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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

membrane proteins [13,25,45]. These membrane proteins are vital for cellular functions, acting as receptors, transporters, and enzymes [13,46]. It has been elucidated that the membrane composition of PUFAs affects the activity of membrane bound enzymes [47], like the Na^+/K^+-ATPase [47–49], influences neurotransmitter binding [50,51], affects ion channels [43] and has an effect on receptor activity [45,52,53]. Therefore, changes in membrane fluidity potentially influence many membrane-associated cellular functions [25,44].

2.4. *Second messengers and regulation of gene expression*

As aforementioned, PUFAs can be incorporated into membrane phospholipids [13,25,31]. For example through G receptor activation of cellular phospholipases, or being available directly from the diet, these PUFAs can act as second messengers [31], and thereby activate protein kinase C (PKC), which phosphorylates a broad range of signal transduction proteins [30,54].

Omega-3 PUFAs have also been shown to modulate the transcription of specific genes [55]. In 1977, Clarke et al. demonstrated the ability of dietary LA and ALA to depress the rate of the fatty acid synthase (*fas*), but not of saturated fatty acids [56]. Later on, in 1989, Clarke et al. proved that the PUFA mediated suppression of *fas* occurs by a major decrease in the level of *fas* mRNA [57], and this depressive effect is larger, when it is mediated through omega-3 PUFAs compared to omega-6 PUFAs [57]. Finally, the suppressive effect occurred within 3 h after a meal, indicating that these PUFAs are able to regulate the mRNA transcription directly [55,57]. Over the last years it has been demonstrated that PUFAs also are involved in the gene regulation of inflammatory proteins [12]. DHA and EPA, compared to AA, are shown to reduce the macrophage production of IL-6 and TNF-α and at the same time to increase the anti-inflammatory IL-10 production, when the macrophages are exposed to lipopolysaccharide [58–61]. This inhibitory effect of the omega-3 PUFAs on the secretion of IL-6 and TNF-α has been accompanied with lower mRNA levels, indicating a direct DNA regulatory effect of EPA and other omega-3 PUFAs [58,59]. Several studies have demonstrated that this regulatory effect is in part mediated through modulations in the activity of the transcription factor nuclear factor κβ (NF-κβ) [58–61], which plays a key role in regulating the expression of IL-6 and TNF-α among others [59]. Omega-3 PUFAs are also shown to reduce the de novo synthesis of endothelial leukocyte adhesion molecules such as vascular cell and adhesion molecule-1 (VCAM-1), which was accompanied by a corresponding reduction in VCAM-1 mRNA [62]. It is hereby apparent that omega-3 PUFAs can regulate gene expression, and the modification of NF-κβ is probably only one mechanism among others [63].

3. The pathophysiology of depression

Despite the high prevalence of depression, the exact pathophysiological mechanisms, involved in depression, still remain unclarified [1,25]. Up to day there are several theories explaining the MDD pathogenesis. Given the heterogeneity of the illness, it is important to mention that all these mechanisms might be involved to a greater or lesser extent (Figure).

3.1. *The monoamine hypothesis*

During the last fifty years the understanding of the pathophysiology of depression has especially been oriented toward

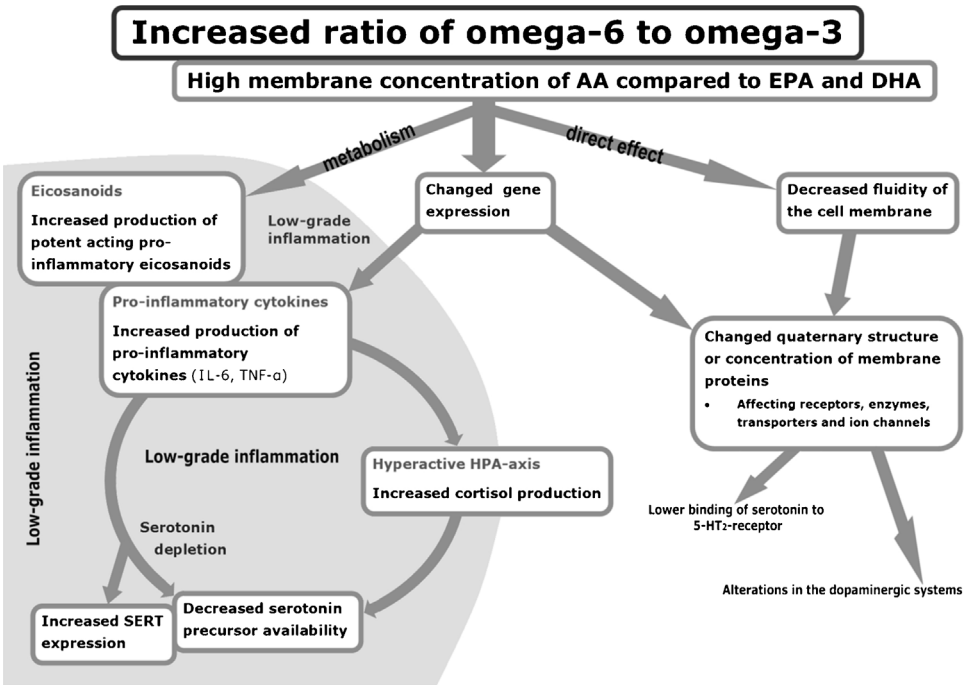

Figure – The role of PUFAs in biochemical pathways involved into development of depression pathology. AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

the level of amine neurotransmitters [64]. This monoamine hypothesis emphasizes that depression is caused by alterations of the monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine in the brain [25,65]. This hypothesis has formed the basis for treatment of depression, whereas most antidepressants are designed to increase the amount of available neurotransmitter within the synaptic cleft, either by inhibiting the neuronal reuptake or by inhibiting the monoamine degradation enzymes [66]. However, this theory has its weaknesses, as it cannot provide a comprehensive explanation of the pathophysiological mechanisms. The theory is unable to explain why the effect of antidepressants is gradual and first seen after months of treatment, despite an almost instant increase in the amount of neurotransmitter; and why a full therapeutic effect is absent in up to 50% of the treated patients [1,13]. Alterations in other neurotransmitters like glutamate, GABA and substance P are also observed [64].

3.2. *Pro-inflammatory cytokines*

A vast number of studies have indicated an association between depression and an excessive production of pro-inflammatory cytokines [13]. Studies show that pro-inflammatory cytokines given to animals or humans generates symptoms much similar to those found in depressed patients [67–69]. Despite ambiguous results for this association, two meta-analyses have demonstrated a significant positive association between depression and the amount of the pro-inflammatory cytokines IL-6 and TNF-α [70,71]. In a recent Scandinavian study Dahl et al. found a significant elevated amount of interleukins in depressed patients compared to healthy controls, and after 12 weeks of treatment, they documented a significant decrease in the plasma levels of cytokines compared to baseline [72]. Furthermore, Suarez et al. found a positive relation between the production of pro-inflammatory cytokines and the severity of depressive symptoms [73]. These results support the role of cytokines in depression (Figure). However, it is difficult to determine the specific mechanisms involved, but a number of possible explanations have been put forward.

3.3. *Hypothalamic–pituitary–adrenal (HPA) axis*

In addition, IL-6, TNF-α and other pro-inflammatory cytokines are activators of the HPA axis, resulting in a release of cortisol [67,74,75]. Hyperactivity of the HPA axis, with increased levels of corticotropin-releasing factor (CRF) in the hypothalamus and in the cerebrospinal fluid together with elevated plasma cortisol concentration, is seen in the majority of depressed patients [1,76,77]. In these patients, the normal suppression of the HPA axis by CRF and cortisol is hereby insufficient, but the involved mechanism is much debated [1]. Among several theories, Maes and Smith state that an increased production of pro-inflammatory cytokines induce the suppression of the negative feedback loop by influencing the glucocorticoid receptor expression [67], but there has also been observed a decreased density of CRF receptors among depressed patients [78]. Christiansen et al. have shown an additional peak in diurnal glucocorticoid secretion associated with the signs of depression using an animal model [79]. However, it is much discussed whether the elevated production of cytokines is the causative reason for the insufficient regulation of the HPA axis [74].

3.4. *Serotonin precursor availability*

As mentioned earlier [25,64,65] reduced level of serotonin is central in the understanding of depression, and recent research indicates that increased production of pro-inflammatory cytokines and cortisol may lower the serotonin precursor availability. Serotonin is derived from the essential amino acid tryptophan, and the production of serotonin in the brain is highly dependent on the bioavailability of tryptophan in the plasma [80]. Tryptophan can also be catabolized through the kynurenine pathway. The conversion of tryptophan to kynurenine is the first step in this pathway, and this conversion can be made by two different dioxygenases, indoleamine 2,3-dioxygenase (IDO), and tryptophan dioxygenase (TDO) [80]. Preliminary results suggest that the IDO activity is inducible by the pro-inflammatory cytokines interferon-γ (IFN-γ), IL-6, and TNF-α, while TDO is induced by cortisol [80,81]. Therefore, increased pro-inflammatory cytokines and cortisol potentially can induce serotonin depletion [13,67,80,81]. Moreover, it is possible that cytokines can alter the production of the serotonin reuptake transporter (SERT), by influencing the SERT mRNA transcription. A number of *in vitro* experiments have demonstrated that IFN-γ, among others pro-inflammatory cytokines, induces an increase in SERT [82,83], and Tsao et al. have demonstrated an increased level of SERT mRNA in leukocytes of depressed patients [84].

4. Possible mechanisms of omega-3 PUFAs in depression

The composition of PUFAs in the cell membrane depends largely on the dietary intake. A diet with a low omega-6 to omega-3 ratio will, due to competitive desaturation and incorporation into phospholipids [30,31,46], result in a high amount of EPA and DHA in the cell membrane, and corresponding lower AA levels [12,37,38,85].

4.1. *Inflammation and the HPA axis*

The composition of membrane PUFAs is of a great importance for the production of eicosanoids, given that EPA competes with AA at the cyclooxygenase level [31,37]. As mentioned earlier (Figure) AA derived eicosanoids act in a pro-inflammatory way, whereas EPA derived eicosanoids in general have the opposite effect [31,38,40]. Since an elevated ratio between omega-6 and omega-3 PUFAs was observed among depressive patients [19–24] and MDD is associated with increased production of pro-inflammatory cytokines [70–73], it seems reasonable to suspect the correlation between high omega-6/omega-3 ratio, low-grade inflammation, and depression. The facts that pro-inflammatory cytokines are demonstrated to induce depressive symptoms [67–69], activate the HPA axis [67,74,75] and finally, together with cortisol, reduce the

serotonin precursor availability [13,67,80,81] indicate that inflammation plays an important causative role in the development of MDD. The strong interaction between the level of pro-inflammatory cytokines and the HPA axis is evident through the increased level of CRF and cortisol observed in the majority of depressed patients [1,76,77]. Apart from the depletion of serotonin precursor availability by cortisol, administration of CRF into the CNS has been shown to be a cause for several depression-like symptoms [1]. At the same time, cortisol, through its binding to intracellular glucocorticoid receptors, acts as a transcription factor for many genes that affect several aspects of neuronal function, such as metabolism, neuronal connections and synaptic transmission [1]. Thereby, the increased omega-6/omega-3 PUFAs ratio might contribute into increased activity of the HPA axis in MDD through the activation of pro-inflammatory cytokines secretion and activation of low-grade inflammation (Figure).

Since the suppression of pro-inflammatory cytokine production modulated through the effects of EPA and DHA on transcriptional level [58–61], the environment with lower ratio between omega-6 and omega-3 PUFAs might be considered as less attractive for the development of low-grade inflammation [86].

4.2. *Membrane integrity*

As described previously, the fluidity of the cell membrane is increasing with increase in number of *cis*-double bounds [32]. LA, ALA, AA, EPA, and DHA have 2, 3, 4, 5, and 6 double bounds, respectively [30,54]. Therefore the biochemical structure of these PUFAs and their ability to displace cholesterol from the cell membrane [13,36] can explain why omega-3 PUFAs increase the membrane fluidity compared to omega-6 PUFAs [32,43]. In the light of this effect, it seems possible that depressive patients in general have decreased membrane fluidity due to alterations in the PUFAs composition, which affect membrane enzymes, neurotransmitter binding, ion channels, and receptor activity [43,47–51]. This can describe some of the alterations in the level of monoamine neurotransmitters and their receptors, which are seen among depressive patients.

A decreased membrane fluidity leads to a lower receptor binding of serotonin to its 5-HT_2 receptor [51,87] and an increased omega-6 to omega-3 ratio has been proven to increase the amount of 5-HT_2 receptors in the frontal cortex [85,88]. Changes in the dopaminergic system have also been proved to depend on omega-3 intake. It is well documented that an omega-3 deficient diet results in a strongly decreased pool of dopamine in presynaptic vesicles of the frontal cortex [85,87–90], potentially due to an decreased level of the vesicular monoamine transporter (VMAT2) [89]. In the same area, a drop in the concentration of dopamine D_2 receptors has also been observed and this decrease is shown on the level of mRNA and protein [89,91]. Finally, an increase in D_2 receptors density and presynaptic level of dopamine is seen in *nucleus accumbens* in rats exposed to omega-3 deficient diet [89,92]. Hereby, there are strong indications that the membrane composition of omega-3 and omega-6 PUFAs has a big impact on the monoaminergic systems. Due to the importance of the monoaminergic systems in the pathophysiology of depression, it seems clear that an increased omega-6 to omega-3 ratio could be an underlying factor. The aforementioned changes in the monoaminergic systems do not have to be caused by alterations in the membrane fluidity alone, as omega-3 PUFAs also are shown to modulate the transcription of specific genes [55–63].

The evidence of an active role of fatty acids in depression is strong, and it is seems hereby reasonable that normalization of the membrane structure by the control for the ratio between omega-6 and omega-3 PUFAs might contribute into the improvement of depressive symptoms (Figure).

5. Clinical studies

Several double-blinded control trials have examined the potential role of omega-3 PUFAs in the treatment of depression. In 1999, Stoll et al. studied the effect of daily omega-3 PUFA supplement (9.6 g/d) vs. placebo in 30 patients with bipolar disorder. They found a significant effect of omega-3 supplement according to a longer period of remission and a reduction in symptoms [93], which was used as inspiration for further research [25].

Nemets et al. found a highly significant effect of EPA supplement (2 g/d) in patients with MDD. After 4 weeks of treatment the patients receiving EPA had a mean reduction by 12.4 points on the Hamilton depression scale compared to 1.6 among patients receiving placebo [94]. Several other studies have found similar effects of EPA supplementation [95–98], although Frangou et al. could not prove any apparent benefit of 2 g EPA over 1 g [95], and Peet and Horrobin found a decreased effect with an increasing dose of EPA [98]. A similar tendency is observed in treatment of MDD with DHA, as Mischoulon et al. found a significant reduction in symptoms with DHA supplementation of 1 and 2 g per day, but no effect of 4 g DHA [99]. This trend points out a possible dose dependent efficacy of EPA [95,98] and DHA [99], although these three studies have limitations due to their small sample sizes. Finally, Mischoulon et al. could not find any advantage of EPA (1 g/d) over placebo in a monotherapy for MDD [100], like Marangell et al. were not able to prove any significant effect of DHA monotherapy (2 g/d) compared to placebo among patients with MDD [101].

Several studies have examined a combination of different omega-3 PUFAs. Su et al. found a significant effect of omega-3 PUFA supplementation (6.6 g/day) compared to placebo among 28 patients with MDD [102], and Nemets et al. found a significant effect of EPA and DHA monotherapy compared to placebo among children with depression [103]. However, the results are not clear in that Silvers et al. could not find any evidence that fish oil improved mood when compared to placebo [104]. The same conclusion was found in a similar study by Grenyer et al. [105].

Although the aforementioned trials contain ambiguity, the tendency points toward a positive effect of an omega-3 PUFA treatment, and importantly all studies reported a good toleration of omega-3 PUFAs [95–98]. In general, these studies were conducted on a limited number of participants, whereby these studies shall be seen as rather suggestive. The different

results can be related to differing antidepressant effects of ALA, DHA and EPA and a potential dose dependent effect.

Several meta-analyses have also been conducted but without any clear trend, which especially is due to huge heterogeneity of the individual trials [25]. Thus, the heterogeneity of the trials and absence of standardized approach lead to inconvenience in interpretation of the results and making deliberately depreciative the importance of the topic. None of the clinical trials provide information on omega 6:3 ratio at the beginning and/or at the end of the study. This means that they have no way of standardizing either their trial subjects, or the effective dose that each subject receives.

6. Concluding remarks

Although omega-3 PUFAs hold great promise in the treatment of depression, large well-designed controlled trials are needed to provide solid evidences for the importance of the low omega-6/omega-3 PUFAs ratio and clarify an optimal dosage of EPA and DHA in prevention of depression.

Conflict of interest

The authors state no conflict of interest.

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