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Review

The role of omega-3 polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids in the treatment of major depression and Alzheimer's disease: Acting separately or synergistically?

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ABSTRACT

Omega-3 polyunsaturated fatty acids (n-3-PUFAs), mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may improve or prevent some psychiatric and neurodegenerative diseases in both experimental and clinical studies. As important membrane components, these PUFAs benefit brain health by modulating neuroimmune and apoptotic pathways, changing membrane function and/or competing with n-6 PUFAs, the precursors of inflammatory mediators. However, the exact role of each fatty acid in neuroimmune modulation and neurogenesis, the interaction between EPA and DHA, and the best EPA:DHA ratios for improving brain disorders, remain unclear. It is also unknown whether EPA, as a DHA precursor, acts directly or via DHA. Here, we discuss recent evidence of EPA and DHA effects in the treatment of major depression and Alzheimer's disease, as well as their potential synergistic action on anti-inflammatory, antioxidant and neurotrophic processes in the brain. We further analyze the cellular and molecular mechanisms by which EPA, DHA or their combination may benefit these diseases. We also outline the limitations of current studies and suggest new genetic models and novel approaches to overcome these limitations. Finally, we summarize future strategies for translational research in this field.

Contents

Abbreviations: Aβ, amyloid β; AA, arachidonic acid; AD, Alzheimer's disease; ALA, α-linolenic acid; APP, amyloid precursor proteins; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CSF, cerebral spinal fluid; COX2, cyclooxygenase 2; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EC, entorhinal cortex; ER, endoplasmic reticulum; EPA, eicosapentaenoic acid; GC-SF, granulocyte colony-stimulating factor; HPA, hypothalamic–pituitary adrenal; IL, interleukin; JNK, Jun-N-terminal kinase; LPS, lipopolysaccharides; MAP, microtubule associated protein; MCI, mild cognitive impairments; MDD, major depressive disorder; MDE, major depressive episode; MRI, magnetic resonance imaging; MAOIs, monoamine oxidase inhibitors; NO, nitric oxide; NFTs, neurofibrillary tangles; NPCs, neural progenitor cells; NPD, neuroprotectin D; Nrf2, nuclear factor erythroid 2-related factor 2; OHDHA, 2-hydroxy DHA; PC, phosphatidylcholine; PD, psychological distress; PE, phosphatidylethanolamine; PS, phosphatidylserine; PFC, prefrontal cortex; PPD, postpartum depression; PG, prostaglandin; PLA_2, phospholipase A_2; RA, retinoic acid; ROS, reactive oxygen species; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; TrkB, tyrosine kinase receptor B; TNF-α, tumor necrosis factor-α.

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1. Introduction

Major depressive disorder (MDD) is a common brain disorder that affects approximately 10% of the world population. According to the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5, 2013), MDD is characterized by the loss of interest in pleasure, low self-esteem, disturbed sleep or appetite, fatigue, and diminished ability to think or concentrate. These problems often become chronic and recurrent, and at the worst, can lead to suicide [1,2]. The etiology of MDD remains poorly understood. For example, the deficits of neurotransmitters (e.g., serotonin, noradrenaline and dopamine) or dysfunctional hypothalamic–pituitary adrenal (HPA) axis may contribute to the illness, with acute or chronic stress serving as a trigger. Continuous elevation of the HPA hormones, such as glucocorticoids, causes neuronal atrophy, reduced neurogenesis in the hippocampus, and eventually, cognitive impairments [3,4].

Alzheimer's disease (AD) is a progressive neurodegenerative disease, presenting as deficits in short-term memory, language, orientation, mood control, motivation, self-care, and behavioral conduct (DSM-5, 2013). The loss of acetylcholine (ACh)-releasing neurons and cholinergic innervation of the cerebral cortex, hippocampus and related structures is responsible for cognitive (especially memory) deficits. Abnormal accumulation of amyloid plaques in the extracellular milieu and neurofibrillary tangles (NFTs) within neurons is the hallmark of AD. Amyloid plaques are primarily composed of amyloid β (Aβ) peptides, whereas NFTs consist of hyperphosphorylated protein tau [5,6]. Among the Aβ peptides, the hydrophobic nature of $A\beta_{1-42}$ allows them to self-aggregate and form dimers or oligomers, protofibrils, fibrils and, ultimately, amyloid plaques. In contrast, α-secretase cleaves APP within the Aβ domain, thus preventing the Aβ formation [7]. Tau is a microtubule-associated protein that is enriched in neurons and regulates motor-driven axonal transport. In AD, hyper-phosphorylation of tau disrupts its binding to microtubules, inducing neurotoxic effects [6]. Despite these findings, current treatments that target MDD and AD remain ineffective and often cause severe side-effects. For example, antidepressants induce weight gain, nausea, violent behavior, sexual difficulties, digestive problems, abnormal bleeding and stroke in the elderly, even increasing suicide in patients under 25 years old. To explore new etiologies of these diseases, the important role of neuroinflammation becomes recognized, and will be discussed here.

