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Biological Mechanism of Antidepressant Effect of Omega–3 Fatty Acids: How Does Fish Oil Act as a 'Mind-Body Interface'?

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Key Words

Major depressive disorder · Depression · Eicosapentaenoic acid · Docosahexaenoic acid · Arachidonic acid · Prostaglandins · Thromboxanes · Leukotrienes · Phospholipase A2 · Cyclo-oxygenase 2

Abstract

The unsatisfactory results of monoamine-based antidepressant therapy and the high occurrence of somatic symptoms and physical illness in patients with depression imply that the serotonin hypothesis is insufficient to approach the aetiology of depression. Depressive disorders with somatic presentation are the most common form of depression. Somatization, the bodily symptoms without organic explanation, is similar to cytokine-induced sickness behaviour. Based on recent evidence, omega–3 polyunsaturated fatty acids (n–3 PUFAs, or n–3 fatty acids) are enlightening a promising path to discover the unsolved of depression, sickness behaviour and to link the connection of mind and body. The PUFAs are classified into n–3 (or omega–3) and n–6 (or omega–6) groups. Eicosapentaenoic acid and docosahexaenoic acid, the major bioactive components of n–3 PUFAs, are not efficiently synthesized in humans and should therefore be obtained directly from the diet, particularly by consuming fish. Docosahexaenoic acid deficiency is associated with dysfunctions of neuronal membrane stability and transmission of serotonin, norepinephrine and dopamine, which might connect to the aetiology of mood and cognitive dysfunction of depression. Likewise, eicosapentaenoic acid is important in balancing the immune function and physical health by reducing membrane arachidonic acid (an n–6 PUFA) and prostaglandin E_2 synthesis, which might be linked to the somatic manifestations and physical comorbidity in depression. The role of n–3 PUFAs in immunity and mood function supports the promising hypothesis of psychoneuroimmunology of depression and provides an excellent interface between 'mind' and 'body'. This review is to provide an overview of the evidence about the role of n–3 PUFAs in depression and its common comorbid physical conditions and to propose mechanisms by which they may modulate molecular and cellular functions.

Introduction

Major depressive disorder (MDD) is a serious psychiatric illness with a high lifetime prevalence rate [1]. However, the current treatment for this high-burden disease is not satisfactory. Less than 50% of patients achieve full remission with optimized medication treatment [2] despite that more than 40 antidepressants with mechanisms related to serotonin, norepinephrine and/or dopamine

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are available on the market. Somatic symptoms, or medically unexplained physical symptoms, are the most common manifestation of depression [3]. Meanwhile, the occurrence of depression is commonly comorbid with physical illnesses. With about 6% experience depression among primary care patients, the prevalence is doubled (12%) among medical inpatients [4]. The unmet need of pharmacotherapy and high occurrence of somatic symptoms and physical illness in depression imply that the current monoamine hypothesis is not enough to approach the aetiology of depression [2, 5].

The phospholipid polyunsaturated fatty acids (PUFAs) hypothesis of depression is enlightening a promising path to discover the unsolved of depression [6–8]. There are two main types of PUFAs in the human body, the omega–6 (n–6) series derived from cis-linoleic acid (LA, 18:2) and the omega–3 (n–3) series derived from α-linolenic acid (ALA, 18:3). n–3 and n–6 PUFAs are important constituents of all cell membranes; they are essential for survival of humans and other mammals, and cannot be synthesized in the body; hence, they have to be obtained from our diet and are, thus, called essential fatty acids [9]. The PUFAs themselves appear to be active in the biological function, while some of their functions require their conversion to eicosanoids and other products. Linoleic acid can be converted to γ-linolenic acid (GLA, 18:3, n–6), and GLA can be elongated to form dihomo-GLA (20:3, n–6), which is the precursor of the 1 series of prostaglandins (PGs). Dihomo-GLA can also be converted to arachidonic acid (AA, 20:4, n–6), which is the precursor of 2 series of PGs, thromboxanes (TXs) and the 4 series of leukotrienes (LTs). α-Linolenic acid can be converted to eicosapentaenoic acid (EPA, 20:5, n–3) and EPA forms the precursor of the 3 series of PGs and the 5 series of LTs. Both PGs and LTs are highly biologically active, have proinflammatory action, and are known to be involved in various pathological processes, such as atherosclerosis, asthma, metabolic syndrome, inflammatory bowel syndrome, neurological diseases, cardiovascular diseases, and cerebrovascular diseases [9–11]. Docosahexaenoic acid (DHA) deficit is associated with dysfunctions of neuronal membrane stability and transmission of serotonin, norepinephrine, and dopamine [6, 12, 13], which might be connected to the aetiology of the mood and cognitive dysfunction of depression. Meanwhile, EPA is important in balancing the immune function and physical health by reducing membrane AA (an n–6 PUFA) and prostaglandin E_2 (PGE2) synthesis [14], and might be associated with medical comorbidity and somatic symptoms in depression.

