Chapter 10

Omega-3 Docosahexaenoic Acid (DHA) and Mood Disorders: Why and How to Provide Supplementation?

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Additional information is available at the end of the chapter

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1. Introduction

The cost of brain disorders and mental ill-health has been rising sharply in the last years and in developed and some developing countries now exceeds the cost of other diseases, such as cardiovascular or metabolic diseases (diabetes) [1]. Cognitive decline, particularly in the forms of Alzheimer's disease, has emerged in the last 20 years as a major challenge to health systems affecting the quality of life of the ancient population and of the social and economic environment of the patients and family. Diseases, such as depression, schizophrenia, Huntington's disease and other mood disorders are also rapidly increasing as the life expectancy of the population increases. To reduce the risk of mood disorders and cognitive decline in the elderly it is necessary to consider the possible impact of life style and other non-genetic, but modifiable, risk factors. Diet is one of these modifiable factors that may contribute to the prevention or amelioration of chronic neurodegenerative diseases. Among the dietary nutrients most closely associated with the optimal development and function of the brain and nervous system, docosahexaenoic acid (22:6, DHA) an omega-3 fatty acid, exclusively of marine origin, is at present particularly relevant [2].

In this chapter various functions of DHA in the nervous system, its metabolism into phospholipids, and its involvement in different neurological and mood disorders, such as Alzheimer's diseases, depression and bipolar disorders, cognitive decline, aggression, hostility and antisocial behavior, schizophrenia, among others are revised. It is also discussed the different alternatives now available to provide DHA supplementation to prevent or ameliorate mood disorders. There is now different dietary and supplementary form to provide DHA, such as ethyl esters, triglycerides, partial glycerides, phospholipids, etc. [3]. The importance of nutraceuticals of new development based on DHA and other components is also included in our discussion. Figure 1 shows the molecular structure of DHA.

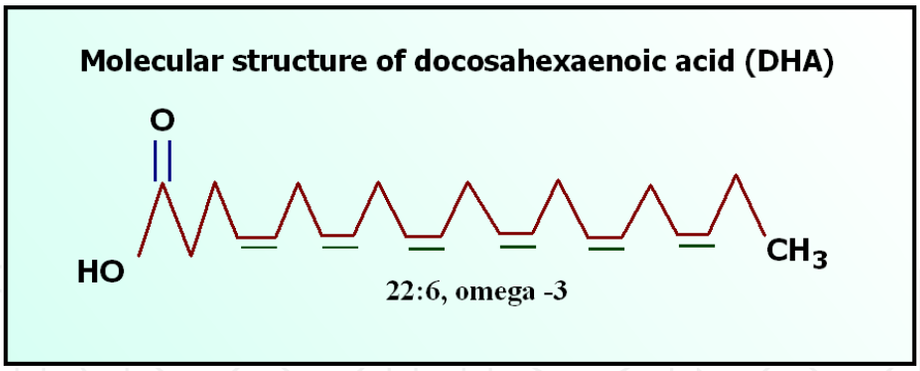

Figure 1.

2. Fatty acids in the brain and nervous system

The brain and the nervous system are the tissues with high content of two polyunsaturated fatty acids: arachidonic acid (20:4, omega-6, AA) and DHA, this last fatty acid being the most important omega-3 long-chain fatty acid in the brain phospholipids, comprising 25% of the total fatty acids of the gray matter. DHA has been the only omega-3 fatty acid used as a major structural and functional component of photoreceptors of the visual system and neurons, and their signaling synaptic structures throughout million years of human evolution [4]. Despite their abundance in these tissues AA and DHA cannot be re-synthesized in mammals. However, the concentration of these fatty acids can be modulated by dietary intake. AA and DHA must be provided by the diet as such (preformed) or through the respective omega-6 and omega-3 precursors from vegetable origin. Linoleic acid (18:2, omega-6, AL) the precursor of AA, is very abundant in the western diet and therefore the formation of AA from AL is not restrictive for humans. On the other hand, alpha linolenic acid, (18:3, omega-3, ALA) the precursor of DHA is less available in our diet and preformed DHA, which is only provided from food of marine origin, is highly restrictive in some populations [5]. The majority of DHA present in the human brain is incorporated during the brain growth spurt which starts at week 26 of gestation and imposes a high demand for the fatty acid until about 2 years of age. DHA is required when neuronal and glial differentiation and migration, and active myelination and synaptogenesis took place in the brain morphogenesis. There is now convincing evidence that neural developmental milestones, determine long-term brain functional capacity in adults [6]. It is supposed that when brain milestones has passed it may be too late to intervene with omega-3 long-chain fatty acids in neurological/neuropsychological disorders such as, depression, and bipolar disorder, mood and cognition, schizophrenia, Alzheimer's disease and Huntington's disease, among others neurological diseases. It has been demonstrate that as the individual ages, a constant reduction of the DHA content of the brain occurs, and in some neurological diseases, such as Alzheimer's disease, a more pronounced reduction of the fatty acid occurs. Epidemiological evidence now suggest that a decrease in brain DHA levels, which normally occurs during aging, and that is exacerbated by reduced dietary intake of DHA, may increase the preva-

