficial effects of omega-3 fatty acids have been linked to Alzheimer's disease,⁵ attention deficit hyperactivity disorder,⁶ autism,⁷ schizophrenia,⁸ hostility,⁹ anxiety,¹⁰ and bipolar disorder,¹¹ the focus of this article will be the role of omega-3 fatty acids in the neurobiology and treatment of major depressive disorder.

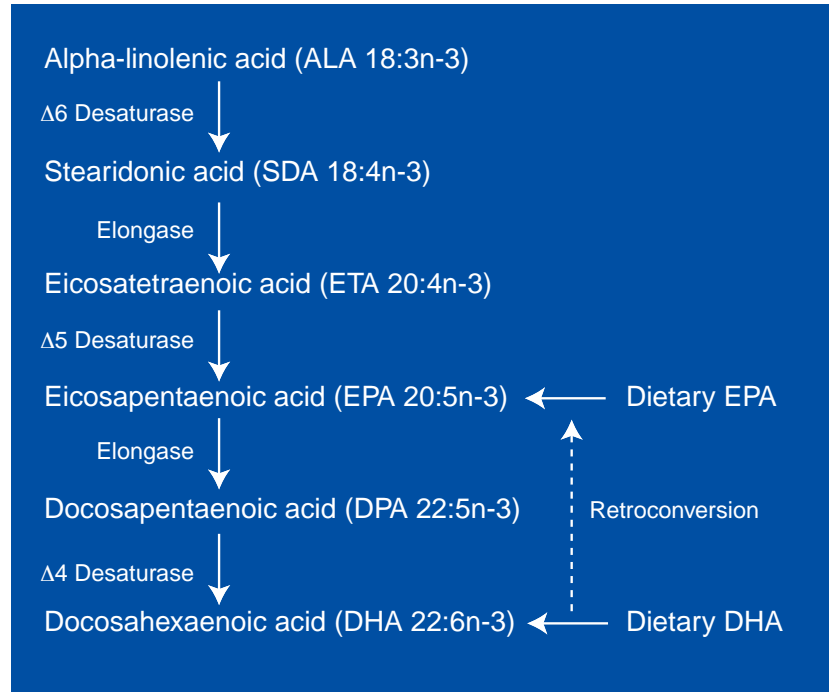
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Major Depression on the Rise

Mood disorders, including major depression, are recurrent, debilitating, and potentially life-threatening illnesses. In the last 100 years, the age of onset of major depression has decreased and its overall incidence has increased in Western countries. For example, severe forms of major depression affect up to five percent of the population in the United States, while up to 20 percent present with milder forms and another two percent have bipolar disorder.¹² This increase cannot be explained merely by changes in attitude of health professionals or society, diagnostic criteria, reporting bias, or institutional or other artifacts.^{13,14} Despite advances in pharmacotherapy, a significant proportion of depressed patients are considered treatment-resistant.¹⁵ Poor compliance, side effects, or lack of desired effects are not uncommon with antidepressant medications. Selective serotonin reuptake inhibitor (SSRI) treatment produces a 50-percent improvement in only about half of those who maintain therapy, while about 30 percent of depressed patients discontinue medications before six-weeks are complete.^{16,17} Such lack of desired results encourages the continued search for improvements in current pharmacotherapy and novel treatments.

In contrast to the increased incidence of depression, the dietary intake of omega-3 fatty acids has dramatically declined in Western countries over the last 100 years. The ideal ratio of omega-3 to omega-6 EFAs is approximately 1:1, according to the conclusion of an international panel of lipid experts published in the *Journal of the American College of Nutrition*.¹⁸ The North American diet currently has omega-6 fats outnumbering omega-3 fats by a ratio of 20:1, largely as a result of the ubiquitous supply of various omega-6-rich oils (corn, sunflower, safflower, cottonseed)

Figure 1. Metabolic Pathway of Dietary Omega-3 Fatty Acids



added directly to the food supply or through animal rearing.¹⁹ It is reported that corn oil has an omega-6:3 ratio of 60:1 and safflower a ratio of 77:1 (Tables 1 and 2).²⁰ The following research indicates these dietary fatty acid alterations and the indiscriminate 20-year-old message that all fat is harmful have not been without neurophysiological and neurobiological consequences.