This review is to provide an overview of the evidence to date about the role of n–3 PUFAs in depression, somatic symptoms, and the common comorbid physical conditions related to depression, and to present some of the mechanisms by which n–3 PUFAs may modulate molecular and cellular functions.

Role of n–3 PUFAs in Depression

It has been observed that societies with a high consumption of fish, which is a good source of n–3 PUFAs, appear to have a lower prevalence of MDD, coronary heart disease mortality, cardiovascular disease mortality, stroke mortality and all-cause mortality [15, 16]. Consistent with the epidemiological finding, it has been found that patients with MDD have lower levels of n–3 PUFAs [17–21], and the level of n–3 PUFAs is significantly negatively correlated with the severity of depressive symptoms [19]. More importantly, two meta-analytic reviews [22, 23] and several clinical trials [13, 24–27] have reported an antidepressant effect of PUFAs. However, another meta-analysis did not support the antidepressant effects of n–3 PUFAs when heterogeneous populations (e.g. community samples) were included [28, 29]; the negative finding needs to be interpreted with caution because of a few limitations such as pooling heterogeneous populations, using different mood assessments, and implementing different intervention methods [30]. In addition, the active component of the antidepressant effect in n–3 PUFAs is still unknown, although it has been argued that EPA might be more effective than DHA [23].

n–3 PUFAs seem to be a promising treatment for depression in several specific populations, including patients with bipolar disorder [26, 31], pregnant women [32], as well as children and adolescents [27]. Patients with bipolar disorder who experience manic episodes also commonly experience depressive episodes or symptoms. In a preliminary trial, Stoll et al. [33] found that n–3 PUFAs could improve the 4-month course of illness in patients with bipolar disorder. According to the data of Stoll et al. [34] and our clinical trial [35], n–3 PUFAs seemed to prevent depression but not mania among the patients with bipolar disorder. This is further supported by the findings that n–3 PUFAs are effective in the treatment of bipolar depression [26, 31], but the result was inconsistent [36]. n–3 PUFA monotherapy has been used for pregnant women because it is thought to be safe and necessary for optimal development in the fetal brain [37]. The use of n–3 PUFA monotherapy for pregnant women

Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN-α therapy and the somatic symptoms in MDD

Symptoms	Prevalence in IFN-α therapy [a], %	Prevalence in MDD [b], %
Fatigue/asthenia	39–90	73
Headache	27–67	33[e]
Gastrointestinal symptoms	50[c, 1]	34–47[f]
Psychomotor slowing	40[c]	59–65[f]
Insomnia	20–39[d]	63
Irritability	35[d]	50
Arthralgia	9–36	31[e]
Musculoskeletal pain	26–32	62–80[g, 2]
Abdominal pain	15–20	21[e]
Anorexia	13–19	40
Anxiety	13–18[d]	57
Poor concentration	14[d]	51

[a] [46], unless otherwise specified; [b] [99], unless otherwise specified; [c] [100]; [d] [101]; [e] [102]; [f] [103]; [g] [104].
[1] Nausea, vomiting, bowel problems.
[2] Result from depressed inpatient population.

with depression has recently been supported by our 8-week, double-blind, placebo-controlled study, revealing that subjects treated with n–3 PUFAs had significant lower scores on the Hamilton Depression Rating Scale, a higher response rate, and a higher remission rate at the end of the study [32].

Role of n–3 PUFAs in Sickness Behaviour and Somatic Symptoms

Depressive disorders with predominantly somatic presentation are the most common forms of depression. In a clinical study, somatic symptoms, particularly somatic anxiety and fatigue, were documented in up to 80% of a sample of major depression [38]. Two of the three most common symptoms (low mood: 76%, fatigue: 73%, sleep disturbances: 63%) reported during a current depressive episode were somatic, as shown in the Depression Research in European Society II study [39]. Somatic symptoms were the main reason for the initial visit to the primary care physician [40]. In a US study, two thirds (69%) of depressed patients complained of general aches and pains, implying the close relationship between painful somatic symptoms and depression [41].

