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Review

The importance of n-6/n-3 fatty acids ratio in the major depressive disorder

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ABSTRACT

This review aims to clarify the relation between the ratio of omega-6 to omega-3 fatty acids and the development of depression. It is explained how these fatty acids are involved in the production of eicosanoids and how these fatty acids can affect the membrane fluidity, by their incorporation into membrane phospholipids. In addition, it is described how omega-3 derivatives are shown to regulate gene transcription. In view of the pathophysiology of depression, the mechanisms of how an altered ratio of omega-6 to omega-3 could be involved in depression are discussed. Possible mechanisms could include an increased production of pro-inflammatory cytokines, which can activate the HPA axis and a changed membrane fluidity, which potentially affects membrane bound enzymes, ion channels, receptor activity and neurotransmitter binding. In view of clinical trials, it is also discussed whether omega-3 supplementation could have a beneficial effect in the treatment of depressive patient. There are strong indications that an increased ratio of membrane omega-6 to omega-3 is involved in the pathogenesis of depression and so far, omega-3 supplementation has shown positive effects in clinical trials.

1. Introduction

Major depressive disorder (MDD) is a severe chronic, recurring mental illness, with high morbidity and mortality and is associated with a substantial reduction in the quality of life [1,2]. According to the WHO rapport The Global Burden of Disease, depressive disorders are among the most important causes of disability and death in the world [3], with a lifetime prevalence of MDD in the Western world of 5%–15% [4–7]. Over the last decades there has been reported an increase in the incidence of depression in the Western world [8–11]. In the same period, the Western diet has changed markedly, with a huge decline in the dietary intake of omega-3 polyunsaturated fatty acids (PUFAs) in favor of an increase in omega-6 PUFAs [12]. This has led to an estimated ratio of omega-6 to omega-3

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fatty acids of 15–20:1 in the present Western diet [12,13], which contrasts sharply with the ideal ratio of around 2:1, recommended by a panel of lipid experts [14]. There are strong indications that alteration in the fatty acid composition is involved into pathogenesis of depression. Numerous epidemiological studies have shown a significant negative correlation between the average fish consumption in a country and its prevalence of depression [15–18]. Although these studies do not prove any causation, and potentially contain several confounders, they support the role of omega-3 fatty acids [13]. At the same time several reports have demonstrated that depressed patients in general have significantly lower amount of omega-3 PUFAs in phospholipids, both in the membrane of erythrocytes and free in plasma [19–24]. Similar results are shown in adipose tissue [13,25] and alterations have been found in the PUFA composition in the brain tissue of MDD patients at the time of death [26]. It is shown that annual variation in PUFAs is related to annual variation in violent suicide [27]. Moreover, studies have demonstrated that low serum omega-3 PUFAs increase the risk of suicide death [28,29]. It is interesting to mention that omega 6:3 ratios in the USA are now averaging 25:1. This is based on data, which is extensive but has not yet been published. These figures provide a persuasive explanation to the high incidence of depressive illness and other inflammatory conditions in the US population, and their disproportionately high consumption of analgesics (personal communication with Dr. Paul Clayton and Dr. Ola Eida, BioActive Foods AS).

Based on the biochemical functions of omega-3 and omega-6 PUFAs, this review will point out possible mechanisms through which an increased ratio of omega-6 to omega-3 can be involved in the pathophysiology of depression and finally, based on clinical trials, whether omega-3 PUFA supplementation could have a beneficial effect in the treatment of depression.

2. The role of omega-3 and omega-6 fatty acids

2.1. *Biochemistry of omega-3 and omega-6 fatty acids*

Omega-3 and omega-6 fatty acids are essential PUFAs which cannot be synthesized in the human body and must therefore be derived through the diet [30]. The difference between omega-3 and omega-6 PUFAs is in the location of the first double bond from the methyl (ω) end of the molecule [31]. Linoleic acid (LA) 18:2ω6 and α-linolenic acid (ALA) 18:3ω3 are precursors for the long chained PUFAs (LC-PUFAs). LA can through series of desaturation and elongation reactions be metabolized to the important LC-PUFA arachidonic acid (AA) 20:4ω6, whereas ALA can be converted to eicosapentaenoic acid (EPA) 20:5ω3 and docosahexaenoic acid (DHA) 22:6ω3 [32]. The conversion of LA and ALA to LC-PUFA derivatives catalyzes by the same desaturases and elongases, and in this process the Δ-5 and Δ-6 desaturases are key and rate-limiting enzymes [33,34]. In addition, both Δ-5 and Δ-6 desaturases have higher affinity for omega-3 derivatives than omega-6 derivatives [12,35]. This creates a competition between LA and ALA in conversion to LC-PUFAs: AA, EPA and DHA [30,31,36]. The omega-3 and omega-6 fatty acids and their long chain derivatives are involved in important functions.

2.2. *Production of eicosanoids*

Eicosanoids are very potent signaling molecules with a very short lifetime. Therefore, they are acting as autocrine and paracrine stimulators through the G-protein-coupled receptors [30,37]. Among many functions, eicosanoids are important mediators and regulators of inflammation. Several of them have opposing effects [38]. EPA, AA and dihomo-γ-linolenic acid (DGLA) 20:3ω are precursors for the production of eicosanoids. These three fatty acids are all precursors for the three main classes of eicosanoids: prostaglandins, thromboxanes (TXs), and leukotrienes (LTs). In the production of prostaglandins and TXs DGLA, AA, and EPA will be converted into class 1, 2, and 3 prostaglandins and TXs and into class 4, 5, and 6 LTs, respectively [30,32]. The class name refers to the number of double bonds outside of the ring structure in the molecule. The number of double bonds does not influence the overall function of eicosanoids, but affects their potency [30,39]. For instance, AA-derived TXA_2 is more potent for the aggregation of platelets compared with the EPA-derived TXA_3 [30] and LTB_5 (from EPA) is 10- to 100-fold less potent as a chemoattractant of neutrophils compared with LTB_4 (from AA) [38]. In general, AA derived eicosanoids act in a pro-inflammatory and pro-thrombotic way, whereas EPA derived eicosanoids act in an anti-inflammatory and anti-thrombotic way [31,38,40]. In the formation of eicosanoids EPA and AA competes in their binding to the cyclooxygenase and lipoxygenase enzymes [31,37]. In addition, Culp et al. have demonstrated that the formation of prostaglandins at the cyclooxygenase level is up to three times faster for AA compared with EPA [41]. Thereby EPA potentially have an ability to attenuate competitively the production of AA-derived eicosanoids [37].

2.3. *Fluidity of the cell membrane*

LA, ALA and their long chain derivatives are important structural components of the lipid bi-layer of cell membrane, due to their incorporation in the phospholipids [13,25,31]. Phospholipids represent more than 60% of the total membrane lipids in neurons [42], and the synaptic membrane consists of phospholipids with a notably high amount of docosahexaenoic acid (DHA) (32%–40%) [13,31,42]. Modifications of the PUFAs composition of the cell membrane has a large effect on membrane permeability [43] and fluidity [13,25,44]. The number of cis-double bounds in the fatty acid is of huge importance for its 3-dimensional structure, given that cis-double bounds result in a more curved carbon chain [32]. Hereby the carbon chain becomes more kinked with an increasing number of double bounds, takes up more space in the cell membrane, and in this way increase the membrane fluidity [32]. Omega-3 PUFAs are especially important, as they through yet unknown mechanism [36] alter neural fluidity by displacing cholesterol from the membranes further increasing their fluidity [13,36,43]. Changes in the composition of membrane lipids and, thereby, of membrane fluidity are affecting the conformation or quaternary structure of