Omega-3 Polyunsaturated Fatty Acids in Prevention of Mood and Anxiety Disorders

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Psychiatric disorders in general, and major depression and anxiety disorders in particular, account for a large burden of disability, morbidity and premature mortality worldwide. Omega-3 polyunsaturated fatty acids (PUFAs) have a range of neurobiological activities in modulation of neurotransmitters, anti-inflammation, anti-oxidation and neuroplasticity, which could contribute to psychotropic effects. Here we reviewed recent research on the benefits of omega-3 PUFAs supplements in prevention against major depression, bipolar disorders, interferon-α–induced depression patients with chronic hepatitis C viral infection, and post-traumatic stress disorder. The biological mechanisms underlying omega-3 PUFAs’ psychotropic effects are proposed and reviewed. Nutrition is a modifiable environmental factor that might be important in prevention medicine, which have been applied for many years in the secondary prevention of heart disease with omega-3 PUFAs. This review extends the notion that nutrition in psychiatry is a modifiable environmental factor and calls for more researches on prospective clinical studies to justify the preventive application of omega-3 PUFAs in daily practice.

KEY WORDS: Omega-3 (N-3) polyunsaturated fatty acids (PUFA); Depression; Anxiety disorders; Psychotic disorders; Clinical trials.

INTRODUCTION

Psychiatric disorders remain the leading cause of morbidity and mortality, accounting for 37% of healthy life years lost globally and five of the top ten causes of Disability Adjusted Life Years (DALY).1) Furthermore, a considerable proportion of people with mental health problems remain untreated. For example, in the USA 67% and in Europe 74% of people with mental illness are untreated.2) Due to stigmatization and cultural differences, the situation is even worse in Asian countries.3)

Rapid urbanization and an overall transition from traditional lifestyles have been linked to increases in both physiological and mental illness.4) Although the psychophysiological responses to environment determinants of urbanization and modernization are complex, the emerging evidence suggests that nutrition is a critical factor for the increasing prevalence and incidence in psychiatric disorders.5) For example, epidemiological, biological and clinical studies implicate that omega-3 fatty acids are important in the development and treatment of various mental illness, including mood and anxiety disorders.6-17)

Omega-3 polyunsaturated fatty acids (PUFAs) (also known as n-3 fatty acids or “fish oil”) are essential macronutrients and must be obtained from dietary sources because the body cannot synthesize them effectively.18) The major types of omega-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and their precursor, alpha-linolenic acid (ALA). EPA and DHA are found primarily in fatty fish, such as salmon, and in fish-oil supplements. Sources of ALA include flax seed, canola, soybean, walnuts, and leafy green vegetables. Fish-oil supplements are among the most widely used dietary supplements.19) Omega-3 PUFAs may provide a range of neurobiological activities via modulation of neurotransmitters, anti-inflammation, anti-oxidation and neuroplasticity,14,16,20,21) which could contribute to their psychotropic effects.
Early intervention and primary prevention is considered as the best strategies for the crisis of under-treatment and under-effectiveness because a majority of patients refuse to take medications due to adverse effects and/or stigmatization. In fact, some researchers are now proposing that high-risk populations could be helped much sooner, by being alert to signs that unfold during months or even years preceding onset of diseases. Nutrition is a modifiable environmental factor that might be important in prevention medicine. For example, the use of omega-3 PUFAs in the secondary prevention of heart disease has been endorsed by the American Heart Association since 2002. This article reviews recent research on the benefits of omega-3 PUFA supplements in prevention of psychiatric disorders.

**MAIN SUBJECTS**

**Omega-3 PUFAs in Depression and Bipolar Disorders**

Psychiatric disorders based on current diagnostic systems are clinically and biologically heterogeneous. The heterogeneity is also reflected by current classification systems for antidepressant drugs (Fig. 1). For example, if the classification is based on serotonin reuptake, the agents with conflicting effects, such as the selective serotonin reuptake inhibitors (SSRI; e.g., fluoxetine or venlafaxine) and enhancers (SSRE; e.g., tianeptine) or the norepinephrine-dopamine reuptake inhibitors (NDRIs; e.g., bupropion), could all work as antidepressants. Interestingly, two common pathways, neuroprotection and anti-inflammation, have been found to be associated with all the antidepressant drugs. More importantly, these two common mechanisms link to antidepressant effects not only for drugs but also for non-pharmacological treatment omega-3 PUFAs. Indeed, the effects on neuroprotection and anti-inflammation support the promising hypothesis of psychoneuroimmunology of mood and anxiety disorders and provide an excellent interface between “mind” and “body”.

