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Review article

Inflammation in psychopathology of depression: Clinical, biological, and therapeutic implications

Kuan-Pin Su [a,b,*]

[a] *Graduate Institute of Neural and Cognitive Sciences, School of Medicine, China Medical University, Taichung, Taiwan*
[b] *Department of Psychiatry and Mind-Body Research Center (MBI-Lab), China Medical University Hospital, Taichung, Taiwan*

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ABSTRACT

Increasing evidence suggests that inflammation responses play an important role in the pathophysiology of depression. Clinically depressed patients manifest higher levels of inflammatory biomarkers, while proinflammatory cytokines induce neuropsychiatric symptoms (sickness behavior) as well as major depressive episode. Mechanisms that might be responsible for inflammation-mediated neuropsychiatric and depressive symptoms are vital in understanding "mind–body" interface; these have been studied in clinical and animal models (e.g., interferon-α-induced depression in patients with chronic hepatitis C, one of the most notable clinical models for testing inflammation theory of depression and an excellent approach to investigate development of depression in a prospective manner). Furthermore, the anti-inflammatory pathway has become a hot topic in looking for new antidepressant therapies. Recently, omega-3 polyunsaturated fatty acids (omega-3 PUFAs or n-3 PUFAs) have gained more attention as a promising treatment for depression. raEicosapentanoic acid and docosahexanoic acid, major bioactive components of omega-3 PUFAs, are both natural anti-inflammatory and antidepressant agents. Here, we review recent epidemiological studies, cross-sectional and longitudinal case-controlled studies, interventional clinical trials, as well as basic animal and cellular studies to prove the linkage among omega-3 PUFAs, inflammation, and depression.

1. Introduction

The growing burden of major depressive disorder (MDD) is evidenced by the projection that depression will become a leading cause of disease or injury worldwide by 2020 [1]. MDD is a serious psychiatric illness with a high lifetime prevalence rate up to one-tenth or one-fifth [2]. In general medical practice, at least one in 10 outpatients has this condition; most cases go unrecognized or are inappropriately treated, leading to loss of productivity, functional decline, and higher mortality [2]. Nevertheless, currently available treatments fail to address many crucial needs of patients adequately, making this illness difficult to treat and burdensome to the patients life, family, and career.

Abbreviations: arachidonic acid, (AA); docosahexaenoic acid, (DHA); eicosapentaenoic acid, (EPA); patients with chronic hepatitis C viral, (HCV); interferon, (IFN); interleukin, (IL); polyunsaturated fatty acids, (PUFAs); tumor necrotic factor, (TNF).

* Department of Psychiatry, China Medical University Hospital, Number 2, Yuh-Der Road, Taichung 404, Taiwan.
E-mail address: cobolsu@gmail.com.

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Clinical features, biological markers, and treatment outcomes are heterogeneous. According to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV), and/or the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision, individuals within diagnostic categories of MDD have distinct clinical manifestations. Use of the current diagnostic schemas thus undoubtedly contributes to difficulties in finding any single biological or genetic marker [3]. Treatment efficacy and occurrence of adverse effects associated with specific antidepressants vary widely among patients. Accordingly, with the unsatisfactory outcome of pharmacotherapy and small-to-moderate effect sizes from most biomarker studies and clinical trials, it is impossible to explain the whole picture of etiology of MDD with any single hypothesis. The inflammation theory lights a promising path to resolve the dilemma of depression. Clinical patients exhibit higher levels of inflammatory biomarkers [4]. Administration of therapeutic cytokine interferon-α (IFN-α) can lead to clinical depression [5]. In fact, it has become a hot topic in medical research to look for antidepressant therapies from anti-inflammatory pathways [4]. Chronic inflammation is linked with early childhood trauma, major psychiatric disorders, and several physical diseases; the inflammation theory provides a window to investigate the mind–body interface.