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lence of neurological diseases. The identification of several DHA-derived metabolites (such as resolvins and neuroprotectins, among others), probably involved in cell signaling suggest that free DHA, liberated from membrane phospholipids, is utilized to perform many other functions beyond a structural role in membrane phospholipids of neuronal cells. The first DHA-derived metabolite is neuroprotectin D1 which can be synthesized from free DHA through a lipoxygenase enzyme [7]. Neuroprotectin D1 is generated during stroke and counteracts pro-inflammatory gene expression that normally results from ischemic damage. Neuroprotectin D1 has anti-inflammatory, antiapoptotic and even neuroregenerative effects, which would help to preserve in general, both the neuronal functioning and the nervous system [8]. This molecule also counteracts potential oxidative damage to DNA in the retinal pigment ephitelium cells [9]. Research about food and/or additives that preferentially provide DHA and molecules that promote its internalization, transport and metabolism will be of basic importance to fully understand the importance in the development, normal function, senescence, and pathology of the nervous system. Basic, clinical and epidemiologic research supports a protective effect of DHA in mood disorders.

3. DHA in the brain cells

Within neurons DHA is almost specifically concentrated in membrane phospholipids, mainly at phosphatidylethanolamine and phosphatidylserine, the latter being the major acidic phospholipid present in brain cell membranes [10]. Phospholipids which make up about one quarter of the solid matter in the brain are also an integral part of the vascular system from which brain cells function and nutrition depend. DHA constitutes 15-20% of the total fatty acid composition of the brain cortex, and when incorporated into phospholipids may improve the efficiency of synaptic membrane vesicles in fusion events (i.e., synaptic vesicles with terminal axonal membrane) which are fundamental for neurotransmission [11]. DHA may also function in synaptic signaling, either as a free fatty acid, as a metabolite (such as, neuroprotectins) or incorporated into phospholipids structure. DHA is also highly concentrated in growth cones during neurite outgrowth were it may be important for maximal neurite growth during brain development, which occurs mainly during the perinatal period [12]. In the adult, DHA is found in neuronal dendrites, where it may be involved in the extension and establishment of the dendritic arborization which occurs during memory formation and acquisition of learning capabilities, modifications which originate the so-called brain plasticity. Additionally, DHA may be important for the efficient regeneration of axons and dendrites in some brain regions, such as cerebellum and hippocampus, after brain injury. Supplementing cultured neuronal cell types with AA and DHA at low concentrations significantly increases neurite outgrowth in several neuronal cell types, principally those from hippocampus [13]. However, there is a limit to the amount of AA to be added because at higher concentrations this fatty acid may be cytotoxic. DHA, however, shows stimulant effects and no cytotoxicity in a wide range of concentrations [14].

3.1. The role of DHA in neuronal phospholipid synthesis

DHA appears to enhance neurite outgrowth be several mechanisms which include an increase in the synthesis of specific phospholipids [13]. In differentiating and mature neurons DHA is preferentially incorporated into phospholipids than into triglycerides. During the synthesis of neuronal phospholipids, DHA is acylated to the sn-2 position of phospholipids to generate phosphatidic acid, which is the precursor of phosphatidylinositol, which in turns is the precursor of inositoltriphosphate (IP3) an important second messenger signal. However, most of the phosphatidic acid is subsequently dephosphorylated to generate diacylglycerol, which is further metabolized into phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine, all of these molecules containing DHA at the sn-2 position [13]. Therefore, it appears that diacylglycerols containing DHA at the sn-2 position are preferentially transformed into phospholipids. This specific transformation occurs through the action of specific enzymes. For example, diacylglycerol molecules that contain DHA at the sn-2 position are the preferred substrate of enzyme ethanolamine phosphotransferase which convert diacylglycerol to phosphatidylethanolamine through the covalent linking of ethanolamine to the sn-3 position of diacylglycerol [15]. Phosphatidylethanolamine may also be converted to phosphatidylserine through the exchange of its nitrogen base with free serine [16].