Epidemiological Data

If omega-3 fatty acids play a role in depressive disorders, then it would be expected that countries consuming greater amounts of these fatty acids (primarily through fish intake) would have a lower prevalence of depression. In his research published in *Lancet*, Joseph Hibbeln of the National Institutes of Health found a significant negative correlation between worldwide fish consumption and prevalence of depression.²¹ In research involving a random sample within a nation, frequent fish consumption in the general population is associated with a decreased risk of depression

Table 1. Omega-6 and Omega-3 Content (%) of Dietary Oils

Oil	Omega-6	Omega-3
Safflower	77	0
Sunflower	65	0
Corn	60	0
Cottonseed	50	0
Sesame	45	0
Peanut	32	0
Soybean	51	7
Canola	20	9
Walnut	52	10
Flax	14	57

and suicidal ideation.²² A recent cross-sectional study conducted in New Zealand found fish consumption is significantly associated with higher self-reported mental health status.²³

Hibbeln recently found a similar negative correlation between total seafood (including shellfish) consumption and the prevalence of postpartum depression in 22 countries. Higher concentrations of DHA in mother's milk and greater seafood consumption both predicted lower prevalence of postpartum depression.²⁴ National per capita fish consumption has also been correlated with protection against seasonal affective disorder.²⁵ While this does not prove causation, and cultural, social, and economic factors are possible confounding factors, it does provide support to the notion omega-3 fatty acids might play a role in depression.

Omega-3 Fatty Acid Status and Depression

One method to determine EFA status is to examine levels in the plasma and red blood cell (RBC) membranes. While not identical, significant correlations exist between blood and brain phospholipids.²⁶ A number of investigations have found a decreased omega-3 content in the blood of depressed patients.²⁷⁻³⁰ In fact, EPA content in RBC phospholipids is negatively correlated with the severity of depression, while the omega-6 FA arachidonic acid to EPA ratio positively correlates with the clinical symptoms of depression.²⁷ In addition, a negative correlation between adipose tissue DHA and depression has been observed. Mildly depressed subjects had 34.6-percent less DHA in adipose tissue than non-depressed subjects. Examining adipose tissue FAs is important because it is more reflective of long-term (1-3 year) intake.³¹

Individuals with depression are more likely to have atopic diseases, a possible indicator of decreased FA intake and/or metabolism.³² Those with atopic disorder have been shown to have low plasma and RBC omega-3 levels.³³ Histamine may also be playing a significant role in the connection between atopy and depression.³⁴ In addition, women with depression are more likely to have spontaneous pre-term births,³⁵ and research indicates omega-3 fatty acids can delay pre-term delivery,^{36,37} an interesting connection warranting further exploration. The overlap between cardiovascular disease and depression has also been noted, with some investigators suggesting omega-3 status is a common thread.³⁸

Depression, Omega-3 Fatty Acids, and CNS Function

In order to appreciate the potential role of omega-3 fatty acids in mental health, some of the neurobiological alterations that exist in depression must first be examined. While the exact mechanisms involved in the pathogenesis of depression remain obscure, there is a growing body of research indicating involvement of the frontal cortex and limbic system, including the hippocampus and the nucleus accumbens (NA).³⁹

The chance discovery of antidepressant medications has led to 50 years of research focusing on monoamines and depression. With the efficacy of modern antidepressants, the involvement of serotonin, norepinephrine, and dopamine in the antidepressant activity of medications and the pathophysiology of depression seems clear. Indeed, a large body of research suggests altered neurotransmission in major depression. However, the relationship between depression and neurobiology is extremely complex and cannot be fully explained by this “monoaminergic hypothesis.” Those receiving antidepressants demonstrate an immediate increase in the availability of various neurotransmitters, yet mood elevation can take months of pharmacotherapy, indicating an adaptation or drug-induced plasticity is taking place. Also, the monoaminergic theory does not account for the large number of depressed patients who do not respond to current antidepressants.^{39,40}

Animal models of depression have resulted in valuable insights into potential biological mechanisms and/or consequences of depression. Research shows decreased levels of dopamine turnover in the prefrontal cortex and dopamine levels that are up to six-fold higher in the NA.^{41,42} Conversely, agents that are NA-dopamine receptor agonists have antidepressant activity.⁴³ The NA is involved in learning, reward, and motivation, and abnormalities in this area have been linked to major depression.⁴⁴⁻⁴⁶ Neurochemical activity in the NA is extremely complex and, while overall increases in total dopamine may be observed, functionality may be altered.

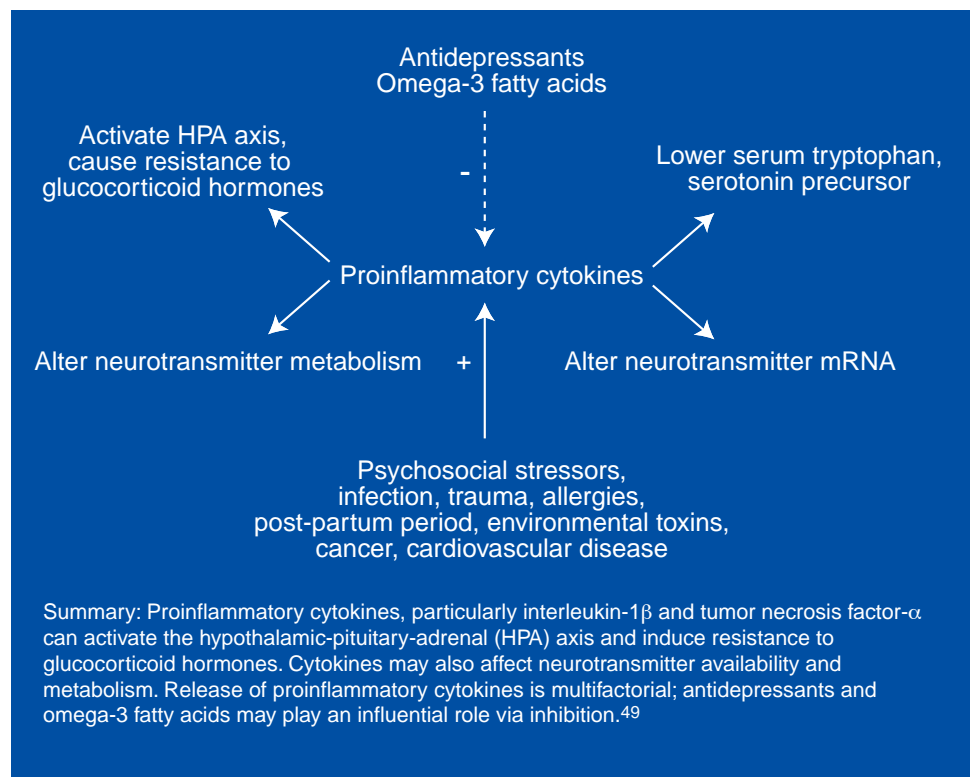
Modern brain imaging technology has allowed investigators to examine cerebral blood flow and glucose utilization in patients with major depression. The findings have been fairly consistent, with researchers reporting that in major depression there are blood flow abnormalities, including hypoperfusion in the limbic system and prefrontal cortex. In addition, depressed patients have decreased glucose metabolism in a number of brain regions and this hypometabolic state correlates negatively with severity of depression.^{47,48}

Table 2. Selected Sources of EPA and DHA

Fish/Seafood	Total EPA/DHA (mg/100 g)
Mackerel	2500
Herring	1700
Chinook salmon	1400
Anchovy	1400
Coho salmon	800
Rainbow trout	500
Pacific halibut	400
Cod	300
Shrimp	300
Catfish	300
Lobster	200

A number of investigators have examined the role of proinflammatory cytokines in the pathophysiology of depression. A growing body of research indicates that depression is associated with excessive production of proinflammatory cytokines. These cytokines, including interleukin-1beta (IL-1 β), -2, and -6, interferon-gamma, and tumor necrosis factor-alpha (TNF- α), can have direct and indirect effects on the CNS. For example, they may lower neurotransmitter precursor availability, activate the hypothalamic-pituitary axis, and alter the metabolism of neurotransmitters and neurotransmitter transporter mRNA.⁴⁹ Researchers have found elevations in IL-1 β and TNF- α are associated with severity of depression.⁵⁰ Psychological stress, infection, trauma, allergies, toxins, and various other factors can be responsible for a rise in these cytokines (Figure 2).⁴⁹ Interestingly, various tricyclic and serotonin re-uptake inhibiting antidepressant medications can inhibit the release of the above-mentioned cytokines.^{49,51}

Figure 2. Potential Mechanisms of Action of Inflammatory Cytokines in Depression



increases the activity and expression of cAMP response element-binding protein (CREB), which in turn increases BDNF.³⁹ Novel ways to increase BDNF include enhancing cAMP by inhibiting the phosphodiesterases (PDE), specifically PDE4, that break down cAMP. PDE4 inhibitors have antidepressant activity but are not in use due to intolerable side effects.⁴⁰ BDNF expression can be inhibited by physical and psychological stress,⁵⁵ and a diet high in saturated fat and sucrose.^{56,57} On the other hand, expression may be enhanced by voluntary exercise, learning activities and, as mentioned, antidepressants.⁵⁵

Research shows major depression is associated with neuronal atrophy in the hippocampus⁵² and prefrontal cortex.⁵³ Antidepressant treatment can lead to the activation of intracellular cascades that regulate gene expression and ultimately control neuronal survival and structural plasticity. Until recently, the notion that neurogenesis takes place in adult humans was not even considered. Now, however, researchers suggest depression may inhibit neurogenesis in the hippocampus,⁵² an idea supported by the findings that antidepressants can promote neurogenesis.⁴⁰ Chronic, but not acute, administration of antidepressants can cause an increase in nerve growth factors, particularly brain-derived neurotrophic factor (BDNF), and these nerve growth factors can play a role in the plasticity and survival of the developed, adult nervous system. Serum BDNF has been found to be negatively correlated with the severity of depressive symptoms.⁵⁴ Enhancing the cyclic AMP (cAMP) signal-transduction cascade

Omega-3 fatty acids are an essential component of CNS membrane phospholipid-acyl chains and, as such, are critical to the dynamic structure of neuronal membranes.³ DHA is continuously secreted by astrocytes, bathing the neuron in omega-3 fatty acid.⁵⁸ The binding of serotonin to the astroglial 5HT_{2A} receptor can mobilize DHA to supply the neuron.⁵⁹ Alterations in membrane lipids can alter function by changing fluidity. Proteins are embedded in the lipid bi-layer and the conformation or quaternary structure of these proteins appears to be sensitive to the lipid microenvironment. The proteins in the bi-layer have critical cellular functions, acting as receptors, enzymes, and transporters.⁶⁰⁻⁶⁴ In addition, EFAs can act as sources for second messengers within and between neurons.⁶⁵ An optimal fluidity is required for neurotransmitter binding and the signaling within the cell.⁶⁶ Omega-3 fatty acids can alter neuronal fluidity by displacing cholesterol from the membrane.⁶⁷

It is not surprising there are functional consequences when animals are fed a diet deficient in omega-3 fatty acids (Table 3). Reduction in omega-3 intake (in the form of ALA) results in a reduction of omega-3 content throughout the brain cells and organelles along with a compensatory rise in omega-6 fatty acid content. This alteration is accompanied by a 40-percent reduction in the Na⁺K⁺ ATPase of nerve terminals, an enzyme that controls ion transport produced by nerve transmission and that consumes half the energy used by the brain.⁶³ There is also a 20-percent reduction in 5'-nucleotidase activity, a decrease in fluidity in the surface polar part of the membrane,⁶³ and a significant reduction in the cell body size of the hippocampal CA1 pyramidal neuron.⁶⁸ A 30-percent reduction in the average densities of synaptic vesicles in the terminals of the hippocampal CA1 region has also been observed as a result

of an omega-3 deficiency combined with a learning task.⁶⁹ Deficiency of omega-3s also results in a 30-35 percent reduction in phosphatidylserine (PS) in the rat brain cortex, brain mitochondria, and olfactory bulb.⁷⁰ On the other hand, fish oil supplemented to rats can increase PS composition of the cerebral membrane.⁷¹ This is an interesting finding, given research showing that PS has antidepressant activity in adults.^{72,73} PS can activate various enzymes, including protein kinase C, Na⁺K⁺ ATPase, and tyrosine hydroxylase, as well as regulating calcium uptake. It is therefore suggested that altering PS in cerebral membranes can alter neurotransmission.⁷¹

A number of studies have specifically examined the effect of an omega-3 deficient diet on dopamine and serotonin levels in animals. Animals on such a diet have a reduction in the dopaminergic vesicle pool⁷⁴ along with a 40-60 percent decrease in the amount of dopamine in the frontal

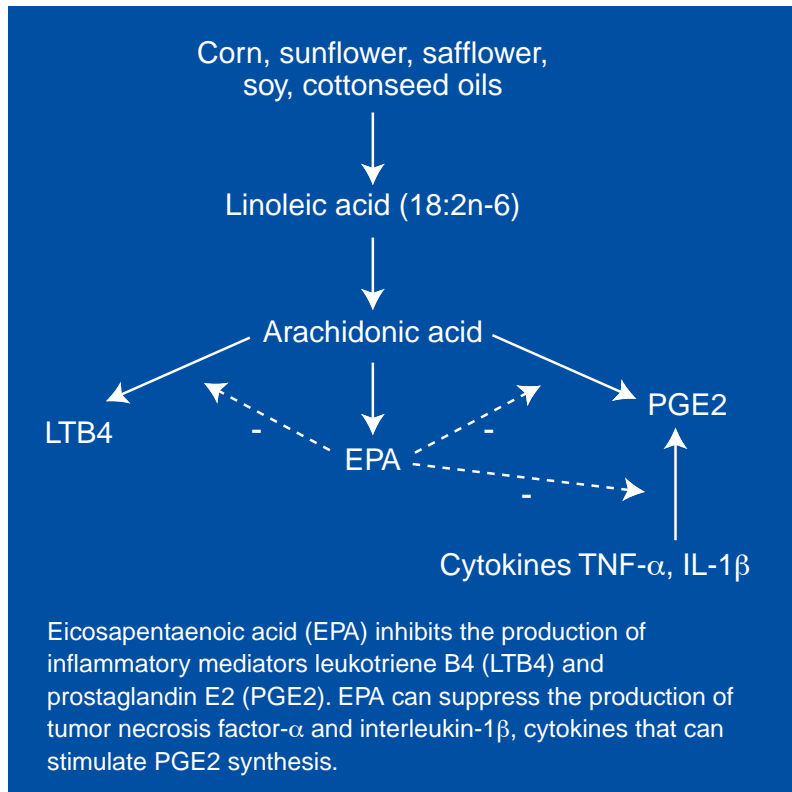
Table 3. Consequences of Omega-3 Deficiency in the Central Nervous System

- ↓ Dopamine vesicle pool
- ↓ Dopamine content in frontal cortex
- ↓ Dopamine content in olfactory bulb
- ↑ Dopamine content in nucleus accumbens (NA)
- ↓ Dopamine release from vesicle storage
- ↓ Normal inhibitory control over NA dopamine
- ↓ Vesicular monoamine transporter (VMAT2)
- ↓ Pre/post synaptic dopamine receptor DR2 in frontal cortex
- ↑ Pre/post synaptic dopamine receptor DR2 in NA
- ↑ Serotonin receptor (5HT2) density in frontal cortex (compensatory response)
- ↓ Glucose uptake by neurons
- ↓ Neuronal cytochrome oxidase activity
- ↓ Blood-brain barrier integrity
- ↓ Normal cerebral microperfusion
- ↓ Sodium/potassium ATPase at nerve terminal
- ↓ Fluidity at surface polar membrane
- ↓ Phosphatidylserine in cortex, olfactory bulb, and mitochondria
- ↓ Hippocampal CA1 pyramidal neuron cell body size

cortex and an increase in the NA,^{75,76} alterations strikingly similar to the animal models of depression described above. Although overall dopamine levels in the NA are higher in an omega-3 deficiency and the animal model of depression, function of the NA-dopaminergic system appears to be abnormal in both. In an omega-3 deficiency, the release of dopamine from the vesicular storage pool under tyramine stimulation is 90-percent lower than in rats receiving an adequate omega-3 intake.⁷⁴ In the animal model of depression, although overall NA-dopamine levels are higher, the extracellular levels of dopamine in the NA are lower than normal controls and do not respond to normal serotonin stimulation.⁷⁷

The increase in dopamine in the NA of omega-3 deficient rats is thought to be a result of loss of normal inhibitory control by reductions in frontal cortex dopamine input.⁷⁸ The frontal cortex dopamine reductions may be due to abnormalities

Figure 3. Effect of Eicosapentaenoic Acid on Inflammatory Mediators



of storage within the presynaptic terminal. The vesicular monoamine transporter (VMAT2) is present on the presynaptic vesicle membrane and allows for dopamine entry and storage in the vesicle. In omega-3 deficient rats, the levels of VMAT2 are significantly decreased in the frontal cortex. In addition, the pre- and post-synaptic dopamine receptor D2R is decreased in the frontal cortex and dramatically increased in the NA, alterations reflective of protein and mRNA expression.⁷⁹ These findings have tremendous implications in the area of nutritional neuroscience, particularly that related to genetic transcription as influenced by dietary modifications. Interestingly, fish oil supplementation in rats leads to a 40-percent increase in dopamine levels in the frontal cortex as well as an increase in binding to the D2 receptor. In addition, fish oil supplementation (15 times greater than previously suggested minimum requirements⁸⁰) caused a decrease in activity of