Nowadays, omega-3 polyunsaturated fatty acids (omega-3 PUFAs or n-3 PUFAs) provide a promising path to understand the neurobiology of depression. The human body holds two main serial types of PUFAs: omega-6 (n-6) derived from *cis*-linoleic acid (LA, 18:2) and omega-3 (n-3) derived from α-linolenic acid (ALA, 18:3). Omega-3 PUFAs like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and omega-6 PUFAs like arachidonic acid (AA) are important constituents of all cell membranes, which are essential for survival of humans and other mammals. They cannot be synthesized in the body but must be obtained from our diet and are thus called essential fatty acids [6]. PUFAs themselves appear active in biological function; some of their functions require conversion to eicosanoids and products like prostaglandins, thromboxanes (TXs), and leukotrienes (LTs). Deficit of omega-3 PUFAs is reported to be associated with neurological, cardiovascular, cerebrovascular, autoimmune, and metabolic diseases, as well as bipolar disorder and depression [6]. This review summarizes current evidence about omega-3 PUFA biological mechanisms of and inflammation in depression.

2. Inflammation theory of depression

Increasing evidence suggests inflammation response playing an important role in pathophysiology of depression: for example, patients with elevated C-reactive protein, acute phase proteins, and proinflammatory cytokines [4]. The latter include tumor necrotic factor (TNF-α), interleukin (IL-1-beta, IL-6, soluble TNF-R2, soluble IL6-R), and interferon (IFN-γ and IFN-α), all found to interact with many pathophysiological domains that characterize depression: neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and behavior [5]. Systemic inflammatory challenges like lipopolysaccharide or proinflammatory cytokine not only cause a systemic inflammation, but also induce central neuroinflammation for sustained periods [7]. A series of behavioral changes induced by neuroinflammation in experiment animals include anorexia, sleep abnormalities, reduction of locomotor activity and exploration, anhedonia, and cognitive disturbances, which share a strong similarity with somatic symptoms of depression. Sick individuals are somewhat depressed and lethargic. The idea of sickness behavior emanates from a series of observed symptoms related to infection and cytokine/prostaglandins administration in humans and animals. It offers us a good model to study the effects of cytokine on the brain and behavior [6,8].

Excessive secretion of proinflammatory cytokines is proposed to cause depression [9]. Microglia are resident macrophages of the brain, acting as chief immune defense in the central nervous system [10]. Neuroinflammatory processes are proposed as contributing to neuropsychiatric disorders like Alzheimer's or Parkinson's disease, as well as depression, via microglial activation [10]. Engagement of immune-to-brain communication pathways by proinflammatory cytokines (e.g., IFN-α, IFN-γ, IL-1) ultimately leads to microglial activation and triggers inflammatory signaling pathways [10,11]. Upon activation, microglia up-regulate the expression of detrimental factors of reactive oxygen species such as nitric oxide via inducible nitric oxide synthase and induce oxidative stress [12], contributing to neuropsychiatric pathogenesis [10,13]. On the other hand, expression of anti-oxidative enzymes like heme oxygenase-1 can reverse oxidative stress and may characterize antidepressant mechanisms [12,14]. In addition, neuroinflammation reduces the survival of serotonergic neurons [15] and decreases neurogenesis [16], while antidepressants exert neuroprotection against microglia-mediated neurotoxicity [17].

Early-life adverse experiences are not only risk factors for psychiatric disorders but also physical diseases for adulthood. Children exposed to adverse psychosocial stressors display enduring low-grade systemic inflammation [18], which is not only a risk factor for depression but also a feature of chronic physical diseases: metabolic syndrome, type 2 diabetes, cardiovascular disease, coronary artery disease, cancer, and dementia. Interestingly, these physical diseases are all commonly comorbid in patients with depression [19]. The inflammation theory thus explains the high comorbidity of physical illness in depression and potential "interface between mind and body" [20].

2.1. *IFN-α-induced neuropsychiatric symptoms: sickness behavior and depression*

Most notably, this theory gains support from prospective clinical observations like major depressive episode (MDE) induced by cytokine therapy. IFN-α is the standard cytokine therapy for chronic HCV infection, yet it is associated with common and severe neuropsychiatric adverse effects. After an initial injection of IFN-α, almost all patients experience acute cytokine-induced sickness behavior: malaise, myalgias, arthralgias, anorexia, fatigue, apathy, poor concentration and attention, nonspecific painful symptoms, and acute flulike symptoms [21,22] (fever, cough, dyspnea, pharyngitis, rhinorrhea, anorexia, rash) that generally subside in 1–2 weeks.

Yet fatigue, malaise, apathy, and cognitive and behavioral changes persist for weeks during treatment; "sickness behavior" induced by IFN-α corresponds to the effects of cytokine administration to animals [5,8,23]. These resemble somatic or vegetative symptoms in major depressive disorder [6,24].

MDE during IFN-α therapy (IFN-α-induced depression) in patients with HCV is common; incidence ranges from 23 to 45% [25]. Onset of symptoms usually occurs within 3 months of therapy initiation [25]. In fact, depression results in poor compliance and is the leading cause of discontinuation of IFN-α therapy [21]. Despite its clinical significance, it is still unsatisfactory to apply specific clinical features when predicting IFN-α-induced depression pathogenesis. Notably, a history of psychiatric disorder before starting IFN-α therapy does not unequivocally predict the occurrence of such symptoms [26]. Other potential clinical predictors include presence of mood and anxiety symptoms before treatment [22], history of major depression, female gender, higher IFN-α dosage, and longer treatment duration [22]. Biological predictors for IFN-α-induced depression are clinically important and can help define the molecular mechanisms of inflammation-associated depression. IFN-α-induced increases in IL-6 have been reported to predict the development of depressive symptoms, rather than MDE [27]. Cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid, but no inflammatory markers, are predictors of depressive symptoms [28]. Other studies have examined biomarkers such as plasma adrenocorticotropic hormone, cortisol [29], serum tryptophan concentrations [30], even brain function [31]; these found depression predicted by changes in biomarkers during IFN-α therapy, rather than by baseline (pretreatment) biomarker levels.

Recent studies identify genetic markers on serotonin transporter and interleukin-6 genes that seem to predict the development of IFN-α-induced depression [32]. Our study in a Han Chinese sample, however, did not support those findings. Instead, we found variations on PUFA metabolic genes associated with risk of IFN-α-induced depression [24]. A recent preliminary report cites inflammatory predictors for depression at baseline: for example, low DHA level [24] and increased soluble interleukin-2 receptor, interleukin-6, and interleukin-10 concentrations [33].

Chronic HCV infection is a major public health issue in Taiwan [34] and has a high rate of progression to liver cirrhosis and hepatocellular carcinoma. Because of the high rate of neuropsychiatric adverse effect like sickness behavior and depression during IFN-α therapy, some clinicians consider prophylactic antidepressant use. The selective serotonin reuptake inhibitor (SSRI) antidepressants are reported to decrease the occurrence of IFN-α-induced depression in HCV patients [35]. However, it has been associated with adverse events, including gastric discomfort, headache, dizziness, and increased risk of retinal hemorrhaging, cotton-wool spots [35], and manic episodes [36]. In addition, symptoms of IFN-α-induced sickness behavior, once they develop, are only partially responsive to SSRIs [37]. The limited efficacy and possible adverse effects of antidepressant medication make it critical to find alternative treatment and prevention measures in patients receiving IFN-α.

2.2. *Anti-inflammatory effect as a common mechanism of antidepressant treatment*

If activated inflammatory response is involved in depression etiology, one would expect antidepressive treatments to have anti-inflammatory effects. Interestingly, current antidepressant agents like tricyclic antidepressants, SSRIs, serotonin reuptake enhancer tianepine, noradrenaline–dopamine reuptake inhibitor bupropion, reversible inhibitors of MAO-A moclobeminde, might be diverse in their actions on neurotransmitters, but they all exert anti-inflammatory effects [4,12]. In animal models of depression, antidepressants increase antioxidant levels, normalize oxidative and nitrosative stress damages [4], and suppress IL-1beta and TNF-α [38,39] production. They decrease inflammation-induced peripheral and brain cytokine production and reverse depressive-like symptoms [40]. In cell cultures, tricyclic antidepressants and SSRIs significantly suppress IL-1beta, IL-6, and TNF-α production [39]. Antidepressants also attenuate microglial activation and nitric oxide metabolism in the brain [12,41]. In addition, anti-inflammatory effects are associated with mechanisms of antidepressant effects not only in traditional antidepressants but also in off-label pharmacological or nonpharmacological treatment for depression: for example, lithium [42], valproate [43], omega-3 PUFAs [12], atypical antipsychotics [44,45], electroconvulsive shock [46], exercise [47], and even psychosocial intervention [48].

Considering the broad evidence supporting the inflammation theory of depression, the anti-inflammatory pathways loom as a hot topic in the search for new antidepressant therapies [49]. Cytokine antagonists might be associated with significant side effects but block one only specific cytokine [50], while cytokine networks are broadly and only mildly activated [4]. The COX-2 inhibitor celecoxib has been shown to be effective [51] but can also cause mild to severe side effects (e.g., cardiovascular events [4]). Non-steroidal anti-inflammatory drugs cause gastrointestinal adverse effects and increase gut permeability, which may drive peripheral inflammation via bacterial translocation [52], and might contribute to pathogenesis of depression [53]. Above all, omega-3 polyunsaturated fatty acids (omega-3 PUFAs or n-3 PUFAs) might be one of the most promising treatments that are safe, health-promoting, and well accepted.

3. Role of omega-3 PUFAs in psychoneuroimmunology of depression

3.1. *Clinical evidence*

It has been observed that societies with high consumption of fish in diet appear to have lower prevalence of MDD, mood disorders, coronary heart disease mortality, cardiovascular disease mortality, stroke mortality, and all-cause mortality [54], which implies the protective effect of omega-3 PUFAs in physical and psychiatric disorders. Consistent with epidemiological findings, patients with MDD show lower levels of omega-3 PUFAs in tissues of blood [55] and brain [56]. Deficits in omega-3 PUFA levels are reported in other populations with

mood disorders: for example, lower DHA and total omega-3 PUFAs in postpartum depression [57], lower DHA and EPA in social anxiety disorder [58], and lower DHA and AA in bipolar disorders [59].

3.2. Clinical applications

Consistent with case-control studies of PUFA levels in human tissues, omega-3 PUFAs are reported to be effective in treatment of MDD. Four meta-analytic reviews from three independent groups have reported the antidepressant effect of PUFAs [60–63], yet two previous meta-analyses from the same group did not support these effects in heterogeneous populations (such as subclinical individuals in community samples) [64,65]. Negative findings must be interpreted with caution due to limitations: for example, differing mood assessments, pooling heterogeneous populations, and implementing different intervention methods.

Omega-3 fatty acids might be "antidepressive" on patients with DSM-defined MDD but not "mood-improving" on symptomatic individuals if the diagnosis was not clinically confirmed. Recent meta-analysis by Bloch and Hannestad [66] found no benefits for depression; their review included clinical trials enrolling individuals according to self-rating scales in settings like general practice surgery, shopping mall, and university freshmen's fair [65], which found no beneficial effect of omega-3 PUFAs and was weighted 31.7% of a pooled estimate among a total of 13 clinical trials. Similar results emerged from the meta-analytic review by Appleton et al [67]. Take one clinical trial [68] included in Appleton et al's meta-analysis, for example. While Ness et al's study enrolled a relatively large number of 452 patients, it did not focus on treating depression or using appropriate tools for diagnosis and severity rating of depression. Intervention with omega-3 PUFA was defined to "advise" patients with angina to "eat more fish." The treatment outcome of omega-3 PUFAs in Ness's study was negative and contributed greatly to the pooled estimate in Appleton et al's meta-analysis.

Omega-3 PUFAs might only prevent depression but not mania in patients with bipolar disorder [69]. Despite the uneven quality of published studies, recent meta-analytic evidence strongly supports the adjunctive use of omega-3 to treat bipolar depression [70]. However, studies regarding the effectiveness of omega-3 PUFAs in the acute manic phase of bipolar disorder are still lacking. To date, one small double-blind placebo-controlled trial has been published and does not support omega-3 PUFAs' anti-manic effects [71]. Future large-scale, double-blind, placebo-controlled trials are needed.

Omega-3 PUFAs offer promise in treating special populations with depression. We first reported a successful treatment with omega-3 PUFAs in a pregnant woman with major depression [72]. Our 8-week, double-blind, placebo-controlled study showed that monotherapy with omega-3 PUFAs was associated with significant improvement of depressive symptoms and higher response rate in pregnant women with depression [73]. Most importantly, omega-3 PUFAs are safe for and well tolerated by depressed women during pregnancy and postpartum [74]. Omega-3 PUFAs are proven effective and safe for children with depression [75]; supplementation lowers risk of suicide [76], alleviates MDD depressive symptoms associated with menopausal transition [77], and diminish aggression in women with borderline personality disorder [78].

