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Review article

The role of n-3 polyunsaturated fatty acids (n-3PUFAs) in affective disorders

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ABSTRACT

Background: Among emerging treatments for depressive disorders several studies suggested that n-3 polyunsaturated fatty acids (n-3PUFAs) supplementation can be used. However, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) differ in terms of biochemistry, metabolism and therapeutic effects. Therefore, a clear picture of their specific and different role on affective disorders has not yet emerged.
Objectives: To investigate the effects of n-3PUFAs on affective disorders including major depression, bipolar disorder and perinatal depression.
Methods: a comprehensive search on PUBMED, Medline and PsychINFO of all RCTs using n-3PUFAs patients with depressive symptoms published up to April 2016 was performed. We included trials that examined unipolar or bipolar disorder and trials that investigated depressive symptoms in relation to pregnancy. Trials were excluded if the depressive symptomatology was related to other primary organic diseases.
Results: 264 RCT studies were identified but only 36 met the inclusion criteria. First, it has been reported that n-3PUFAs supplementation might have clinical benefits on depressive symptoms. Second, EPA supplement, rather than DHA, seems to be more effective in treating major depression. Third, n-3PUFAs can have beneficial effects in bipolar depression but not in perinatal depression.
Conclusions: there are only some evidence on the efficacy of n-3PUFAs in affective disorders especially to unipolar and bipolar depression not powered enough to confirm a therapeutic effect for affective disorder. Therefore, further studies with larger and more homogeneous samples, are required to confirm these effects.

1. Introduction

Depressive disorders are common mental diseases with specific neurobiological signatures (Delvecchio et al., 2012; Dusi et al., 2015; Bellani et al., 2011) that affect approximately 10% of the population (World Health Organization, 2014). Symptoms include sadness, loss of interest in activities, decreased energy, loss of confidence and self-esteem, inappropriate guilt, diminished concentration, disturbance of sleep and appetite, thoughts of death and suicide (NIMH, 2012). Depressive disorders are very weakening, difficult to nurse, with very frequent recurrences, and with deleterious consequences for both depressed patients and the society (DSM5, American Psychiatric Association, 2013). Particularly, major depressive episode (MDE) is a common phenotype characterizing both unipolar and bipolar depressive disorders (DSM5, American Psychiatric Association, 2013) and it affects the outcome and the course of both illnesses even when the duration is very short (Altamura et al., 2011). There are several different treatments for depression, including psychotropic drugs, psychotherapies, electrotherapical and bright light therapies (NICE guideline, 2009). However, the pharmacological treatment, especially with antidepressants (AD), is the most common and effective therapy for depressive disorders, although up to 20% of patients may be resistant (Keller et al., 2002).

In this context, n-3 polyunsaturated fatty acids (n-3PUFAs; also known as ω-3 fatty acids) are considered potential alternative or add-on emerging treatments (Ravindran et al., 2013). They are part of two

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main families of long chain polyunsaturated fatty acids (LC-PUFAs) and their names derived from the presence of the first double carbon bond on the third atom from the methyl end of the acyl chain (Haag, 2003; Ruxton et al., 2005). In the human body, the principal n-3PUFAs is docosahexaenoic acid (DHA) while minute quantities of α-linolenic acid (ALA) and eicosapentaenoic acid (EPA) are generally present in tissues. DHA generally exceeds EPA 5- to 30-fold in most organs, and it is several hundred-fold more abundant than EPA in brain and retina (Arterburn et al., 2006). All members of the family are derived from parent fatty acid 18:3n-3 (α-linolenic acid - ALA), via desaturation and elongation ALA. Briefly, EPA is produced from ALA and intermediates stearidonic acid (SDA; 18:4n-3) by Δ5 desaturase (Fads1), and by shortening the carbon chain. Docosapentaenoic acid (DPA, 22:5 n3) is formed from EPA by addition of C2. Followed by further carbon chain elongation and Δ6 desaturation, DPA is converted to 24:5n-3 and 24:6n-3. Subsequently, from the endoplasmic reticulum (ER) the 24:6n-3 is carried to peroxisome, where the peroxisomal β-oxidation, removing C2, synthesizes DHA that then goes back to ER where, by esterification, is rapidly included into the membrane.

Humans cannot synthesize ALA, which can be supplied from certain kinds of food like walnuts, flaxseed and rapeseed oil. In contrast, EPA and DHA can be introduced by diet but can be originated also by the conversion of ALA. However, isotope tracer studies in mammals have shown limited bioconversions of ALA to EPA and docosapentaenoic acid DPA as well as a constrained synthesis of DHA (Barcelo-Coblijn et al., 2009; Burdge et al., 2002; Pawlosky et al., 2001). For this reason, good levels of n-3PUFAs are best obtained by eating fish and seafood rich of EPA and DHA (representing about 30% of the total fatty acids) such as salmon, tuna, halibut, algae and krill. The importance of a diet rich of n-3PUFAs is linked to their central role as structural components of phospholipids in cellular and intracellular membranes (Molfino et al., 2014; Calder P.C. 2012). Furthermore, they have been shown to control cell growth, all types of cells, and vitality through their effects of reducing oxidative stress, caused by excessive free radicals in the blood. In addition to building membranes, n-3PUFAs are essential for the synthesis of eicosanoids, which are important signaling hormones with numerous complex functions (Soberman et al., 2003). Among those derived from n-3 LC-PUFA, we can find factors with anti-inflammatory, antithrombotic and vasodilatory effects while the actions of eicosanoids derived from n-6 LC-PUFA tend to be more pro-inflammatory and vasoconstrictive (Simopoulos, 1991). Therefore, it seems that n-3PUFAs are fundamental in several biochemical processes, in particular during early post-natal development, such as photoreceptor membrane biogenesis, cellular differentiation and active synaptogenesis (Haag, 2003; Ruxton et al., 2005).