Somatic symptoms are similar to typical symptoms of sickness, including general weakness, malaise, fatigue, muscle and joint aches, loss of interest in the surroundings, loss of appetite, and inability to concentrate [42, 43]. The idea of sickness behaviour sprang from a series of observed symptoms related to infection and cytokine/PG administration in humans and animals [44]. For example, in patients receiving interferon-α (IFN-α) therapy for chronic hepatitis C virus (HCV) infection or cancers, almost all patients experience an acute cytokine-induced sickness behaviour [45–48]. Table 1 indicates that the symptoms of acute sickness behaviour induced by IFN-α therapy also commonly manifest as somatic symptoms in patients with MDD. In fact, somatisation in patients with or without depression has been proposed as 'the outward manifestation of sensitization of the brain cytokine system that is normally activated in response to activation of the innate immune system and mediates the subjective, behavioural, and physiological components of sickness [49]'.

Symptoms of cytokine-induced sickness behaviour are mediated by PGs [43, 50–52]. The endogenous metabolism of PGs can be modulated by dietary supplementation with PUFAs [53]. AA, an n–6 PUFA, is the major substrate for PGE2. An AA-enriched diet can increase glucocorticoid and PGE2 secretion as well as anxiety behaviour [54]. In contrast, EPA can suppress proinflammatory effects of AA [55], thereby reducing PGE2 synthesis [55] and attenuating interleukin (IL)-1β-induced activation of PGE2 [56]. Foods enriched with ethyl-EPA, but not soybean oil, significantly attenuated most of the IL-1β-induced sickness, stress and anxiety-like behaviours [57].

According to the evidence on the effects of EPA on antagonizing sickness behaviour in animals, we hypothesised that EPA might be specifically deficient in patients with cytokine-induced sickness behaviour. As mentioned previously, IFN-α can induce sickness behaviour and depression in a significant proportion of patients receiving this treatment; hence, this can provide an excellent model to study somatic symptoms in depression. By using this model, we have found that patients with HCV who had lower EPA levels at the early stage of IFN-α therapy developed more IFN-α-induced sickness behaviour [Su et al., in preparation].

Role of n–3 PUFAs in Medical Conditions

Chronic low-grade systemic inflammation is a feature of chronic diseases such as metabolic syndrome, type 2 diabetes [58], cardiovascular disease [59], coronary artery

disease, cancers [60], and dementia [61], which are all commonly comorbid in patients with depression [4, 62]. It is evident that PUFAs and their metabolic derivatives participate in the pathobiology of inflammation. The proinflammatory eicosanoids PGE2 and LTB4 are derived from AA, whereas anti-inflammatory LTs, PGD2, PGE1, PGIs, are derived from EPA and DHA [55]. Proinflammatory cytokines induce oxidative stress by enhancing the production of free radicals by monocytes, macrophages, and leukocytes. Increased production of proinflammatory cytokines, such as IL-1, IL-2, IL-6, and TNF-α, and free radicals, occur due to shear stress, hyperglycaemia, clinical or sub-clinical infections, and low-grade systemic inflammation, as seen in type 2 diabetes mellitus, hypertension, hyperlipidaemia, and metabolic syndrome X. EPA, DHA, and high-density lipoprotein (HDL) inhibit free radical generation and thus prevent oxidant stress [9].

The amount and type of PUFAs released in response to inflammatory stimuli depends on the cell membrane phospholipid fatty acid composition, which is determined by dietary intake and the regulatory enzymes. The beneficial effect of fish consumption with a high amount of EPA and DHA might be attributed to the displacement of AA from the cell membrane phospholipid pool and to a preferential formation of less proinflammatory PGs (such as PGE3, PGF3α, TXA3), and LTs (such as LTB5, LTC5, and LTD5) [9]. In summary, the role of n–3 PUFAs on medical conditions might be mediated by the inflammatory function related to themselves or their active bio-products.

Biological Mechanism of the Effect of n–3 PUFAs on Depression and Medical Illness Comorbidity

The biological mechanisms to explain the role of n–3 fatty acids in depression are the regulation of neurotransmitters and signal transduction by PUFAs. The change in fatty acid concentration in the brain, induced by chronic deficiency in dietary n–3 fatty acids, could lead to an increase in serotonin 2 (5-HT_2) and decrease in dopamine 2 receptor density in the frontal cortex [63–68]. The upregulation of 5-$HT_{2A/C}$ receptors and downregulation of dopamine receptor are thought to play a role in the pathophysiology of depression [69]. Furthermore, high cerebrospinal fluid concentration 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 n–3 PUFAs among healthy subjects [70]. Biochemical studies have also shown that n–3 PUFAs increased cerebrospinal fluid 5-HIAA concentration and somatotrophin release [71], which are commonly associated with the improvement of depressive symptoms.