3.3. Preclinical evidence

Preclinical studies further support the omega-3 PUFA hypothesis. Omega-3 PUFAs have antidepressant effects in the animal model of depression in rats [79,80]. Likewise, the level of brain DHA negatively correlates with immobility time and positively correlates with swimming time [80]. Interestingly, rats fed with lithium chloride, valproate, or carbamazapine showed reduced AA turnover within brain phospholipids, which may give rise to the hypothesis that lithium and anti-manic anticonvulsants act by targeting parts of "arachidonic acid cascade" that may be functionally hyperactive in mania [81]. Empirical evidence supports this "arachidonic acid cascade" hypothesis identified as a mechanism of mood stabilization: for example, higher ratio of AA [59,82] along with hyperactivity of its major metabolic enzyme phospholipase A2 in mood disorders [83], inhibitory effect on phospholipase A2 activity of mood stabilizers [84], and therapeutic effect of omega-3 PUFAs in mood disorders [61]. Another cellular mechanism underlying the antidepressant effects of omega-3 PUFAs is the biological regulation of neurotransmitters and signal transduction. Changes in omega-3 PUFA concentration in the brain, induced by chronic deficiency in dietary omega-3 PUFAs, could increase serotonin 2 (5-HT_2) and decrease dopamine 2 receptor density in the frontal cortex [85]. Finally, EPA might be improving the hypothalamic–pituitary–adrenal axis dysfunction through the action of p-glycoprotein and multidrug resistance receptors [86].

3.4. Safety and tolerability

Numerous clinical studies have shown that omega-3 PUFAs are well tolerated by patients with chronic medical illnesses and mental disorders [60,87]. Adverse reactions are rare; if they occur, they usually involve belching, eructation, or perhaps fishy taste [88]. It is theorized that the potential antithrombotic effect of omega-3 PUFAs may increase the risk of bleeding. Clinical trials show high-dose omega-3 PUFAs consumption as safe, even when concurrently administered with other agents that increase bleeding, such as aspirin and warfarin [87]. According to Harris's [89] systematic review of 19 available clinical trials with n-3 PUFAs supplementation for patients with high risk of bleeding ($n = 4397$), the risk of clinically significant bleeding is virtually nonexistent! Another potential safety concern is the susceptibility of omega-3 fatty acids to undergo oxidation, which may contribute to patient intolerance and potential toxicity, yet conclusions are quite inconsistent [90]. Adding antioxidant vitamin E to omega-3 PUFAs is a common way to reduce oxidation and rancidity, maintain freshness, and increase shelf life. The concurrent use of vitamin E with omega-3 PUFAs may also overcome the potential risk of oxidative stress. Yet most published studies show either unchanged or decreased oxidation [90]. Given omega-3 PUFAs' antidepressant effects, another possible

adverse effect is drug-induced mania. Until now, only one case report has shown omega-3 PUFAs inducing hypomania [91]; a comprehensive assessment of manic symptoms in patients receiving omega-3 PUFAs is recommended for future clinical trials.

4. Conclusions

The inflammation theory of depression draws support from several lines of evidence: for example, increasing inflammatory biomarkers in clinical depression and observed behavioral changes related to inflammatory activation. Interferon-α-induced depression in chronic HCV cases is the most notable clinical observation to support the inflammation theory of depression and an excellent model to probe the etiology of depression in a prospective manner. Chronic low-grade inflammation links not only with psychiatric disorders but also certain physical diseases. The inflammation theory might thereby provide an interface between mind and body, along with a promising path for developing new treatments. Anti-inflammatory omega-3 PUFAs prove beneficial in depression and several inflammation-related physical diseases. Omega-3 PUFAs may particularly benefit children, pregnant women, and/or patients with comorbid cardiovascular or metabolic disorder, who face greater risks of adverse effects from antidepressants, antipsychotics, and mood stabilizers. The cost of omega-3 PUFAs is relatively modest as compared to many psychiatric treatments and other over-the-counter natural products. Given the potential benefits and safety, omega-3 PUFAs deserve greater attention and wider application.

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