monoamine-oxidase B, an enzyme responsible for breaking down dopamine.⁷¹

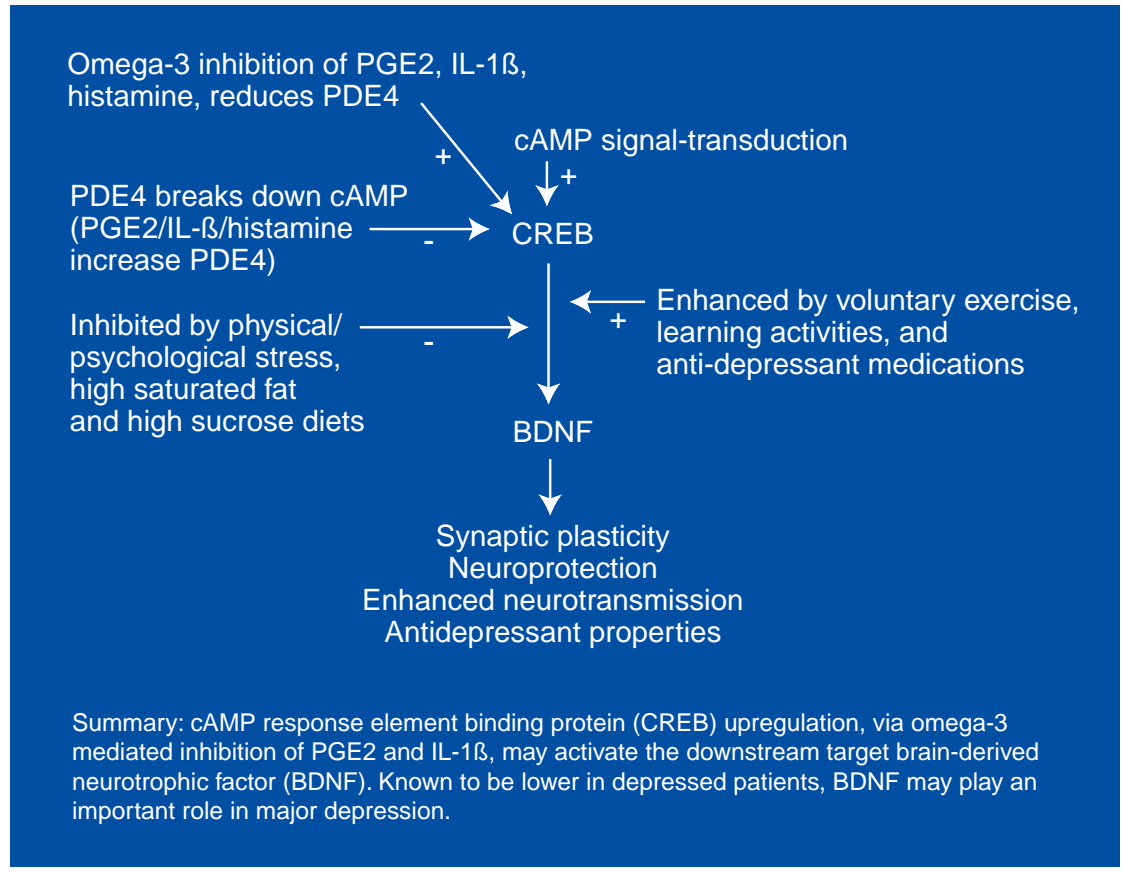
In animal research, an omega-3 deficiency results in as much as a 46-percent increase in serotonin receptor (5HT2) density in the frontal cortex.⁷⁵ This finding is thought to reflect an adaptation to reduced serotonin function and similar observations have been made regarding 5HT2 receptors in suicide victims.⁸¹ In healthy adults, higher concentrations of plasma DHA predict higher cerebrospinal fluid (CSF) 5-hydroxyindolacetic acid (5-HIAA), a metabolite that reflects serotonin turnover, particularly in the frontal cortex.⁸² Numerous studies link low CSF 5-HIAA with psychiatric conditions, including violent suicide attempts during depression.⁸³

When an animal diet is omega-3 FA deficient, widespread reductions in DHA levels are observed, although reductions are particularly pronounced in the frontal cortex (40% reduction). Another area with a marked

DHA reduction is the olfactory bulb (35% reduction), which may also have behavioral consequences.⁸⁴ Olfactory bulbectomy in the rat causes serotonergic- and dopaminergic-associated, depression-related behavioral changes.^{85,86}

In addition, dietary omega-3 deficiency can affect nerve growth factor in different areas of the rat brain,⁸⁷ while research indicates DHA can promote neurite outgrowth of cells induced by nerve growth factor.⁸⁸ These findings have important implications, given the research on BDNF and depression. An omega-3 deficiency has also been shown to decrease glucose uptake of brain cells by 30 percent and decrease cytochrome oxidase activity by up to 40 percent.⁸⁹ Glucose uptake and cytochrome oxidase activity are indicators of neuronal functional activity. An omega-3 deficiency can also alter the delivery of amino acids and sucrose across the blood-brain barrier.⁹⁰ It has also been shown that an omega-3 deficiency may compromise normal cerebral microperfusion,

Figure 4. Neurotrophic Mechanisms in Depression – Possible Omega-3 Modulation



whereas supplementation may improve cognitive abnormalities related to cerebral hypoperfusion.^{91,92}

Finally, omega-3 fatty acids are well-documented inhibitors of proinflammatory cytokines, particularly TNF- α and IL-1 β ,⁹³ although the precise mechanism remains unclear. It is possible the omega-3 induced suppression of prostaglandin E2 (PGE2), thromboxane A2, and histamine are involved in anti-inflammatory effects⁹⁴⁻⁹⁶ and therefore, alleviation of depressive symptoms (Figure 3). It has been shown that, in addition to elevated cytokines, patients with major depression are more likely to have high levels of plasma and salivary PGE2.⁹⁷⁻⁹⁹ Recently it was shown that PGE2, histamine, and IL-1 β might, under certain circumstances, up-regulate PDE4 activity.¹⁰⁰⁻¹⁰² If this is the case in the CNS, then

omega-3 fatty acids may actually trigger the cAMP cascade, leading to expression of CREB and BDNF. An investigation into the effects of omega-3 fatty acids on the cAMP cascade warrants investigation (Figure 4).

Clinical Studies

While there is evidence that essential fatty acids may play a biological role in depression, there is very little published clinical data. One well-designed trial did demonstrate that four months of treatment with 9.6 g omega-3 fatty acids can be of benefit in the treatment of bipolar disorder. This study showed a highly significant effect of omega-3 fatty acids in lengthening remission and a highly significant effect in treating depression ($p < 0.001$ Hamilton Rating Scale for

Depression scores).¹⁰³ Case reports in the literature also indicate flaxseed oil, a source of ALA, may be of benefit in the treatment of bipolar depression and agoraphobia.¹⁰⁴

Depressive symptoms associated with premenstrual syndrome have been shown to be responsive to marine oil extracted from Antarctic krill. Krill oil is particularly rich in phospholipids as well as EPA and DHA (240 mg and 120 mg per g, respectively). Canadian researchers compared 2 g krill oil to 2 g standard fish oil capsules (180 mg EPA and 120 mg DHA per g) in the treatment of premenstrual syndrome and dysmenorrhea. In the three-month trial (n=70), patients took 2 g krill oil or fish oil daily for one month, then for eight days prior to and two days during menstruation for the following two months. Evaluations at 45 and 90 days revealed the patients taking krill oil showed a significant improvement in depressive symptoms of premenstrual syndrome. The same effect was not observed with the standard fish oil capsules, indicating that the presence of the phospholipids and/or higher amounts of EPA may be responsible for the therapeutic effect of krill oil.¹⁰⁵

One interesting case report published recently used objective measurements to corroborate the reported clinical improvements of a patient with major depression. The patient was classified as treatment-resistant and placed on a daily dose of 4 g purified EPA. Within one month the patient reported significant improvement, including in a co-morbid social phobia, and after nine months was reportedly symptom free. During the nine-month period, the relative concentration of cerebral phosphomonoesters increased 53 percent, and the ratio of cerebral phosphomonoesters to phosphodiesterases increased 79 percent, indicating reduced neuronal phospholipid turnover. The EPA treatment was also associated with structural brain changes that may be the result of increased phospholipid biosynthesis and decreased phospholipid breakdown (observed through MRI), including a reduction in lateral ventricular volume.¹⁰⁶ This may be an indication that omega-3 fatty acids can influence depression-related brain atrophy. These observations are important in light of recent MRI studies indicating a decrease in volume of various areas of the brain in depressed patients.^{107,108}

There is some evidence that adding fish oil to standard antidepressant medication may enhance the effectiveness of that therapy. One double-blind, placebo-controlled study (n=22) showed the addition of 2 g EPA to standard antidepressant medication enhanced the effectiveness of that medication compared to the medication plus placebo after three weeks of treatment. EPA had an effect on insomnia, depressed mood, and feelings of guilt and worthlessness. Importantly, no clinically relevant side effects were noted.¹⁰⁹

The results of an eight-week, double-blind, placebo-controlled trial investigating the use of EPA in women with borderline personality disorder were recently published in the *American Journal of Psychiatry*. Borderline personality disorder is characterized by mood instability and impulsive aggression. The researchers from Harvard Medical School reported 1 g EPA led to a reduction in scores assessing both aggression (Modified Overt Aggression Scale) and depressive symptoms (Montgomery-Asberg Depression Rating Scale). Although this was a small pilot study (n=30), the results are encouraging, indicating omega-3 fatty acids, and EPA in particular, should be the subject of larger trials. Remarkably, 90 percent of participants remained in the study and no clinically relevant side effects were elicited during the two months of EPA therapy.¹¹⁰

Researchers from Taiwan Medical University recently conducted an eight-week, double-blind, placebo-controlled trial comparing high doses of fish oil (9.6 g/day) to placebo in addition to standard antidepressant therapy in 28 patients with major depressive disorder. The patients who received the omega-3 fish oil capsules (each capsule contained 440 mg EPA and 220 mg DHA; dosage 5 capsules twice daily) had a significantly decreased score on the Hamilton Rating Scale for Depression compared to those on placebo (p<0.001). This relatively high dose of fish oil was well tolerated and no adverse events were reported during the two-month trial.¹¹¹

The most impressive clinical study to date on omega-3 fatty acids and unipolar depression (n=70) was recently published in *Archives of General Psychiatry*. In this 12-week, randomized, double-blind, placebo-controlled trial, patients

Table 4. Controlled Clinical Studies on Omega-3 Fatty Acids and Depression

Investigators	Condition	n	Protocol	Outcome
Stoll, et al	Bipolar disorder	30	4-months, 6.2 g EPA, 3.4 g DHA daily vs. placebo	Positive. Longer period of remission, significant reductions in Hamilton Rating Scale for Depression (HRSD) scores
Sampalis, et al	Premenstrual syndrome	70	3-months, 2 g Antarctic krill oil (480 mg EPA, 240 mg DHA and phospholipids) daily vs 2 g standard fish oil (360 mg EPA, 240 mg DHA)	Positive for krill oil. Improvements in depressive symptoms at 45 and 90 days. No effect observed for standard fish oil.
Nemets, et al	Treatment-resistant unipolar depression	22	1-month, 2 g pure EPA daily added to ongoing antidepressants vs. placebo added to antidepressants.	Positive. Mean reduction in HRSD scores: 12.4 points vs. 1.6 in placebo group. Improvements in depressed mood, insomnia, feelings of guilt and worthlessness.
Su, et al	Unipolar depression	28	2-months, 4.4 g EPA, 2.2 g DHA daily vs. placebo in addition to current antidepressants.	Positive. Statistically significant improvements in HRSD scores (<0.001) vs. placebo group.
Peet, Horrobin	Treatment-resistant unipolar depression	70	3-months, three dosage groups (1,2, or 4 g pure EPA) daily vs. placebo. Patients continued on current antidepressants.	Positive for 1 g of EPA. Half of those taking 1 g reported a 50% reduction in HRSD scores. Improvements noted in depression, sleep, anxiety, lassitude, libido, suicidal ideation.
Zanarini, Frankenburg	Borderline personality disorder	30	2-months, 1 g EPA daily vs. placebo	Positive. Reductions in depressive symptoms on Montgomery-Asberg Depression Rating Scale (MADRS) and aggression on Modified Overt Aggression Scale.
Marangell, et al	Unipolar depression	36	6-weeks, 2 g pure DHA vs. placebo	Negative. No statistically significant difference on MADRS scores.

receiving ethyl-EPA were divided into three dosage groups (1, 2, or 4 g daily). Subjects had experienced persistent depression, despite ongoing standard pharmacotherapy at adequate dosages. The patients who received 1 g EPA had the best outcome, with 53 percent achieving a 50-percent reduction on Hamilton depression scores. This was the only group that showed statistical significance. The 1 g EPA dose led to improvements in depression, anxiety, sleep, lassitude, libido, and suicidal ideation.¹¹² These reports suggest omega-3 fatty acids can alleviate depression by entirely different means than standard antidepressants, they improve the functionality of antidepressants, or both.

To date, the published clinical data on the effect of marine-derived omega-3 fatty acids (combination EPA/DHA or pure EPA alone) on major depression have been positive. Table 4 summarizes the studies. A recently published trial on DHA alone as monotherapy in the treatment of major depressive disorder, however, was inconclusive. Researchers from Baylor University randomly assigned 36 patients with depression to receive 2 g/day DHA or placebo for six weeks. The response differences between the groups, as measured by scores of the Montgomery-Asberg Depression Rating Scale, did not reach statistical significance.¹¹³

Conclusion

Limited clinical data, combined with rapidly growing support of laboratory and epidemiological studies, suggest omega-3 fatty acids may play a role in the prevention and management of depression. Fish oil supplements are usually well tolerated, with an impressive long-term safety record at doses of 1 g daily.^{114,115} EPA supplements rich in omega-3 fatty acids are also generally inexpensive, making them attractive as an adjuvant or alternative to standard pharmacotherapy. At this time, however, there is no established clinically appropriate dose of omega-3 fatty acids for depression. In addition, it is unclear whether the most clinically active component is EPA, DHA, or a combination of the two.^{26,116} Supplementation with marine extracts that contain EPA, DHA, and phospholipids is an

area warranting further investigation. For now, the bulk of clinical evidence indicates the EPA component of fish oils may be most important in mood stability, and that relatively low levels are required (1 g daily) for successful outcomes.

It should be noted that administration of omega-3 fatty acids, most often via high doses of flaxseed oil, may induce hypomania, mania, or other behavioral changes in a small percentage (less than 3%) of individuals.^{104,117}

Further research is necessary before firm conclusions can be drawn regarding the neurobiological influences of omega-3 fatty acids and their clinical value in the treatment of depression. It is anticipated that additional research will shed further light on the neuropsychological aspects of dietary lipids. In the meantime, given the current excess intake of dietary omega-6 fatty acids and the available evidence pertaining to omega-3 fatty acids and brain function, clinicians should ensure adequate intake of omega-3 fatty acids, particularly in patients with mood disorders such as depression.

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