The involvement of n–3 PUFAs' effects in depression, sickness behaviours and comorbid physical illness may be associated with the 'PUFAs-PGE2 cascade'. In brief, the PUFAs and their metabolites, the eicosanoids (PGs, LTs, or TXs), might be important in modulating biological processes related to brain and physical functions. The PUFAs-PGE2 cascade hypothesis in mood disorders has been supported by a large body of evidence, including higher levels of AA [20, 72] and PGE2 [73, 74] in patients with mood disorders [75], the inhibitory effect on phospholipase A2 (PLA2) activity of mood stabilizers [76, 77], and the antidepressant effect of n–3 PUFAs in mood disorders [23, 33]. Chronic low-grade systemic inflammation plays a significant role in several chronic medical diseases as well as depression [78]. Interestingly, animals fed high AA diet or treated with PGE2 produced sickness behaviours of anorexia, low activity, change in sleep pattern and attention [56, 57]. n–3 PUFAs have an anti-inflammatory effect by antagonizing membrane AA and reducing PGE2 synthesis [79]. Interestingly, the fundamental works by Stanley Rapoport and colleagues have revealed that the current mood stabilizers, including lithium, valproate, and carbamazepine used in treating mood disorders all have an effect on this 'PUFAs-PGE2 cascade' pathway [80, 81].

The other possible biological mechanisms of the beneficial effects of n–3 PUFAs on mood and physical illness [22, 82] are: regulation of the corticotropin-releasing factor, inhibition of protein kinase C, suppression of phosphatidylinositol-associated second messenger activity, modulation of heart rate variability via parasympathetic nervous system, increased dendritic arborization and synapse formation, promotion of neuroprotection and prevention of neuronal apoptosis, and synthesis of neuroprotectin D1 [83] inhibit angiotensin-converting enzyme and 3-hydroxy-3-methylglutaryl coenzyme A reductase activities, and their competition with AA for enzymatic action and the resultant reduction in the inflammatory response.

How Does Fish Oil Act as a 'Mind-Body Interface'?

Based on the extensive evidence that supports the role of n–3 PUFAs in depression, sickness behaviour, and comorbid physical conditions, and the molecular and cellular mechanisms that link them, I propose that n–3 PUFAs act as an interface between 'mind' and 'body'. Fig-

