Review Article

Mind-body interface: the role of n–3 fatty acids in psychoneuroimmunology, somatic presentation, and medical illness comorbidity of depression

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With the unsatisfaction of monoamine-based pharmacotherapy and the high comorbidity of other medical illness in depression, the serotonin hypothesis seems to fail in approaching the aetiology of depression. Based upon the evidence from epidemiological data, case-control studies of phospholipid polyunsaturated fatty acids (PUFAs) levels in human tissues, and antidepressant effect in clinical trials, PUFAs have shed a light to discover the unsolved of depression and connect the mind and body. Briefly, the deficit of n-3 PUFAs has been reported to be associated with neurological, cardiovascular, cerebrovascular, autoimmune, metabolic diseases and cancers. Recent studies revealed that the deficit of n-3 PUFAs is also associated with depression. For example, societies that consume a small amount of omega-3 PUFAs appear to have a higher prevalence of major depressive disorder. In addition, depressive patients had showed a lower level of omega-3 PUFAs; and the antidepressant effect of PUFAs had been reported in a number of clinical trials. The PUFAs are classified into n-3 (or omega-3) and n-6 (or omega-6) groups. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the major bioactive components of n-3 PUFAs, are not synthesized in human body and can only be obtained directly from the diet, particularly by consuming fish. DHA deficit 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. On the other hand, EPA is important in balancing the immune function and physical healthy by reducing arachidonic acid (AA, an n-6 PUFA) level on cell membrane and prostaglandin E2 (PGE2) synthesis. Interestingly, animals fed with high AA diet or treated with PGE2 were observed to present sickness behaviours of anorexia, low activity, change in sleep pattern and attention, which are similar to somatic symptoms of depression in human. Therefore, the deficit of EPA and DHA in depression might be associated with mood disturbance, cognitive dysfunction, medical comorbidity and somatic symptoms in depression. Indeed, the role of n-3 PUFAs in immunity and mood function supports the promising psychoneuroimmunologic hypothesis of depression and provides an excellent interface shared by body and mind.

Key Words: major depressive disorder, depression, polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), Phospholipase A2 (PLA2), cyclo-oxygenase 2 (COX2)

INTRODUCTION

The growing burden of depression is evident by the projection that depression will be the second leading cause of disease or injury in the world by 2020.[1] Less than 50% of patients achieve full remission with optimized medication treatment,[2] despite the good availability of antidepressants on the market, among which are more than 40 drugs developed with the mechanisms related to serotonin, norepinephrine and/or dopamine. Depression frequently presents with medical comorbidity. The prevalence of major depression increases from 3%–5%, 5%–10%, to 10%–14% when the studied subjects moved from community settings, primary-care settings, to inpatient medical settings, respectively.[3] The unsatisfactory outcome of pharmacotherapy and high comorbidity with physical illness imply that the monoamine hypothesis is insufficient to approach the aetiology of depression.[2,4]

The phospholipid polyunsaturated fatty acids (PUFAs) hypothesis of depression is shedding a light to discover the unsolved of depression.[5-7] There are two main types of PUFAs in 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 components of all cell membranes, essential for humans and other mammals, and they cannot be synthesized in the body; hence, they have

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Manuscript received 9 September 2007. Accepted 3 December 2007.

to be obtained in our diet and, thus, are called essential fatty acids (EFAs).[8] The PUFAs themselves appear to be active in biological function, while some of their functions require their conversion to eicosanoids and other products. ALA can be converted to eicosapentaenoic acid (EPA, 20:5, n-3) and docosahexaenoic acid (DHA). EPA forms the precursor of the 3 series of PGs and the 5 series of LTs. LA can be converted to γ-linolenic acid (GLA, 18:3, n-6) and GLA can be elongated to form dihomo-GLA (DGLA, 20:3, n-6), which is the precursor of the 1 series of prostaglandins (PGs). DGLA can be further 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). Both PGs and LTs are highly biologically active, have anti- or pro-inflammatory actions, and are known to be involved in various pathological processes, such as atherosclerosis, asthma, metabolic syndrome X, inflammatory bowel disease, neurological, cardiovascular, cerebrovascular, autoimmune, and several other inflammatory conditions.[8-10] DHA deficit is associated with dysfunctions of neuronal membrane stability and transmission of serotonin, norepinephrine and dopamine, which might connect to aetiology of mood and cognitive dysfunction of depression. On the other hand, EPA is important in balancing the immune function and physical healthy by reducing membrane arachidonic acid (AA, an n-6 PUFA) and prostaglandin E2 (PGE2) synthesis, and might be associated with medical comorbidity and somatic symptoms in depression.

The role of omega-3 polyunsaturated fatty acids (PUFAs) on depression

Major depressive disorder (MDD) is a serious affective illness with a high prevalence rate.[11] The occurrence of depression is commonly comorbid with other medical illnesses. While 6% of primary care patients experience depression, the prevalence is higher (12%) among medical inpatients.[12] Furthermore, the annual prevalence of major depressive disorder shows nearly a 60-fold variation across countries.[13] It is similar to the cross-national differences in coronary artery disease mortality, which suggests that similar dietary risk factors might be important.[14,15] Specifically, societies with a high consumption of fish, in which contains more n-3 PUFAs, appear to have a lower prevalence of major depressive disorder, coronary heart disease mortality, cardiovascular disease mortality, stroke mortality and all cause mortality.[15-17]

Interestingly, n-3 PUFAs have been reported recently to be effective in treatment of depressive disorders. A mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in high dosage was effective in a case report of a pregnant depressive woman.[18] EPA alone[19-21] or a combination of EPA and DHA[22] had positive effects for patients with major depressive disorder; however, two studies of DHA treatment showed no effect.[23,24] Moreover, omega-3 PUFAs might be effective in treatment of bipolar depression,[25,26] but the result was inconsistent.[27] In the preliminary trial, Stoll et al. found that n-3 PUFAs could improve the 4-month course of illness in patients with bipolar disorder.[28] Along with further analysis with Stoll's data,[29] and our clinical trial,[30] n-3 PUFAs were found a preventive effect on depression but not "antimania" among the patients with bipolar disorder. However, 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.[31]

The mechanism of the antidepressant effect of n-3 PUFAs is not yet elucidated. One of the explanations is the biological regulation of neurotransmitters and signal transduction by PUFAs.[5,32,33] The change of PUFAs concentration in the brain could alter serotonergic and dopaminergic neurotransmission and then leaded to an increase in 5-HT_2 and decrease in D_2 frontal cortex receptor density.[34] The upregulation of 5-$HT_{2A/C}$ is thought to play a role in the pathophysiology of depression.[35] The other explanation is that omega-3 PUFAs play an important role on mood stabilization by targeting on parts of the "arachidonic acid cascade", which has been identified as one of the mechanisms of mood stabilization.[36] The "arachidonic acid cascade" hypothesis in mood disorders has been supported by a number of evidences, including the higher ratio of AA[37-39] and hyperactivity of its major metabolic enzyme phospholipase A2 (PLA2) in patients with mood disorders,[40] the inhibitory effect on PLA2 activity of mood stabilizers,[41-44] and the therapeutic effect of n-3 PUFAs in mood disorders.[18-22,28]

EPA and DHA, the major bioactive components of omega-3 PUFAs, can not be synthesized in human body and can only be obtained directly from the diet, particularly in by consuming fish.[45] DHA, the main omega-3 fatty acid in brain, comprises 10–20% of total fatty acids composition, whereas the other omega-3 fatty acids like α-linolenic acid (ALA), EPA, and docosapentaenoic acid (DPA) comprise only 0.1% of total brain composition.[46] DHA is associated with neuronal membrane stability and functions of serotonin and dopamine transmission, which might connect to depression.[5,22,34] On the other hand, EPA is important in balancing the immune and neuronal functions by antagonizing membrane arachidonic acid (AA, an n-6 PUFA) and reducing prostaglandin E2 (PGE2) synthesis.[47] Interestingly, animals fed with high AA diet or treated with PGE2 were found to demonstrate sickness behaviours like anorexia, low activity, change in sleep pattern and attention,[48,49] which are similar to somatic symptoms of depression in human.[50] In addition to immune modulation, EPA might have a beneficial effect on improving the hypothalamic-pituitary-adrenal axis dysfunction and treatment-resistant depression through the action of p-glycoprotein (p-gp) and multi-drug resistance receptors.[51,52]

Consistently, with the findings from epidemiological data and recent clinical trials, the abnormal fatty acid compositions on cell membrane in patients with mood disorders have been reported extensively.[37-39,53-61] In 1996, Maes and colleagues reported that depressive patients had significantly higher levels of AA in phospholipids, AA/EPA ratio in both serum cholesteryl esters and phospholipids and n6/n3 ratio in cholesteryl esters; and lower levels of EPA in both serum cholesteryl esters and phospholipids and total n-3 fatty acid in cholesteryl esters.[39] Adams et al reported that there was a significant correlation between the ratio of erythrocyte AA/EPA and severity of depression.[56] However, Peet and colleagues reported that the only abnormal erythrocyte PUFA's level

was lower DHA, but not EPA or AA.[60] In contradiction to their previous report,[39] the level of AA was reported to be significantly lower in depressive patients in Maes's later report.[38] Depressed elderly patients had lower levels of DHA and higher levels of AA, higher ratio of n-6/n-3, AA/EPA and AA/DHA, than healthy volunteers.[61] In a sample of patients with acute coronary syndromes, the depressive patients had lower DHA, EPA and total n-3 PUFAs; and higher AA, higher ratio of n-6/n-3, AA/EPA and AA/DHA than those without depression.[53] In the subjects with suicide risk, a lower DHA and a higher n-6/n-3 ratio had been reported to predict more future suicide attempts.[54] The similar finding of lower DHA, EPA and total n-3 PUFAs and higher n-6/n-3 ratio had been report in the case-control study of Chinese patients who had suicide attempt.[59] The deficit in PUFA levels and abnormal compositions had been reported in other mood disorders, including lower DHA and total omega-3 PUFAs in postpartum depression;[57] lower DHA and EPA in social anxiety disorder;[55] and lower DHA and AA in bipolar disorder.[37]

As mentioned previously, DHA, EPA and n-6 PUFA AA, are different in their biological functions. Since depression is heterogeneous in terms of aetiology and symptom presentation, the differentiation of depressive symptom clusters could be due to the various patterns of PUFAs deficits. However, the association between depressive symptom clusters and the variation of individual PUFAs level has not been determined yet.

Somatic symptoms in depression: Role of AA and EPA on sickness behaviour and somatic symptoms

Depressive disorders with predominantly somatic presentation are the most common form of depression. In a clinical study, somatic symptoms, particularly somatic anxiety and fatigue, were accounted for up to 80% of major depression.[62] Two out of the three most common symptoms (low mood: 76%, fatigue: 73% and sleep disturbances: 63%) reported during a current depressive episode could be determined as somatic ones, as shown in the European Study Society study (DEPRES II).[63] Somatic symptoms were the main reason for the initial visit to the primary care physician.[64] In a US study, two thirds (69%) of depressed patients complained about general aches and pains, implying the close relationship between painful somatic symptoms and depression.[65]

Typical symptoms of sickness include weakness, malaise, fatigue, muscle and joint aches, loss of interest in their surroundings, loss of appetite, and inability to concentrate, which are similar to somatic symptoms of depression.[66,67] The idea of sickness behaviour[68] is from a series of observed symptoms related to infection and cytokine/prostaglandins administration in human and animals. Sick individuals are somewhat depressed and lethargic. Symptoms of sickness behaviour are not specific to identify the underlying pathological process, therefore most physicians do not pay much attention to them.[69] However, since cytokine-induced sickness behaviours provide a good model to study the effect of cytokine in the brain and behaviours, more neuroscientists show a greater interest on it (see reviews[67,69-72]).

Symptoms of cytokine-induced sickness behaviour are mediated by prostaglandins (PGs).[67,73-75] The endogenous metabolism of PGs can be modulated by dietary supplementation with PUFAs.[45] N-6 PUFA, AA is the major substrate for PGE2. An AA-enriched diet can increase glucocorticoid and PGE2 secretion, as well as anxiety behaviour.[76] In contrast, EPA can suppress proinflammatory effects of AA, thereby reducing PGE2 synthesis [77] and attenuating IL-1β's effect to activate PGE2.[48] Food enriched with ethyl-EPA (n-3 PUFA), but not soybean oil (n-6 PUFA), significantly attenuated most of the IL-1β and thus induced sickness, stress and anxiety-like behaviours.[49] According to the evidence of EPA effect on antagonizing sickness behaviour in animals, we form the hypothesis that EPA might be specifically impair in depressed patients with prominent somatic symptoms and will respond well to EPA treatment in this proposal.

The role of n-3 polyunsaturated fatty acids (PUFAs) on medical conditions

Chronic low-grade systemic inflammation is a feature of chronic diseases, such as metabolic syndrome, type 2 diabetes,[78] cardiovascular disease,[79] coronary artery disease, erectile dysfunction,[80] cancers,[81] dementia,[82] which are highly comorbid in depression.[3,12] It is evident that PUFAs and their products participate in the pathobiology of inflammation. The proinflammatory eicosanoids PGE2 and LTB4 are derived from the n-6 PUFAs AA, whereas anti-inflammatory LTs, PGD2, PGE1, PGIs, are derived from n-3 PUFAs EPA and DHA.[77] Proinflammatory cytokines induce oxidant stress, which enhances 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 occurs due to 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.[8]

The amount and type of PUFAs released in response to inflammation depends on the phospholipid fatty acid composition on cell membrane, which is determined by the dietary intake and the regulatory enzymes. The beneficial effect of fish consumption with high contents of EPA and DHA might be attributed to the displacement of AA from the cell membrane phospholipid and to a preferential formation of less proinflammatory PGs (such as PGE3, PGF3α, TXA3), and LTs (such as LTB5, LTC5, and LTD5).[8] In summary, the role of n-3 PUFAs on medical conditions might be mediated with the inflammatory function related to themselves or their active bioproducts.

The regulatory enzymes for PUFAs have effects on inflammatory process and pathogenesis of several medical conditions. Phospholipase A2 (PLA2) is the key enzyme of the phospholipids metabolism. The superfamily of PLA2 enzymes currently consists of 15 Groups and many subgroups includes five distinct types of enzymes, namely the secreted PLA2s (sPLA2), the cytosolic PLA2s (cPLA2), the Ca2+ independent PLA2s (iPLA2), the platelet-activating factor acetylhydrolases (PAF-AH), and the lysosomal PLA2s.[83] The main subtype of PLA2

enzymes is the cPLA2, which has a 50-fold preference for catalyzing the release of AA from membrane phospholipids.[84] The cPLA2 is involved in inflammation, intestinal ulceration, acute lung injury, polyposis, brain injury through ischemia/reperfusion, anaphylaxis, parturition and pain reaction.[85,86] PAF-AH, or lipoprotein-associated phospholipase A2 (LP-PLA2), is an important inflammatory marker that is used to assess the risk for cardiovascular disease (CVD) and associated conditions.[87] Cyclooxygenase 2 (COX2) converts AA into PGE2, which is participant in many cellular responses and pathophysiologic processes including modulation of the inflammatory reaction, erosion of cartilage and juxtaarticular bone, gastrointestinal cytoprotection and ulceration, angiogenesis and cancer, hemostasis and thrombosis, renal hemodynamics, and progression of kidney disease,[88] as well as mood disorders.[36]

Genetic regulation of PUFAs and PGE2 metabolism in depression and somatization

The gene for cPLA2, *PLA2G4A*, has been cloned and localized to chromosome 1q25.[89,90] Interestingly, the gene coding for COX2 (also known as prostaglandin-endoperoxidase synthase 2, hence the name, *PTGS2*) is immediately centromeric of the *cPLA2* locus. These two gene loci are arranged in a head-to-head configuration, and hence potentially share a common regulatory region. Six single nucleotide polymorphisms (SNPs) present in the PTGS2/PLA2 locus have been detected among 118 British family trios of schizophrenia patients, and a SNP termed by the authors as SNP4 (located in the 5'-flanking region in the first intron of the gene which creates a *Ban*I polymorphic site) was associated with schizophrenia.[91] Some studies have repeated the findings of association between this *Ban* I polymorphism of the PLA2 gene and schizophrenia,[91-93] but the other studies failed to demonstrate the association.[94-97] Recently, Pae and colleagues found an association between this *Ban*I polymorphism of the cPLA2 gene and depression in a Korean population, which showed a significant excess of A2/A2 (G/G genotype precisely) homozygotes.[98]

The hypothesis here is that this *Ban*I polymorphism, and other variations of genes involved in PUFAs and PGE2 metabolism, might have an effect on PUFAs' levels and somatic/anxiety symptom clusters rather than depressive disorder as a whole. For example, Tao et al. found that *Ban*I polymorphism is likely to contribute to the development of negative symptoms of schizophrenia.[99] When examining the association of *Ban*I polymorphism with every symptom cluster in 82 patients with major depressive disorder, we found that *Ban*I is associated with only somatic anxiety symptom cluster (Chen et al, *submitted*). With chronic hepatitis C patients receiving interferon-α (IFN-α) treatment as a model of somatic symptoms in depression, we found that there are significant effects of cPLA2 *Ban*I and COX-2 rs4648308 polymorphisms on IFN-induced depression and somatic symptoms. Specifically, the allelic association of *Ban*I polymorphism of cPLA2 gene revealed that G allele had a significant effect on the development of IFN-induced depression. Subjects with the genotype G/G of *Ban*I polymorphism had an increased risk of IFN-induced depression. In addition, subjects with the A/G of COX-2 rs4648308 polymorphism also had an increased risk than those with G/G (Su et al, *submitted*). In the future, the studies would need to focus on the associations among *PLA2G4A*, *PTGS2* genes, levels of PUFAs, and the somatic symptoms in depression.

SUMMARY

The phospholipid hypothesis of depression seems to be promising and has been supported by numerous evidences of omega-3 PUFAs effects on immunomodulation, signal transduction, neurotransmission and neuroprotection. Indeed, omega-3 PUFAs are safe, health promoted, and have several advantages for pregnant mothers, newborns, children, and patients with cardiovascular, cerebrovascular, immunological, or oncologic diseases. This review, with anticipation, can provide an insight of better understanding of depression and the interface between body and mind.

AUTHOR DISCLOSURES

Kuan-Pin Su, no conflicts of interest.

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