1.1. New hypotheses for depression and Alzheimer's disease

In MDD patients, a significant increase in macrophage activity and peripheral pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-6, is commonly observed [7–9]. Elevated proinflammatory cytokines can stimulate the HPA axis to produce glucocorticoids and impair neurotransmission, thereby causing "sickness behavior" similar to those observed in depressed patients [10,11]. In the brain, microglia are activated in depressed patients [12]. Serving as brain resident macrophages, activated microglial cells secrete multiple inflammatory mediators, whose overproduction may induce neuroinflammation [13], depressive symptoms and neuronal apoptosis [14]. For instance, interferon (IFN)-α or lipopolysaccharide (LPS) can induce depressive episodes in individuals infected by hepatitis C virus [15,16], also increasing glucocorticoid and neurotransmitter metabolism in experimental rodents [17,18]. In contrast, some effective antidepressant treatments can suppress inflammatory cytokines [19] and prevent cytokine-induced depression [20].

In AD patients, Aβ and NFTs both provoke microglia-mediated inflammatory responses, including the production of proinflammatory cytokines IL-1β, IL-6 and tumor necrosis factor (TNF)-α, as well as reactive oxygen species (ROS) [21–23]. Therefore, removal of abnormal protein aggregates may prevent the excessive inflammatory responses and reverse the AD progression. Similar to MDD, the HPA dysfunction and hypersecretion of glucocorticoids are found in patients with AD. Glucocorticoids are implicated in the misprocessing of Aβ precursor proteins (APP), elevating Aβ peptides and reducing clearance of Aβ peptides and phosphorylated tau. In contrast, glucocorticoid receptor antagonists reduce Aβ levels and tau pathology [24], suggesting that control of HPA axis may attenuate neuroinflammation in AD by decreasing insoluble protein aggregates.

Epidemiological studies have shown a pathological association between MDD and AD, since chronic/severe MDD accompanies cognitive impairments and AD [25]. Depressive symptoms are also common in AD, occurring in approximately 50% of patients [26]. Collectively, such overlap suggests shared factor(s) which may contribute to common MDD and AD pathogeneses [3]. For example, mounting evidence suggests that neuroinflammation-induced dysfunction of neurotransmission, neuronal apoptosis and/or reduction of neurogenesis may be potential shared risk factors for both diseases [3]. In line with this, proinflammatory cytokine IL-1β plays a critical role in both MDD and AD [27], and its genetic variance can increase the risk of clinical AD onset [28]. We have previously reported that IL-1β can induce neurodegeneration via microglia-triggered neuroinflammation and suppressing astrocyte-produced neurotrophins in rodents [29]. Paralleling increased IL-1β levels in MDD or AD patients, intracerebroventricular administration of exogenous IL-1 β in rodents decreases noradrenaline and acetylcholine in the hippocampus, inducing depression/anxiety-like behaviors and cognitive deficits [30]. Furthermore, kynurenine pathway-related enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) are both activated by pro-inflammatory cytokines, such as IL-1β, IL-6 and IFN-γ. In MDD and AD, TDO and IDO activation increases the production of neurotoxins, 3-hydroxykynurenine (3-OHK) and quinolinic acid (QA), stimulating N-methyl-D-aspartate (NMDA) receptors [31,32]. Given microglia activation in MDD and AD [33], this major source of proinflammatory cytokines may also produce QA and 3-OHK [31].

Another recently proposed hypothesis links MDD to reduced neurogenesis and neurotrophic factors — crucial regulators of the formation/plasticity of neuronal networks and neurogenesis [34]. The neurotrophin family includes the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophins NT-3 and NT-4. Among all neurotrophic factors, BDNF is the best-studied molecule in MDD and AD, and acts via two specific receptors, tyrosine kinase eceptor B (TrkB) and $p75^{NTR}$. The activation of TrkB facilitates neuronal survival, differentiation and synaptogenesis [35,36], whereas $p75^{NTR}$ triggers apoptosis [37,38]. BDNF is reduced in patients with MDD and AD [39–42], but can be rescued by antidepressant intervention [43,44] and anti-dementia drugs [45]. We have reported that microglial hyper-activation suppresses astrocyte-mediated neurotrophin functions and induces neurodegeneration [29]. Taken together, shared mechanisms of MDD and AD may include i) hypercortisolism-induced neuronal atrophy, ii) activated microglia-evoked neuroinflammation, iii) reduction of neurotrophins and their receptors and/or iv) elevation in endogenous neurotoxins. Therefore, medications which target these mechanisms may provide therapeutic strategies for both MDD and AD.

1.2. Changes in concentrations of n − 3 and n-6 PUFAs in depression and AD

Based on epidemiological findings, the deficiency of omega (n)-3 polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid