

Omega-3 fatty acids and neuropsychiatric disorders

Genevieve YOUNG^a, Julie CONQUER^{a,b*}

^a Human Biology and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada

^b RGB Consulting, London, Ontario, Canada

(Received 24 September 2004; accepted 24 November 2004)

Abstract – Epidemiological evidence suggests that dietary consumption of the long chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), commonly found in fish or fish oil, may modify the risk for certain neuropsychiatric disorders. As evidence, decreased blood levels of omega-3 fatty acids have been associated with several neuropsychiatric conditions, including Attention Deficit (Hyperactivity) Disorder, Alzheimer's Disease, Schizophrenia and Depression. Supplementation studies, using individual or combination omega-3 fatty acids, suggest the possibility for decreased symptoms associated with some of these conditions. Thus far, however, the benefits of supplementation, in terms of decreasing disease risk and/or aiding in symptom management, are not clear and more research is needed. The reasons for blood fatty acid alterations in these disorders are not known, nor are the potential mechanisms by which omega-3 fatty acids may function in normal neuronal activity and neuropsychiatric disease prevention and/or treatment. It is clear, however, that DHA is the predominant n-3 fatty acid found in the brain and that EPA plays an important role as an anti-inflammatory precursor. Both DHA and EPA can be linked with many aspects of neural function, including neurotransmission, membrane fluidity, ion channel and enzyme regulation and gene expression. This review summarizes the knowledge in terms of dietary omega-3 fatty acid intake and metabolism, as well as evidence pointing to potential mechanisms of omega-3 fatty acids in normal brain functioning, development of neuropsychiatric disorders and efficacy of omega-3 fatty acid supplementation in terms of symptom management.

Alzheimer's disease / attention deficit hyperactivity disorder / autism / depression / neuropsychiatric disorders / omega-3 fatty acids / post partum depression / schizophrenia

Abbreviations

Ach: acetylcholine, AD: Alzheimer's disease, AA: arachidonic acid, ADD: attention deficit disorder, ADHD: attention deficit hyperactivity disorder, AI: adequate intake, ALA: alpha-linolenic acid, BPD: borderline personality disorder, CE: cholesterol ester, DGLA: dihomo-gammalinolenic acid, DHA: docosahexaenoic acid, DPA: docosapentaenoic acid, EPA: eicosapentaenoic acid, EFA: essential fatty acid, GLA: gamma linolenic acid, IFN: interferon, IL-1: interleukin-1, IL-2: interleukin-2, IL-6: interleukin-6, LTB4: leukotriene B4, LTB5: leukotriene B5, LA: linoleic acid, LCPUFA: long chain polyunsaturated fatty acids, MMSE: mini mental state examination, NE: norepinephrine, OCD: obsessive compulsive disorder, PPAR: peroxisome proliferated activated receptor, PANSS: positive and negative symptom scale, PPD: post partum depression, PG: prostaglandin, PL: phospholipids, PLA2: phospholipase A2, RBC: red blood cell, SSRI: selective serotonin reuptake inhibitor, SREBP: sterol regulatory element binding protein, TG: triglycerides, TNF: tumour necrosis factor.

* Corresponding author: jconquer@uoguelph.ca

1. INTRODUCTION

In the past decade, interest has surged in the area of omega-3 fatty acids and their role in normal brain functioning and neuropsychiatric disease treatment and prevention. Although omega-3 fatty acids are present in plant-based sources such as alpha-linolenic acid (ALA; 18:3n-3), this review will focus mainly on the animal derived long chain n-3 polyunsaturated fatty acids (eicosapentaenoic acid; EPA; 20:5n-3 and docosahexaenoic acid; DHA; 22:6n-3). As indicated herein, epidemiological evidence suggests that dietary consumption of omega-3 fatty acids may decrease the risk for certain neuropsychiatric disorders. This review will summarize the knowledge of omega-3 fatty acids in terms of dietary intake and metabolism, as well as evidence pointing to potential mechanisms of omega-3 fatty acids in normal brain functioning and development of neuropsychiatric disorders. Evidence for altered omega-3 fatty acid status and supplementation trials will be given for disorders such as Attention Deficit (Hyperactivity) Disorder, Alzheimer's disease and other dementias, Schizophrenia, Depression and Post-Partum Depression, as well as various developmental disorders. The information in this review was obtained after extensive MedLine searching of each topic area. References from obtained papers that were not available on MedLine were also used.

2. OMEGA-3 FATTY ACIDS: BIOCHEMISTRY AND DIETARY CONSUMPTION

ALA, EPA and DHA are the most common omega-3 fatty acids in the diet and will be discussed in more detail below. Until fairly recently, the commonly accepted pathway for the metabolic conversion of ALA to DHA involved the sequential utilization of delta-6, 5-, and 4-desaturases along with elongation reactions (2 carbon additions) (Fig. 1). It has been demonstrated, however, that the metabolism of docosapentaenoic acid

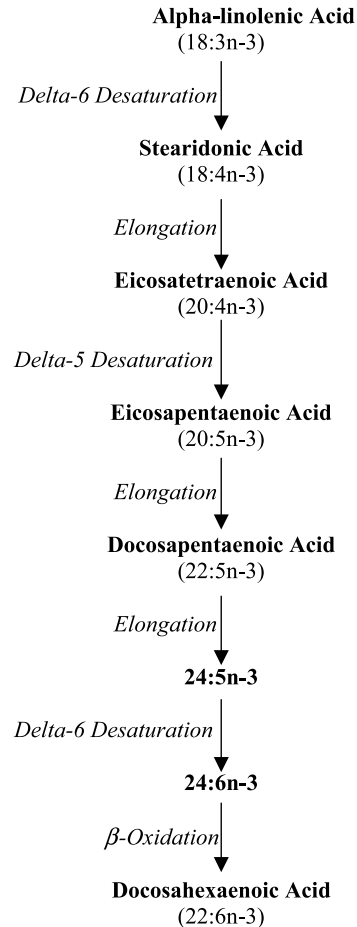


Figure 1. Pathway by which unsaturated omega-3 fatty acids are converted to long-chain polyunsaturated fatty acids in animals.

(DPA; 22:5n-3) is independent of delta-4 desaturase, and instead involves microsomal elongation of 22:5n-3 to 24:5n-3, followed by desaturation to 24:6n-3 and peroxisomal retroconversion to 22:6n-3 [1]. The conversion of ALA to LCPUFA (EPA, DPA, and DHA) is limited in humans and has been estimated to be anywhere from less than 1% to 6% [2, 3], reviewed in [4]. Interestingly, DHA can also be “retroconverted” to EPA at rates in humans of about 10% [5, 6].

Historical evidence suggests that human beings evolved consuming a diet that contained approximately 1–2 n-6 fatty acids for each n-3 fatty acid [7]. However, the current Western diet contains a ratio of up to 20–30:1, which means that the present diet is deficient in n-3 fatty acids compared to that on which our genetic patterns were established [8]. Today's intake of n-3 fatty acids is lower because of the decrease in consumption of fish and wild game, and because modern agriculture emphasizes consumption of cereal grains by animals destined for meat production. Also, the consumption of plant-derived oils which contain large amounts of n-6's and minimal n-3's has increased. Furthermore, cultured fish and eggs, cultivated vegetables, and domestic animals contain fewer n-3 fatty acids than do their wild counterparts [7]. Some common vegetable oils, including soybean, canola and flaxseed oil, are concentrated sources of ALA in the diet, while fatty fish, such as halibut, mackerel, herring, and salmon are concentrated sources of EPA and DHA. Other sources of dietary n-3 fatty acids are nuts, seeds, fruits, vegetables, and egg yolks [9]. It has also recently been demonstrated that meat, which is a concentrated source of DPA, is a significant contributor of long-chain dietary n-3 fatty acids, with beef and lamb contributing more of these fatty acids than pork and poultry [10]. Table I shows the ALA, EPA, and DHA fatty acid content of fish, shellfish, fish oils, nuts and seeds, and plant oils that contribute n-3's to the diet.

An analysis of the consumption of n-3 fatty acids in various populations shows that modern societies consume low levels of these dietary lipids, and this has led to the establishment of guidelines concerning their recommended daily intake. In the United States, it has been recommended that EPA and DHA be consumed at an intake of $0.65 \text{ g}\cdot\text{d}^{-1}$, which is a 4-fold increase from the current level of consumption of $0.1\text{--}0.2 \text{ g}\cdot\text{d}^{-1}$ [9]. The adequate intake (AI) for LNA has been set at 1.6 and 1.1 g per day (adult men/women), and the target intake

for EPA and DHA has been set at 160 or 110 mg per day (adult men/women) [11]. In Britain, the British Nutrition Foundation Task Force on Unsaturated Fatty Acids recommends a daily intake of 0.5–1.0 g of long-chain polyunsaturated n-3 fatty acids, which they suggest can be achieved through the consumption of an intake equivalent to 1–2 portions of oily fish per week [12]. Even in Japan, where seafood has traditionally been consumed at very high levels, the ratio of n-6 to n-3 fatty acids is increasing as diets become more westernized, leading some authors to suggest that fish consumption be increased, particularly amongst young people [13]. In addition to increasing fish consumption, alternative strategies for increasing levels of n-3 fatty acids in the diet, and/or decreasing the n-6:n-3 fatty acid ratio, include use of n-3 fatty acid supplements, consumption of other n-3 containing foods such as flax, and decreasing the intake of n-6 rich vegetable oils such as corn and sunflower oil [9]. There are also several new products available in North America that have been supplemented with n-3 fatty acids (both short and long chain) including eggs, milk, and bread. Table II shows the fatty acid content of some commercially available n-3 supplemented food products.

3. N-3 FATTY ACIDS AND THE BRAIN

In the human body, ALA is found primarily in triglycerides (TG), in cholesterol esters (CE), and in very small amounts in phospholipids (PL); EPA is found primarily in CE, TG, and PL; and DHA is found primarily in PL, and is highly concentrated in the cerebral cortex, retina, testes and sperm [8]. In fact, DHA makes up a large proportion of the brain's lipids, and is the predominant n-3 fatty acid found in this organ [14]. The structural predominance of DHA in the brain suggests functional significance, and as will be demonstrated, both DHA and its long-chain counterpart EPA can be linked with several aspects of neural function, including, but not limited to, phospholipase A₂

Table I. The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, fish oils, nuts and seeds, and plant oils that contain at least 5 g of omega-3 fatty acids per 100 g*.

Food Item	EPA	DHA	ALA
Fish (raw)			
Anchovy, European	0.6	0.9	–
Cod, Atlantic and Pacific	Trace†	0.1	Trace
Haddock	Trace	0.1	Trace
Halibut, Atlantic and Pacific	Trace	0.3	Trace
Mackerel, Pacific and Jack	0.6	0.9	Trace
Ocean Perch, Atlantic	Trace	0.2	Trace
Pike, Walleye	Trace	0.2	Trace
Roughy, Orange	Trace	–	Trace
Salmon, Atlantic, Farmed	0.6	1.3	Trace
Salmon, Atlantic, Wild	0.3	1.1	0.3
Seabass, Mixed Species	0.2	0.4	–
Swordfish	0.1	0.5	0.2
Trout, Rainbow, Farmed	0.3	0.7	Trace
Trout, Rainbow, Wild	0.2	0.4	0.1
Tuna, Fresh, Bluefin	0.3	0.9	–
Tuna, Fresh, Yellowfin	Trace	0.2	Trace
Whitefish, Mixed Species	0.3	0.9	0.2
Wolffish, Atlantic	0.4	0.3	trace
Shellfish (raw)			
Clam, Mixed Species	Trace	Trace	Trace
Crab, Blue	0.2	0.2	–
Lobster, Northern	–	–	–
Mussel, Blue	0.2	0.3	Trace
Oyster, Pacific	0.4	0.3	Trace
Scallop, Mixed Species	Trace	0.1	–
Shrimp, Mixed Species	0.3	0.2	Trace
Fish Oils			
Cod Liver Oil	6.9	11.0	0.9
Herring Oil	6.3	4.2	0.8
Menhaden Oil	13.2	8.6	1.5
Salmon Oil	13.0	18.2	1.1
Sardine Oil	10.1	10.7	1.3
Nuts and Seeds			
Butternuts, Dried	–	–	8.7
Flaxseed	–	–	18.1
Walnuts, English	–	–	9.1
Plant Oils			
Canola (Rapeseed)	–	–	9.3
Flaxseed	–	–	53.3
Soybean	–	–	6.8
Walnut	–	–	10.4
Wheatgerm	–	–	6.9

* Adapted from [265].

† Trace = < 0.1.

Table II. Omega-3 fatty acid content of commercially available omega-3 enriched foods.

Product	Total omega-3 content	DHA content
Omega-3 enriched eggs Gray Ridge® egg farms [266]	0.4 g·egg ⁻¹	0.085 g·egg ⁻¹
Omega-3 enriched milk Neilson Dairy® Oh! [267]	0.02 mg·cup ⁻¹ (homogenized) 0.01 mg·cup ⁻¹ (2%)	0.02 mg·cup ⁻¹ (homogenized) 0.01 mg·cup ⁻¹ (2%)
Omega-3 enriched bread Tip Top® UP [268]	0.27 g·2 slices ⁻¹	0.27 g·2 slices ⁻¹

(PLA₂) activity, inflammation, neurotransmission, membrane fluidity, oxidation, ion channel and enzyme regulation, and gene expression. Each of these functions will be considered in terms of their relationship with the n-3 polyunsaturated fatty acids, and when available, evidence linking them with various neuropsychiatric disorders will be presented.

3.1. Phospholipase A2

PLA₂ is an enzyme that acts on the *sn*-2 position of phospholipids, thereby generating a free fatty acid, such as arachidonic acid (AA; 20:4n-6), EPA or DHA, and a lysophospholipid [15]. Several classes of PLA₂ exist in the brain [16], with the highest expression of PLA₂ seen in the hippocampus [17], a region of the brain that is related to learning and memory [18]. While the function of PLA₂ in the human nervous system has not been fully elucidated, it has been implicated in the processes of phospholipid turnover, neurotransmitter release, detoxification, exocytosis, and membrane remodelling [19], and the free fatty acid and lysophospholipid produced by its action are known to be highly active cell signalling molecules [20].

A pathological increase in the activity of PLA₂ has been observed in several neuropsychiatric disorders, including schizophrenia. Analysis of the serum levels of PLA₂ in schizophrenics showed increased levels of activity [21], and magnetic resonance imaging of the cerebral cortex of

schizophrenics confirmed an increased rate of phospholipid breakdown [22]. Consequently, Horrobin et al. [23] proposed the membrane phospholipid hypothesis of schizophrenia, which states that the disease is caused by variations in phospholipid biochemistry associated with increased loss of highly polyunsaturated fatty acids from membranes owing to enhanced activity of PLA₂. Genetic abnormalities have since been observed in a gene linked to PLA₂ in schizophrenics thus further substantiating this hypothesis [24]. Similarly, levels of PLA₂ have been shown to be increased in the blood of dyslexics, leading to the suggestion that dyslexia may be on a continuum with schizophrenia [25].

Elevated serum PLA₂ has also been found in patients with depression and bipolar disease [26]. Further evidence supporting the association between increased PLA₂ activity and these conditions comes from analysis of the biochemical mechanisms of the drug lithium, which has been used successfully in the treatment of both disorders. Lithium has been shown to be a strong inhibitor of PLA₂ in the brain via interference with transcriptional or post-translational regulation of the enzyme [27]. This occurs within the human therapeutic range, unlike some of the other biochemical effects of lithium, making inhibition of PLA₂ a likely primary mechanism of action of this drug [28]. Similarly, carbamazepine, an anti-convulsant drug with mood regulating properties also used in the treatment of bipolar disorder, has similar down-regulating effects

on PLA₂ [29]. While structural variations at or around the PLA₂ gene appear to increase susceptibility to depression [30], the same observation has not been made in bipolar disease [31]. Moreover, brain activity of PLA₂ was found to be normal in a study of bipolar patients [32].