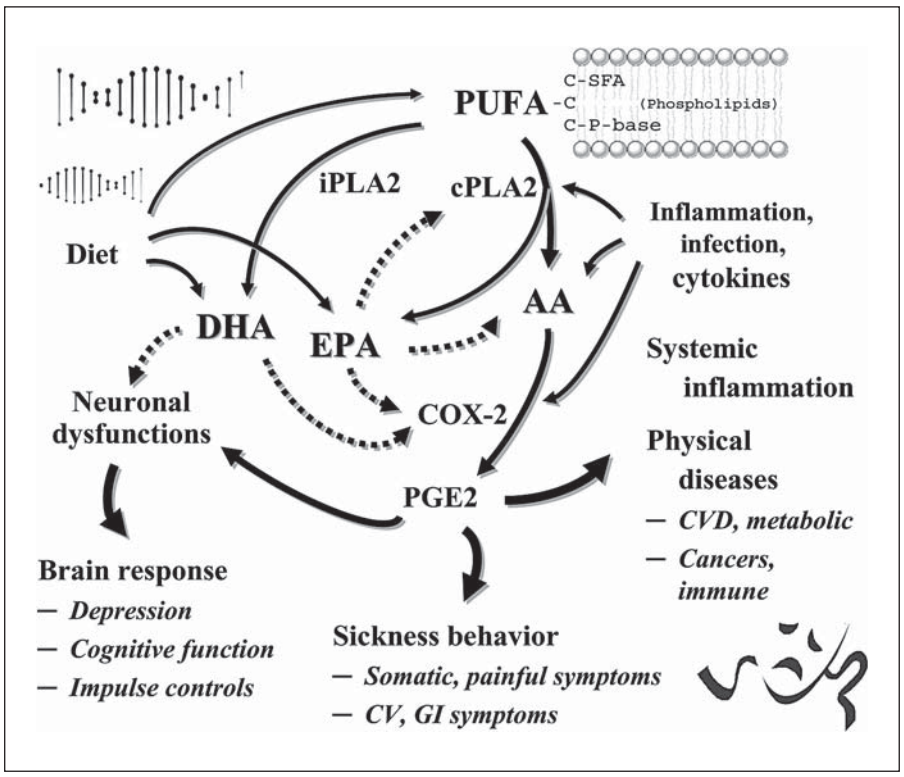

Fig. 1. Genetic and environmental factors related to n–3 fatty acids hypothesis of sickness behaviour and depression. The levels of EPA and DHA are influenced by genetic (e.g. PLA2 and COX2 genes) and environmental (e.g. diet, infection, inflammation or cytokines) factors. DHA comprise 10–20% of total fatty acid composition in the brain, and play a major role in neuronal membrane stability and functions of signal transduction and neurotransmission. EPA, although comprising only 0.1% of total brain fatty acid composition, is important in balancing the immune/inflammatory functions by antagonizing membrane AA and reducing PGE2 synthesis. PLA2 is a large family of enzymes, with the iPLA2 preferentially functioning in DHA metabolism and the cPLA2 preferentially in AA and EPA metabolism. COX2 is the key enzyme that converts AA to PGE2. PGE2 participates in immune regulation, neuronal function, and signal transduction, which might be associated with brain dysfunctions related to somatic symptoms of depression, sickness behaviours and several physical diseases. Diet, inflammatory reactions, PLA2 and COX2 activities, and variations of PLA2 and COX2 genes, might all have an effect on depression and sickness behaviours. Enhancement is shown by a solid line, attenuation by a dashed line. CV = Cardiovascular; CVD = cardiovascular disease; GI = gastrointestinal; P-base = phosphatidyl base.

ure 1 illustrates the genetic and environmental factors related to the n–3 fatty acids hypothesis on physical illness, sickness behaviour and depression.

As reviewed previously, DHA is important in neuronal membrane stability, neuroplasticity, signal transduction and neurotransmission, which might be connected to the aetiology of mood and cognitive dysfunction of depression. Meanwhile, EPA can regulate the synthesis of AA and PGE2 to modulate inflammatory and immune functions, which might be connected to the somatic manifestations and physical health. The levels of EPA and DHA can be influenced by genetic and environmental factors. PLA2 is a large family of enzymes, with the Ca^{2+}-independent PLA2 (iPLA2) preferentially functioning in DHA metabolism and the cytosolic PLA2 (cPLA2) preferentially in AA and EPA metabolism. The cPLA2 has been reported to be involved in inflammatory reaction, intestinal ulceration, acute lung injury, polyposis, brain injury through ischemia/reperfusion, anaphylaxis, parturition and pain reaction [84, 85]. Furthermore, a G allele of Ban I polymorphism on cPLA2 has been found to increase the risk of developing depression in a Korean population [86]. Using the model of IFN-α-induced sickness behaviour and depression, we also have found that patients with HCV who had Ban I GG genotype had a higher risk of developing depression and physical symptoms than pa-

tients with Ban I AA/AG genotypes [87]. Cyclo-oxygenase-2 (COX2) is the key enzyme that converts AA to PGE2. PGE2 participates in immune regulation, neuronal function, and signal transduction, which might be associated with brain dysfunctions related to depression, sickness behaviours and several physical diseases [88].

Furthermore, it has been extensively reported that proinflammatory cytokines, such as IL-1, IL-2, and IFN-γ, have effects on activities of PLA2 or COX2 and levels of n–6 PUFA AA. For example, treatment with IL-1 can induce the activations of cPLA2 in human airway smooth muscle (ASM) cells [89], sPLA2 and cPLA2 in rat dorsal root ganglion cells [90], and COX2 in human neuroblastoma cell line [91] and ASM cells [92]. Similarly, IFN-α can induce the activation of PLA2 and a rapid release of AA from the pre-labelled membrane phospholipid in mouse fibroblasts [93]. IFN-γ can increase the cPLA2 mRNA in the human bronchial epithelial cell line after 2–24 h of treatment [94]. In patients receiving IL-2 therapy, a systemic release of PLA2 has also been found by assessing the serial plasma sample during the first day after IL-2 infusion [95]. Consequently, the activation of PLA2 or COX2 can induce the release of AA from the membrane phospholipid [94, 96, 97]. n–3 PUFAs, on the other hand, can reduce the activation of cPLA2 and the release of AA and PGE2 induced by IL-1 [98].

Conclusions

The phospholipid hypothesis of depression is promising, and it can be supported by numerous data on the effects of n–3 PUFAs on immunomodulation, signal transduction, neurotransmission and neuroprotection. Indeed, n–3 PUFAs are safe, important in health, and beneficial for depressed patients in specific populations such as pregnant women, children, and patients with cardiovascular, cerebrovascular, immunological, or oncologic disease comorbidities. It is hoped that this review provides an insight into understanding depression and the link between the body and the mind.

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