3.2. The role of DHA in membrane neuronal function

The quantity of double bonds in a fatty acid is directly related to the flexibility of the molecule. Saturated fatty acids, such as palmitic acid (16:0) or stearic acid (18:0) are rigid. This rigidity allows saturated fatty acids to pack together tightly and form a solid structure at lower temperatures. Phospholipids formed by these fatty acids are also rigid structures. The introduction of double bonds into a fatty acid introduces a "kink" in its structure which modifies its spatial conformation. DHA, which has six double bonds, may adopt many countless conformation because the molecule can rotate around C-C bonds but not around the rigid C=C bonds that conform its high polyunsaturation [17]. The highly flexible structure of DHA will not allow phospholipids containing DHA to pack tightly together, resulting in a significant increase in membrane fluidity relative to phospholipids formed only by saturated fatty acids. Membranes having high content of DHA may also increase the efficiency of membrane fusion events which are important in neurotransmission [18]. Additionally, an increased fluidity of membrane appears to be important for increasing the rate at which membrane protein-protein interaction occurs within the phospholipid membrane bilayer. Fluidity is especially relevant in the outer segments of retinal photoreceptors where the activation of G type protein transducin by the rhodopsin-metarhodopsin interaction events occurs within the phospholipids of photoreceptors cells. This process does not occur efficiently when the level of DHA in the phospholipids of vision cells is reduced either during normal aging or by pathological causes [19]. Mitochondrial phospholipids are also enriched in DHA. High DHA in mitochondrial membranes may increase the efficiency of the electron transport chain and the ADP-phosphorilation process by increasing the lateral movement of protein within the membrane bilayer, thus facilitating protein-protein interactions [20]. Additionally, there is a direct correlation between the DHA content of mitochon-

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drial phospholipids and the permeability of the inner membrane to protons [21], thus improving the efficiency of energy production through oxidative phosphorylation. It is generally concluded that DHA positively influences mitochondrial energy production, which is crucial in a cell highly demanding of energy, such is the neuron.

3.3. DHA and the activity of neuronal enzymes

Receptor functioning and the activation of membrane proteins involved in signaling transduction can be influenced by DHA, either as a free fatty acid and/or when it is incorporated into membrane phospholipids. DHA is concentrated in the phospholipids of neuronal tissues, including hippocampus and cerebellum, which are involved in learning as well as in memory storage [22]. Most recently we demonstrated that DHA supplementation to mother rats during the perinatal period, increases the DHA content of different brain segments of the pups, including hippocampus and cerebellum, and improves the learning and memory capacities of the pups when evaluated through the Skinner box test [23]. As part of the diacylglycerol molecule, DHA may enhance the diacylglycerol-dependent activation of the protein kinase C (PKC) [24]. It is interesting that PKC has an essential requirement for phosphatidylserine [25], which contains a high concentration of DHA. However, in vitro evidence is suggesting that unesterified DHA may competitively inhibit phosphatidylserine dependent PKC inhibition. Unesterified AA either stimulates or has no effect on PKC activity [26], showing that activation of the enzyme by omega-3 fatty acids may be specific to these fatty acids. Another example of an enzyme whose function is modified by DHA is Na +/K+ ATPase, also known as sodium pump, which is an integral protein of the neuronal membrane found in higher concentration at the axonal nodes (Ranvier nodes). The primary neuronal function of these ATPases is to generate and maintain Na+ and K+ gradients which are necessary to maintain the resting potential of the neuronal membrane. The activity of Na +/K+ ATPase is increased in the sciatic nerve of rats that are supplemented with DHA [27].

3.4. Inhibition of neuronal apoptosis by DHA

Neuronal cell survival is highly dependent on the presence of trophic nerve factors which influence downstream signalling pathways. Modifications in the concentration and/or number of these factors may lead to apoptotic cell death. Early signs of apoptosis include the loss of intracellular water, an increase in cytoplasmic calcium concentration, the releasing of cytochrome c from mitochondria and the translocation of phosphatidylserine to the outer leaflet of the plasma membrane [28]. The activation of the caspase-3 enzyme by self-cleavage results in the death of cells by apoptosis [29]. The prevention of apoptosis by DHA incorporation into phospholipids has been reported for rat retinal photoreceptors [30], HL-60 cells [31], and Neuro 2A cells [32]. Additionally, an increased dietary intake of DHA prevents apoptosis in mouse retinal photoreceptors when subjected to N-methyl-N-nitroso urea, a potent inducer of apoptosis [33]. DHA accumulation in phospholipids, mainly in phosphatidylserine, appears to promote neuronal survival under adverse conditions [32]. As discussed above, in the nervous system, DHA is incorporated primarily into anionic phospholipids such as phosphatidylserine and phosphatidylethanolamine [34]. Phosphati-

dylserine is synthesized from phosphatidylethanolamine or phosphatidylcholine by the serine replacement of ethanolamine or choline, respectively, in a base-exchange reaction. Phosphatidylserine is involved in a series of cell signaling events. The supplementation of cells with unesterified DHA promotes phosphatidylserine biosynthesis [35]. The enrichment of DHA in phosphatidylserine and its effect on phosphatidylserine biosynthesis are most likely due to the fact that phospholipid species containing DHA are the best substrates for phosphatidylserine synthesizing enzymes [36]. There is not a direct correlation between the level of phosphatidylserine and DHA content in different brain segments. The antiapoptotic effect of DHA in neurons occurs only when the fatty acid is added to cultured cells or when experimental animals have been treated previously with DHA, which may suggest that these effects are due to the incorporation of DHA into different phospholipids. It is interesting to note that in other non-neuronal cell types, DHA actually promotes apoptosis. For example, in CaCo-2 cells, a colon cancer cell line, DHA induces apoptosis by "down regulating" reducing the expression of antiapoptotic genes and increasing the expression of proapoptotic genes [37]. Therefore, the antiapoptotic effects of DHA-containing phosphatidylserine are probably specific to neuronal cells and critical for the long-term survival of these cells.

3.5. DHA and the regulation of gene expression in neurons

It has been demonstrated that polyunsaturated omega-3 fatty acids can modify gene expression by binding to specific receptors and transcription factors in the liver and adipose tissue. Receptors activated by DHA include retinoid X, peroxisome proliferator activated receptors (PPARs), hepatic nuclear receptor, and sterol regulatory element binding protein (SREBP) receptor [38]. The activation of each of these proteins modulates the expression of genes involved in the metabolism of glucose, fatty acids, triglycerides, and cholesterol. Of these proteins, the retinoid X receptor is present in significant levels in the brain, and DHA is an effective ligand and activator of the retinoid X receptor protein [39]. Activation of gene expression by DHA is not restricted to brain cells, the fatty acid activates several genes in other tissues, like liver or adipose tissue [40]. In rat brain cells, the stimulation of peroxisomal proliferator activated receptor β (PPAR β) resulted in the up regulation of the mRNA encoding a protein that converted DHA to the acyl-CoA derivative [41]. Upon alteration of the expression of genes involved in lipid metabolism, the optimal environment for neurite outgrowth can be achieved during neuronal differentiation and brain formation. For example, omega-6 and omega-3 PUFAs have been shown to decrease the expression and the activity of Δ-9 desaturase, the enzyme that converts stearic acid (18:0) to oleic acid (18:1, omega-9). This effect may be important to ensure that saturated fatty acids, whether newly synthesized or taken in from the diet, are available for the insertion of phospholipids into the sn-1 position as they are synthesized. Several studies have demonstrated that the DHA increasing effect on neurite outgrowth may be, in part, a consequence of the DHA stimulation of the expression of genes that promote phospholipids synthesis [42,43]. Using microarray gene expression methodology, it has been demonstrated that fish oil or DHA supplementation can modify the expression of many of the genes of the brain and retina involved in signal transduction, eicosanoid production, synaptic plasticity, and energy metabolism in rats [44].

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4. DHA and alterations of neuronal functioning in mood disorders

Accelerated cognitive decline in middle age can make an individual more vulnerable to mood disorders in later life. Experts agree that once cognitive decline is accelerated and properly identify, it is advisable a prompt intervention [2]. During periods of nutritional deficiency of omega-3 fatty acids, DHA is retained to depletion from the phospholipids of neurons through two possible mechanisms: a) DHA released from membrane phospholipids is rapidly reacylated to specific phospholipids. b) It is produced a significant reduction in the rate of transfer of DHA out of the nervous system through the blood brain barrier. Many neurodegenerative conditions, such as Alzheimer's disease, retinal affections, and some peroxisomal disorders (Zellweger syndrome and adrenoleucodistrophy) are associated with reduced levels of omega-3 fatty acids. Mood disorders, such as depression, schizophrenia, and post-partum depression, have also been associated with modification of DHA metabolism. Epidemiological, experimental and clinical research support the hypothesis that DHA may play a role in the pathogenesis and eventually in the prevention and/or in treatment of these diseases [45,46].

4.1. Alzheimer's disease

Alzheimer's disease is a late-onset progressive, neurodegenerative disease of heterogeneous origin which is devastating both to the afflicted person and to the person's family. Before the dementia which characterizes the pathology is established, Alzheimer's disease may manifest through subtle cognitive decline greater than expected for an individual's age and education but with minimal impact on daily living. This transitory and still reversible stage is usually termed mild cognitive impairment [47]. However, once it is clinically diagnosed there is little prospect of improving the prognosis. The pathology is characterized by the formation of amyloid plaques, neurofibrillary tangles, and dystrophic neuritis. Data from numerous epidemiological studies suggest an inverse correlation between DHA intake and the likelihood of developing Alzheimer's disease. A reduction in the level of total phospholipids, as well as a decrease of DHA, has been described in various cerebral areas in Alzheimer's disease patients [48]. With aging, neural membrane fluidity is compromised due to the increased presence of cholesterol, and reduced activity of glial desaturase enzymes and blockages to phospholipids pathways of transduction signals and oxidative stress, all of which are inversely associated with omega-3 polyunsaturated fatty acids [49]. These processes are highly exacerbated in Alzheimer's patients. Brain autopsies of Alzheimer's disease patients have shown significantly higher saturated fatty acid and lower omega-3 polyunsaturated fatty acid content in the hippocampus and frontal lobes which govern memory and executive functions, respectively [50]. Studies have demonstrated that the levels of phosphatidylethanolamine, which is enriched in DHA, and phosphatidylinositol, which is enriched in AA, are significantly reduced in the brain of individuals affected by Alzheimer's disease. Specifically there is a significant reduction in the amount of DHA in the frontal cortex and hippocampus phospholipids of patients with Alzheimer's diseases. Alzheimer's disease is characterized by the accumulation of various β amyloid (Aβ) peptides resulting from the cleavage of the amyloid precursor protein, in particular peptides composed of 40 (Aβ 40)

and 42 (Aβ 42) aminoacids. Aβ peptide is produced constitutively during cell metabolism but under normal conditions, the peptide does not accumulate in brain. It has been proposed that the central event in Alzheimer's disease pathogenesis is an imbalance between Aβ peptide production and clearance, with increased Aβ peptide production and/or decreased Aβ clearance during the onset of the pathology [51]. The pretreatment of rats with DHA protected the animals against the memory loss which typically occurs when animals are infused with Alzheimer's disease Aβ peptide, which triggers synapse destruction [52]. DHA inhibits the accumulation of insoluble Aβ peptide, partially by decreasing cholesterol levels in the detergent insoluble neuronal membrane domains (rafts) of the cerebral cortex [53] and this effect is strongly influenced by the age of animals [54]. It has been demonstrated that the effect of DHA in the reduction of insoluble Aβ peptide is attributable to a decrease in steady-state levels of presenilin 1 [55]. In cognitive test animals expressing high levels of a mutant amyloid precursor protein, showed low levels of DHA in brain phospholipids. Additionally, the activity of phospholipase A2, which is involved in the liberation of AA from brain phospholipids, increases in the brain of patients with Alzheimer´s disease, suggesting that an increased generation of AA-derived eicosanoids, which are antagonist of DHA-derived docosanoids, may contribute to the etiology of Alzheimer's disease. It has been proposed that DHA-derived neuroprotectin D1 induces an antiapoptotic and neuroprotective gene expression program that regulates the secretion of Aβ peptide, resulting in the modulation of inflammatory signaling, neuronal survival, and the preservation of brain function [7]. The typical Western diet provided < 30% of the 200-300 mg/day of DHA recommended by Expert Panels. Epidemiology show a risk reduction of 60% associated with a modest increase in DHA intake or plasma levels. DHA may works well in slowing down Alzheimer´s disease pathogenesis in mice with a human Alzheimer's disease gene [56]. DHA provided by supplementation (e.g. fish meals, fish oil capsules, or other forms of DHA supplementation), could restore DHA deficiency in membrane phospholipids in the cerebral cortex of patients with Alzheimer's disease [57]. DHA together with natural antioxidants, may exert general anti-Alzheimer's and anti-aging benefits [58]. Studies have indicated the apparently crucial role of DHA in preventing Alzheimer's disease in its very mild, precocious stages [46]. However, studies on the exact molecular mechanism underlying the beneficial effects of DHA are required to validate the hypothesis that changing dietary habits or promoting dietary supplementation with DHA can considerably improve human health and specially may prevent, or delay, the onset of cognitive impairment in mild cases of Alzheimer's disease.

4.2. Depression and postpartum depression

Depression is characterized by high levels of depressed or low mood, a lost in interest or pleasure in nearly all activities, changes in appetite, weight, sleep or activity, decreased energy, difficulties in thinking, concentration or making decisions, feeling or worthlessness or guilt, and recurrent thoughts of death or suicidal ideation, plans or attempts. Depression and major depressive disorder are serious affective illness with a high lifetime prevalence rate that particularly involves neurotransmission processes, especially serotonin receptors and membrane transporters [59]. The World Health Organization estimates that depressive

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disorder will become the second leading cause of disability worldwide by 2020, second to ischemic heart disease, and will be the leading cause in developing regions [60]. The etiology of the illness is multifactorial and is influenced by genetic, environmental and nutritional factors. Epidemiologic, neurobiologic, and clinical studies suggest that a relative deficiency in omega-3 polyunsaturated fatty acids contributes to depression. Support for a nutritional contribution to the disease derives from studies that report an inverse correlation between the level of omega-3 fatty acids as measured either in red blood cells phospholipids or adipose tissue, and symptoms of depression. An increasing ratio omega-6/omega-3 is frequently observed in patients with depression [61]. Numerous studies carry-out over the last few years are involving omega-3 long-chain fatty acid supplementation with the reduction of any of the symptoms of different forms of depression, including bipolar disorders, postpartum depression (included forward), agoraphobia, and anorexia nervosa. According to meta-analysis realized by Lin and Su [62], it is concluded that DHA supplementation may reduce the symptoms of depression. Depression and coronary artery disease often occurs in the same individuals who frequently have low plasma levels of DHA and high levels of AA. Omega-3 supplementation shows as effective for the treatment of these disorders. Reducing omega-6 polyunsaturated fatty acid intake as well as increasing omega-3 polyunsaturated fatty acids, specifically DHA, for a more balanced ratio may be beneficial [63]. However, the mechanism by which DHA may reduce depression is still unclear, and more research is needed. As discussed, increasing the nutritional level of omega-3 fatty acids may modify the activity of integral membranes proteins (receptors, ion channels, molecular pumps, etc.), and/or counteract the proinflammatory action of AA-derived eicosanoids. However, there is no consensus about the positive effect of omega-3 fatty acids in depression which is accompanied with other comorbid. Lespérance et al. [64] not observed significant differences of omega-3 supplementation over placebo in reducing depressive symptoms in patients with anxiety comorbid, but the same researchers observed a clear benefit of omega-3 supplementation in patients without comorbid anxiety disorders.

Depression during pregnancy and postpartum depression have negative impact on the development and health of the newborn. Maternal stress in humans is associated with fetal hypoxia, reduced gestational age, and low birth weight. Evans et al., in an study comprising different countries found that 13.5% of women (n= 14,451) experienced serious symptoms of depression during pregnancy and postpartum [65]. A cross-national analysis of seafood consumption, and the DHA content of breast milk, demonstrated an inverse correlation with the prevalence of pregnancy and postpartum depression. The prevalence varied from 0.5% in Singapore to 24.5% in South Africa, with a mean prevalence worldwide of 12.4%. Both, higher national seafood consumption and higher DHA content in the mother's breast milk predicted a lower prevalence of postpartum depression. The mean DHA intake of western women is estimated at 15-20 mg/day, whereas intake of countries with high fish consumption (e.g Japan, Korea and Norway) is approximately 1000 mg/day. During the third gestational trimester, the fetus accumulates an average of 67 mg/day of DHA, in excess of dietary intake of many mothers. Such transfer to the baby through the placenta and, subsequently through breast milk poses a risk to women to significant depletion of omega-3 fatty acids during lactation, contributing to the perinatal risk of depression. A review by Parker et al.,

about omega-3 fatty acids and postpartum depression, proposed that DHA supplementation in the perinatal period may have additional benefits to the infant's neurodevelopment. Women and their physicians prefer options to standard antidepressant medication during pregnancy and postpartum. DHA supplementation during these periods may be a plausible alternative. However, more clinical trials are needed to confirm the recommendation of omega-3 fatty acid supplementation to avoid or reduce symptoms of depression [3].

4.3. Schizophrenia

Schizophrenia is defined by a mixture of characteristics (positive and negative) signs and symptoms which have been present for a significant proportion of time during a one-month period with indications of the disorder persisting for at least six months. Positive symptoms reflect an extension or distortion of normal functions, for example, delusions, hallucinations, and disorganized speech or behavior. Negative symptoms reflect a diminution or loss of normal functions, for example, restrictions in the range or intensity of emotional expression, restriction in the fluency or productivity of thought or speech, and restrictions in the initiation of goal-directed behavior [66]. Schizophrenia is a psychiatric disease that affects 1-1.5% of the population with higher prevalence in males than in females. The predominant hypothesis regarding the pathophysiology of the disease is dysfunction of the dopaminergic system. However further finding concerning the disease suggests a close relationship with reduced tissue levels of omega-6 and omega-3 fatty acids specially AA and DHA [67]. A "phospholipid membrane hypothesis of schizophrenia" emerged in the late 1970's [68]. This hypothesis encompasses abnormalities of long-chain omega-6 (AA) and omega-3 (DHA) fatty acids. Fenton et al., list multiple analyses of red blood cell membranes (recognized markers for essential fatty acid status) that consistently document depletion of AA and DHA [68]. This depletion is also observed in plasma, thrombocytes and post-mortem brain tissue of schizophrenia patients. Several mechanism could explain these deficits, including an increased activity of phospholipase A2 thus producing the extraction of AA and DHA from cerebral membrane phospholipids [69]. Another argument in favor of a relationship between schizophrenia and omega-6/omega-3 fatty acids is that dietary supplementation of either AA and DHA or their precursors is able to alleviate the symptoms of the disease [70]. Tissue omega-3 and omega-6 levels are negatively and positively associated with the hostility and aggressive behavior in patients with schizophrenia [71]. It has been proposed that an alteration of DHA metabolism in the brain is involved in the pathophysiology of schizophrenia and that omega-3 fatty acid supplementation may be an important coadjutant in the treatment of the disease [72]. It seems therefore that schizophrenia might be an example of a disease in which omega-6 and omega-3 supplementation, presumably AA and DHA, associated with pharmacological treatment might be beneficial, although extended evaluation of such complementary treatment is still required [68].

4.4. Aggression, hostility and anti-social behavior

The role of diet in aggression, hostility and anti-social behavior has been extensity revised and a relationship with omega-3 fatty acid has been established [73]. Epidemiological stud-

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ies have suggested a link between poor omega-3 fatty acid status and aggression, hostility and anti-social behavior. A negative correlation between seafood consumption and homicide mortality statistics has been observed in many countries [74]. The result of intervention studies with omega-3 fatty acids (DHA) plus other ingredients have been, however, equivocal. The study populations have been heterogeneous, sometimes with a small number of subjects. Despite this, there are some encouraging data emerging. Studies in prisoners in the USA have provided some support regarding micronutrients and omega-3 fatty acids as it was observed a 30% reduction in violence among a small population of young violent offenders in prison. However for more accurate results, the study needs to be replicated on a larger scale. The general conclusion is that high dietary intake of DHA may be related to lower likelihood of high hostility in young adulthood [75]. This is clearly an area where more research is required, particularly in defined populations with large number of subjects.

4.5. Retinal function and pathologies

Retinal pathologies are not directly involved with mood disorders. However, retinal tissue is derived from neuronal cells and DHA is essential for the proper development and functioning of this visual tissue. The fatty acid is particularly concentrated in the outer membrane segments of the photoreceptors cells, cones and rods. DHA is required for the survival of retinal photoreceptors and exerts a protective effect on apoptosis of these photoreceptors during visual development [36]. Retinitis pigmentosa is a visual disease with a worldwide prevalence of 1 in 4000 individuals [76]. Photoreceptor cell degeneration is a feature of the disease and the death of these cells in many instances seems to involve closely associated retinal pigment epithelial cells. Under normal circumstances, both cell types are subjected to potentially damaging stimuli (e.g. sunlight and high oxygen tension). However, the mechanism by which homeostasis is maintained in this part of the ye, which is crucial for sight, are an unsolved riddle. A correlation between retinitis pigmentosa and low retinal DHA levels has been observed, were evidence show that the synthesis of DHA is impaired in patients suffering from X-linked retinitis pigmentosa [32]. Supplementation with DHA (400 mg/day) for four years produces a significant reduction in the loss of functionality of rods in patients with retinitis pigmentosa, as assessed by an electroretinogram which measures the photoreceptor activity. For patients with retinitis pigmentosa beginning vitamin A therapy, together with DHA (1200 mg/day), slowed the evolution of the decline in visual field sensitivity [77]. It has been suggested that DHA upon its transformation in neuroprotectin D1 may inhibit oxidative stress-mediated proinflammatory gene induction and apoptosis, and consequently promotes retinal pigment epithelial cell survival [78]. Results suggest that early intervention with DHA, may be important in slowing down the progression of retinitis pigmentosa.

5. Possible mechanism for links between DHA and mood disorders

Several neurophysiological mechanisms have been proposed to explain the relationship between omega-3 polyunsaturated fatty acids and mood disorders [79]. DHA appears to decrease the production of inflammatory eicosanoids from AA by means two mechanisms:

First, DHA compete with AA for incorporation into membrane phospholipids, thus decreasing both cellular and plasma levels of AA. Second, DHA, compete with AA for cyclooxygenase enzyme system, inhibiting the production of proinflammatory eicosanoids derived from AA (e.g. prostaglandins, leukotrienes, thromboxanes). Prostagladin E2 and thromboxane B2 have linked to depression. DHA also inhibits the release of proinflammatory cytokines such as interleukin-1 beta, interleukin 2, interleukin 6, interferon gamma, and tumor necrosis factor alpha, which depends on eicosanoid release and are also associated with mood disorders, such as depression [80]. Another possible mechanism relates to the abundance of DHA in brain phospholipids were they play a vital role in maintaining the integrity and fluidity of neuronal membranes. By varying the lipid concentration in cell membranes, changes in fluidity can affect either the structure and/or functioning of proteins embedded in the membrane, including enzymes, receptors, ion channels, molecular pumps, leading to changes in cellular signaling [45]. Support for the involvement of DHA in receptor functioning, neurotransmitter levels and the metabolism of monoamines implicated in mood disorders has been provided by animal studies [81].

6. How to provide DHA supplementation

After the suggestion years ago of Expert Committees to include omega-3 long-chain polyunsaturated fatty acids from marine origin in infant formulas, efforts were made to identify suitable sources for these fatty acids, mainly DHA. Refined and deodorized fish oil was initially used because of it availability and relatively high content of DHA. However many concerns related to different levels of contamination of fish oil with heavy metals and organic compounds encouraged seeking others sources for DHA supplementation. Today the recommendation has been also extended to adults and especially to those going to elderly, due the possible beneficial effect of DHA supplementation to prevent mood and neurodegenerative diseases. At present, new other sources for DHA supplementation are available to provide the fatty acids in variable amounts and degrees of purity. The advantages/disadvantages of these DHA sources are discussed.

6.1. Free DHA and DHA-ethyl ester

Since fish oil contains a mixture of triacylglyerols with various fatty acids, the concentration of DHA may be relatively low (not higher than 18%, such as tuna or salmon oil). However, higher concentrations of DHA can be achieved from the hydrolysis of fish oil and further separation of selected fatty acids, such as DHA, by column chromatography or molecular distillation. Pure preparations of DHA as free fatty acid or as DHA-ethyl ester have been developed for supplementation. Pure DHA, as free fatty acid, may cause gastrointestinal complaints [82] and is very unstable to oxidation and difficult to be incorporated to food preparations (milk, dairy products, juices, etc.). Ethyl ester preparations have not side-effect and are less unstable than DHA free form. Although DHA-ethyl ester preparation has been used in several experimental protocols [83], the efficacy of these products is controversial due the low absorption efficiency observed in the intestinal tract [84]. Emulsions, soft capsu-

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les and beverages containing DHA ethyl ester are widely available in some western and oriental countries

6.2. Single cell algae DHA-rich oil

Some marine algae produce naturally large amounts of DHA that can be extracted from collected cells as a clear, odorless algae oil having concentrations up to 40% of DHA [85]. Antioxidants (tocopherols or some others natural antioxidants) are added to the oil to prevent oxidation. Algae oil rich in DHA has been considered a substance "Generally Recognized as Safe" (GRAS) by the US-FDA having good stability and biological availability. Algae oil can be added to a wide variety of food and nutraceutical products. The oil can also be microencapsulated allowing its incorporation to powdered foods to be reconstituted just when served.

6.3. DHA from egg yolk and marine phospholipids

Much evidence gleaned from animal studies (rodents and primates) indicates fatty acids are more available when provided in the form of phospholipids than triglycerides or ethyl esters [86]. Egg yolk is a complex oil/water emulsion containing 32% lipids. A substantial fraction of these lipids are phospholipids containing on average 0.4 – 0.6% of DHA. These concentrations can be increased by feeding laying hens with linseed oil, canola oil or directly with fish oil. Under these conditions DHA can be increased to 1.5 – 2.0% (150 – 170 mg DHA/yolk). Industrially, egg yolk powder is treated with solvents to isolate lipids and phospholipids and thereafter phospholipids are extracted by emulsifying with water followed by spray-drying. Egg yolk phospholipids can be safety incorporated to a wide variety of food products as has been used for many years to increase DHA content (and also AA content) of infant formulas and represent an interesting alternative for the development foods or supplements for the aged population.

Marine phospholipids are a more recently alternative to provide DHA. The main source for these phospholipids which have up to 20% DHA is krill (*Euphausia superba*), a small crustacean which is massively captured in the Antarctic sea. Krill is thought to be the largest single biomass on the planet and is life sustaining food for diverse marine animals [87]. The product obtained after processing krill is intense red colored oil, due its high concentration of carotenes (mainly astaxantin) which provided high stability to the oil. Due its coloration it is not suitable to be added to foods and is used mainly for the preparation of dark capsules. Also, dietary oils extracted from other crustacean (*Calanus finmarchicus*), have interesting features. Calanus oil is comprised of omega-3 fatty acids incorporated to phospholipids and to wax esters having a relatively high content of astaxantin [88]. Phospholipids containing DHA are also obtained from the enzymatic digestion of whole fatty fish, salmon or sardine by-products (viscera's) or salmon eggs [89].

6.4. sn-2 DHA monoacylglyceride

This is a new experimental source for providing DHA supplementation. It is a monoacylglyceride containing DHA at the sn-2 (central position) of the glycerol molecule, which is ob-

tained from the controlled enzymatic hydrolysis of refined salmon oil [90]. The bioavailability of the product has been assayed in rats showing a high intestinal absorption and producing a high tissue accretion of DHA in animals [91]. The product, which contains added tocopherols as antioxidant, can be easily incorporated into water due its emulsifying properties that allow its incorporation into water-containing beverages, milk, milk-derived products, and also to baked products and sausages. The product is currently assayed by our group in the development of juices and soups for the elderly population which receive public nutritional support in Chile.

7. Conclusions and future prospects

The effectiveness of strategies involving DHA to reduce the risk of Alzheimer's disease or other cognitive and mood disorders depend on a good understanding of how the low intake or low tissue levels of DHA would increase the risk of these diseases. Solid basis now exist to believe that low DHA intake may contribute significantly to the early onset of cognitive and mood diseases, and that the supplementation with DHA may have substantial benefits. Epidemiological evidence suggest that a decrease in brain DHA levels, which normally occurs during elderly, and that it is exacerbated by reduced dietary intake of DHA, may increase the prevalence of several neurological diseases as such discussed in this chapter. However at present we do not understood at all the complex functions that DHA performs as either as free fatty acid and/or incorporated to neuronal phospholipids. The identification of several DHA-derived metabolites, probably involved in cell signaling, suggest that DHA is utilized to perform many functions beyond a structural role in phospholipids and membrane structure. Future research about food and/or additives that preferentially provide DHA and molecules that promote its internalization, transport and metabolism is clearly needed to understand the importance of DHA in the development, normal function and senescence of the brain and nervous system. Establishing the functions of DHA in the brain will be critical to evaluate the health implications of a reduced dietary intake of DHA as occurs in western populations, and the importance of DHA supplementation at the early stages of human life. The optimal duration of DHA supplementation, allowing a clinical benefit to be observed, still needs to be established. Basic, clinical and epidemiological research supports the importance of DHA in mood disorders. However, results are at present not fully convincing and in some case confounding and more research is definitively needed. Probably in the next years we will have more solid evidences about the function of DHA in the brain and nervous system and of its preventive or ameliorative effect in mood disorders.

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