Also, it seems that some effects of n-3PUFAs are involving changes in cell membrane fatty acid composition. Changing membrane composition can, in turn, affects membrane order, formation of lipid rafts, intracellular signaling processes, gene expression, and the production of both lipid and peptide mediators (Lauritzen et al., 2016; Simopoulos, 1991, 1996). Moreover, the effects of n-3PUFAs appear to be mediated by, or at least are associated with, changes in fatty acid composition of cell membranes. Changes in these compositions can modify membrane order, lipid raft formation, cell signaling leading to altered gene expression, and the pattern of lipid and peptide mediator production (Kliewer et al., 1997).

In particular, the brain is composed, in large part, of n-3PUFAs, which have been demonstrated to have neuroprotective properties that can explain their role in the onset of certain neuropsychiatric diseases (Galli et al., 1972; Yehuda et al., 2002; Hashimoto et al., 2014). Indeed, n-3PUFAs deficiencies have been reported in people with a wide range of mental disorders, including attention deficit hyperactivity disorder (ADHD), depression, bipolar disorder, and dementia (Assisi et al., 2006; Haag, 2003; Young et al., 2005; Richardson, 2006; Sinn, 2008; Sinclair, 2007). Therefore, n-3PUFAs might be useful as a potential therapy for some psychiatric disorders.

However, not all the subtypes of n-3PUFAs have the same effects on the brain and although evidence showed that EPA, DPA and DHA shared the same neuroprotective effects in aging and neurodegenerative disorders, they are different in terms of their biochemistry, metabolism and therapeutic effect (Dyall et al., 2015). Specifically, DHA is the most common n-3PUFAs in the brain and it has strongly been demonstrated to have unique and indispensable role in the neuronal membrane. Instead, some clinical trials reported more consistent benefits for EPA in mood disorders (Martins, 2009). Indeed, data suggest that n-3PUFAs deficiency might explain the potential etiology of this disorder (Lin et al., 2010, 2012; Lauritzen et al., 2016). In this regard, an ecological study discovered an inverse association between fish consumption and the annual prevalence of major depression (Hibbeln et al., 1998), showing that patients with depression have an abnormal n-3PUFAs composition in their peripheral tissues (e.g., plasma, serum, and red blood cells). Similarly, a recent meta-analysis confirmed that depressive patients have significantly lower levels of total n-3PUFAs, EPA and DHA levels compared to control subjects (Lin et al., 2010; Peet et al., 1998). Additionally, post-mortem studies have shown significant DHA level decrease in people affected by major depression and bipolar disorder in orbitofrontal cortex with preserved levels in hippocampus, anterior cingulate cortex, amygdala, caudate, and entorhinal cortex (Hamazaki et al., 2013).

In this article, we carried out a systematic review of all the studies investigating the role of n-3PUFAs on affective disorders. After providing an overview of the biochemistry and metabolism in relation to their function in the brain, we elucidated the mechanisms of action of EPA and DHA, the two n-3PUFAs most important for the brain, followed by the analysis of their possible role in the genesis of mood disorders. Finally, we carried out a systematic review of all Randomized Control Trials (RCTs) studies investigating the effects of n-3PUFAs on unipolar depression, bipolar depression and perinatal depression (Fig. 1).

2. Methods

A comprehensive search on PUBMED, Medline and PsychINFO of all RCTs using n-3PUFAs on patients with depressive symptoms published up to April 2016 was performed. Articles of potential interest were identified by using the following search terms: “omega-3”, “polyunsaturated fatty acids”, “PUFAs”, “trial”, “EPA”, “DHA”, combined with the following term: “depression”, “affective disorder” or “affective symptom” or “mood disorder”, “unipolar”, “bipolar”, “postnatal”, “postpartum”. In this review, RCTs examining the efficacy of omega-3 fatty acids in adults, adolescents and children with MDD and BD as well as adult women with perinatal depression were selected. Trials were included if they examined the efficacy of n-3PUFAs to target depressive symptoms as a primary outcome and in case they investigated the efficacy of omega-3 PUFAs in treating depressive symptoms in the context of another affective disorder, such as bipolar disorder. Similarly to the inclusion criteria used by Rogers et al. (2010) in their meta-analysis, we included trials that described depressive symptoms in relation to pregnancy and we considered only trials in which the authors used an exposure of n-3PUFAs as a unique treatment or as an adjunctive therapy to antidepressant or mood stabilizers’ drugs compared to placebo.

To limit the heterogeneity of this review and to reduce selection biases we decided to exclude: trials examining the efficacy of n-3PUFAs in treating MDD in subjects with medical comorbidity (i.e. cardiac disease, diabetes, chronic fatigue syndrome, pre-mestrual syndrome); trials where depressive symptoms were secondary to dementia, Parkinson's disease, or multiple sclerosis; trials involving healthy subjects or at risk of psychosis; trials where the primary diagnosis was schizophrenia or schizoaffective disorder, obsessive compulsive