The PUFAs hypothesis is enlightening a promising path to discover, at least partially, the unsolved of depression. Firstly, it has been observed that countries with a high consumption of fish diet appear to have a lower prevalence of major depressive disorder (MDD) and bipolar disorders (BD), implying a preventive effect of omega-3 PUFA on mood disorders. Secondly, patients with MDD have lower levels of n-3 PUFAs in tissues of blood and brain. In our recent meta-analytic review including 3,318 subjects, the results further support omega-3 fatty acid deficits in MDD by showing a significant decrease in the levels of EPA (effect size [ES]=−0.18, p=0.004), DHA (ES=−0.35, p=0.0002) and total n-3 PUFA (ES=−0.51, p<0.0001).

The deficits in omega-3 PUFA levels have been reported in other populations with mood disorders, including lower DHA and total n-3 PUFAs in postpartum depression and lower DHA and EPA in social anxiety disorder. In the elderly patients, lower DHA and higher AA, n-6/n-3, AA/EPA, and AA/DHA ratios were associated with depressive disorders compared to healthy volunteers. In samples of patients with acute coronary syndromes, the depressed patients had lower DHA, total DHA and EPA; and higher AA, n-6/n-3, AA/EPA and AA/DHA than those without depression. Interestingly, lower DHA levels before starting interferon (IFN)-α therapy predicted IFN-α-induced depression in patients with chronic hepatitis C viral (HCV) infection.

Six case-control studies have shown lower omega-3 PUFA status in erythrocyte membranes or plasma in patients with BD. Compared to healthy controls, significantly decreased DHA levels have been described in both manic patients under treatment and in medication-free patients. Moreover, Ranjekar et al. found significantly decreased omega-3 ALA and EPA levels in eryth-
The beneficial effects of n-3 PUFA in depression are further supported in pre-clinical studies of animal and cellular models. N-3 PUFAs are associated with a preventive and reductive effects of depression-like behaviours in animal model in rats. In addition, the level of brain DHA is negatively correlated to the immobility time and is positively correlated to the swimming time. We proposed several biological mechanisms of the antidepressant effect of n-3 PUFAs in previous reviews, including: (1) neurotransmitter regulations, (2) anti-inflammation and anti-oxidation, and (3) neuroplasticity effects.

Omega-3 PUFAs in Prevention of IFN-α-induced Depression

Due to the heterogeneity of depression, half of patients with MDD fail to achieve remission with optimized medication treatment and every antidepressant treatment is expected to have only modest effects. For example, the effect sizes of omega-3 PUFAs range from 0.17-0.23 in treating DSM-defined MDD patients. However, the effect sizes of current standard antidepressant drugs are not much better. In an excellent meta-analytic review, the effect sizes are 0.11 for mild to moderate, 0.17 for severe, and 0.47 for very severe type of MDD. As omega-3 PUFAs are safe and well accepted and the current antidepressant drugs have significant adverse effects, it is of great clinical important to identify patients to treat or high-risk subjects to prevent with this safe and yet effective natural component. There is one example to demonstrate the potential preventive effect of omega-3 PUFAs in specific high-risk population of major depression induced by IFN-α therapy. IFN-α is the standard therapy for HCV infection; however, its clinical impact is reduced by its common and severe neuropsychiatric adverse effects. For example, up to 30% of patients develop IFN-α-induced major depression. Finding the best strategy to prevent IFN-α-induced depression will improve clinical outcome, but previous clinical trials with SSRIs have had mixed results. In addition, SSRIs-induced gastrointestinal bleeding is concerned in HCV patients, who may already have esophageal varices, cirrhosis, low platelet count, and tendency toward bleeding. Furthermore, the use of antidepressants in patients receiving IFN-α therapy has been associated with rare but severe adverse effects, including retinal haemorrhaging and cotton-wool spots, bone marrow suppression, hepatotoxicity, and manic episodes. As most patients receiving IFN-α do not develop clinically significant depression, the routine pre-treatment with anti-
depressant drugs might expose patients to unnecessary medications. More importantly, we have previously demonstrated that lower omega-3 PUFA levels in the peripheral blood are associated with an increased risk of developing IFN-α-induced depression over the following weeks. Taking together, we conducted a 2-week, double-blind, placebo-controlled trial, to test the differential effects of the omega-3 PUFAs in the prevention of IFN-α-induced depression.

Two hundred and seven patients with HCV were screened, 162 of them consented to participate and were randomized to the study to receive EPA, DHA or placebo, and all of them completed the two-week trial; 152 participants were followed throughout the 24 weeks of IFN-α treatment, and were included in the analysis. Compared with placebo, the incident rates of IFN-α-induced depression were significantly lower in EPA-, but not in DHA-treated patients (rates: 10% and 28%, respectively, vs. 30% for placebo). Both EPA and DHA pre-treatment significantly delayed the onset of IFN-induced depression (average weeks of onset: 12.0 and 11.7, respectively, vs. 5.3 for placebo). EPA and DHA were both well tolerated in this population. The study shows that EPA appears to be effective in the prevention of IFN-induced depression and suggests that omega-3 PUFAs are potentially a suitable preventive strategy for a wider pool of patients with depression associated with inflammation.

**Omega-3 PUFAs in Prevention of Anxiety Disorders**

Some preclinical data support omega-3 PUFA as an effective treatment of anxiety disorders. For example, Song et al. found that an EPA-rich diet could reduce the development of anxiety-like behaviors in rat as well as normalizing dopamine levels in the ventral striatum. Regarding therapeutic intervention, Fux et al. conducted a placebo-controlled cross-over trial of adjunctive EPA treatment in patients with obsessive-compulsive disorder (OCD). Eleven patients with OCD were randomly allocated to begin 6 weeks of placebo followed by 6 weeks of 2 g/d of EPA or EPA followed by placebo. Unfortunately they found no benefit of EPA augmentation on symptoms of anxiety, depression and obsessive-compulsiveness. Similarly, 2 g/d of EPA augmentation was ineffective in relieving anger, hostility, or depressive symptoms among seven posttraumatic stress disorder (PTSD) patients in open-label case series. These 2 studies are unfortunately limited by small sample sizes.

Buydens-Branchey et al. conducted a randomized-controlled trial and showed the daily administration of 2,250 mg/d of EPA plus 500 mg/d of DHA for 3 months was accompanied by significant decreases in anger and anxiety scores compared to placebo group in 22 substance abusers. They also showed that these changes were associated with increases in plasma levels of both DHA and EPA but an increase in EPA was more robustly correlated with low end-of-trial anxiety symptom and an increase in DHA was more robustly correlated with low end-of-trial anger symptom. These studies suggested that EPA might be effective in control of anger and anxiety, but more well-designed larger studies focusing on specific condition are needed to clarify the efficacy of omega-3 PUFA.

Haberka et al. conducted a randomized non-placebo controlled trial to determine the efficacy of 465 mg/d EPA plus 375 mg/d DHA on top of the regular pharmacotherapy in 52 patients with post myocardial infarction. They found that omega-3 PUFA supplementation revealed additional effects on decreasing depressive and anxiety symptoms. In a randomized double-blind controlled trial, Kiecolt-Glaser et al. firstly showed that omega-3 PUFA supplementation could reduce inflammation and anxiety among healthy young adults who faced stressful major examination. The medical students who received 2,085 mg/d of EPA and 348 mg/d of DHA for 12 weeks showed a 14% decrease in stress-stimulated interleukin 6 production and a 20% reduction in anxiety symptoms compared to subjects who received placebo. No significant change in depressive symptoms was shown between the two groups. These studies suggested that EPA rather than DHA might be efficacious in selective prevention of anxiety under serious physical condition or stressful situation.

Despite that many clinical trials testing efficacy of omega-3 PUFA in anxiety disorders have been done, the investigation about preventive intervention is still lacking. Recently, we administered 1,470 mg/d of EPA plus 147 mg/d of EPA for 12 weeks in accidentally injured patients to prevent PTSD. We found a beneficial effect of omega-3 PUFAs for minimizing PTSD symptoms compared with the hypothetical means in our previous data. In April 2011 when Japan was hit by the Great East Earthquake, we conducted a randomized non-placebo controlled trial in medical rescue workers during the acute distressing phase to determine whether omega-3 PUFA can attenuate PTSD symptoms compared to psycho-education alone. Although there were no significant differences between the two groups, we found the benefit of 1,568 mg/d of DHA and 157 mg/d of EPA for attenuating PTSD symptoms in women. In addition, we recently reported a result of a randomized double-blind controlled trial to prevent PTSD.
among 110 accidentally injured patients admitted to an intensive care unit. All patients received psycho-education and were randomly assigned to receive 1,470 mg/d of DHA plus 147 mg/d EPA or placebo for 12 weeks. Unfortunately we did not find significant differences in PTSD symptoms at 3-month follow-up visits between the two groups (Matsuoka, revision under review).

Biological Mechanisms Underlying Omega-3 PUFAs’ Psychotropic Effects

The brain is highly enriched with omega-3 PUFAs and their derivatives, which regulate several biological processes, such as neurotransmission, cell survival and neuroinflammation, and thereby mood and cognition. The beneficial effects of omega-3 PUFAs in preventing depression and anxiety are supported in pre-clinical studies of animal and cellular models. For example, omega-3 PUFAs are associated with a preventive effect of depression-like and anxiety-like behaviors in animal model in rats.66-69) In addition, the level of brain DHA is negatively correlated to the depression-like behaviors, measured by immobility time in the forced-swimming test.67) Although the biological mechanisms underlying the psychotropic effects of omega-3 PUFAs are not fully understood, we summarize a few possible explanations.

The role of omega-3 PUFAs in neurotransmission

The change in omega-3 PUFA concentrations in the brain, induced by chronic deficiency in dietary omega-3 PUFAs, could lead to an increase in serotonin 2 (5-HT₂) and decrease in dopamine 2 (D₂) receptor density in the frontal cortex.89-91) The upregulation of 5-HT₂AC receptors and downregulation of dopamine receptors are thought to play a role in the pathophysiology of depression.92) In addition, higher cerebrospinal fluid levels of 5-hydroxy-indoleacetic acid (5-HIAA), a metabolite of serotonin and an indicator of brain serotonin turnover, has been shown to be associated with high plasma concentration of omega-3 PUFAs among healthy subjects.29 Biochemical studies have also shown that omega-3 PUFAs increased cerebrospinal fluid 5-HIAA releases,93 which are commonly associated with the improvement of depression and anxiety symptoms.

The role of omega-3 PUFAs in anti-inflammation and anti-oxidation

The inflammation theory of depression has been supported from several lines of evidence including increasing inflammatory biomarkers in clinical depressed patients and the observed behavioral changes related to inflammatory changes.20 Upon activation, microglia, the resident macrophages of the brain, up-regulate expression of detrimental factors of reactive oxygen species such as nitric oxide via inducible nitric oxide synthase (iNOS) and induce oxidative stress, contributing to neuropsychiatric pathogenesis.20 On the other hand, expression of anti-oxidative enzymes like heme oxygenase-1 (HO-1) can reverse oxidative stress and may characterize antidepressant mechanisms.21 Omega-3 PUFAs are anti-inflammatory and anti-oxidative, and therefore could be beneficial in depression and anxiety.16,20,21

The role of omega-3 PUFAs in neuroplasticity

Various chronic antidepressants, which are the current standard treatments, increase adult hippocampal neurogenesis,94,95) and animal studies suggest that the behavioral effects of chronic antidepressants may be mediated by an induction of neuroplasticity and neurogenesis in the brain.95) EPA has been shown to increase cortical concentrations of N-acetyl aspartate, a putative marker of neuronal integrity and function, thereby protecting against excitotoxic apoptosis in a small clinical study.47) In addition, pre-clinical studies have shown that omega-3 PUFAs promote hippocampal neurogenesis in adult animals.96,97) Moreover, omega-3 PUFAs may modulate neurotrophins,98-100) which might be a direct mechanism to mediate neurogenesis and antidepressant effects.

SUMMARY

Nutrition is a modifiable environmental factor that might be important in prevention medicine. Omega-3 PUFAs are well tolerated and accepted, and have been applied for many years as the secondary prevention in various chronic medical diseases and mental disorders. In this review, we found that the clinical evidence about omega-3 PUFAs’ preventive benefits on mood and anxiety disorders is supported by their regulatory effects on immunomodulation, anti-inflammation, signal transduction, neurotransmission and neuroprotection. Our current review calls for more prospective clinical trials in identified high-risk populations to justify the preventive application of omega-3 PUFAs in daily practice.

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