Like lithium, EPA has been shown to inhibit PLA₂ activity [33], and administration of EPA has shown some success in the treatment of schizophrenia [34] and bipolar disorder [35]. Dietary lipids began to be suspected in the aetiology of schizophrenia more than two decades ago, when it was found that the ratio of saturated to polyunsaturated fat was a strong predictor of the outcome of schizophrenia [36]. Subsequently, nutritional analysis revealed that a lower intake of EPA was associated with more severe psychopathology and tardive dyskinesia [37].

3.2. Inflammation

Many mood disorders appear to be linked to immune system activation, as evidenced by overactivity of the inflammatory response. In patients with major depression, there is a higher expression of T-cell activation markers, suggesting a systemic immune activation [38]. Similarly, plasma levels of interleukin-6 (IL-6) and interleukin-2 (IL-2) in bipolar patients were found to be significantly higher than normal controls, suggesting an increase in cell mediated immune function [39]. An increase in IL-2 concentrations has also been shown in schizophrenics [39], and all three of the aforementioned conditions are accompanied by an acute phase protein response, which is thought to reflect an increased production of various cytokines [40]. Psychotropic drugs have a suppressive effect on IL-6 secretion in schizophrenic patients [39], and acute phase proteins can be suppressed by treatment with psychotropic drugs in patients with mania, depression, and schizophrenia [40].

There is also evidence supporting the role of inflammation in neurodevelopmental

diseases. Genetic studies have shown that in children with ADHD, genetic polymorphism in the interleukin-1 (IL-1) antagonist gene can both increase and decrease ADHD risk, depending on the allelic variation [41]. Biochemical studies have shown that children with autistic spectrum disorders display an increase in the production of TNF-alpha relative to controls when challenged with a stimulant for innate immunity [42], and that there is an increase in the production of IL-1 receptor antagonist and interferon-gamma (INF-gamma) in children with autism [43].

N-3 fatty acids, when consumed in adequate amounts, can exert anti-inflammatory actions *in vivo*. This is primarily accomplished through modification of the production of cytokines and eicosanoids. IL-1 has been shown to decrease [44], while tumor necrosis factor (TNF) has been shown to increase, as a consequence of fish oil feeding [45], thereby reducing inflammation. The reduction in levels of IL-1 may have behavioral consequences, since this cytokine has been shown to induce stress, anxiety-like behavior, and deficits in spatial memory in rats, changes which are attenuated by administration of dietary EPA [46, 47]. Similarly, increasing the consumption of n-3 fatty acids, particularly the long-chain polyunsaturated n-3's, tends to shift the balance of eicosanoid production from pro- to anti-inflammatory mediators [48]. For example, increasing the amount of EPA in the diet causes a shift in the production of the inflammatory eicosanoid leukotriene B4 (LTB4) to the production of the anti-inflammatory leukotriene B5 (LTB5), thereby attenuating the inflammatory response [49]. Because of the relationship between inflammation and the pathology of many neuropsychiatric diseases, the influence of n-3 fatty acids on this physiological process is important to consider.

3.3. Neurotransmitters

Neurotransmitters are molecules that mediate intercellular communication [50].

Dopamine is a neurotransmitter that influences cognitive functions such as learning and motivation [51], while serotonin is involved in modulating emotion and cognition [52]. Levels of neurotransmitters have been shown to be affected by diet, which is not surprising considering that many, including serotonin and dopamine, are derived from nutrient precursors. Serotonin is derived from the amino acid tryptophan while dopamine is derived from the amino acid tyrosine [53].

Modulation of neurotransmitter levels has long been viewed as a causative factor in both unipolar and bipolar depression [52]. In unipolar depression, therapeutic drugs of the selective serotonin reuptake inhibitor (SSRI) class act to increase serotonin neurotransmission; for example, fluoxetine (Prozac) increases the concentration of serotonin in the synapse by inhibiting reuptake into the cell [54]. In contrast, pimozone, which is used in the treatment of bipolar disease, acts on dopamine receptors [55]. *In vivo*, serotonin transporter density is reduced in depressed patients [56], and certain variants of the serotonin transporter gene have been associated with the disease [57]. Genetic variation of the serotonin transporter gene has also been associated with bipolar disease, as it appears to be a predictor of abnormal response to antidepressant therapy [58].

Modulation of neurotransmitter levels have also been suspected in neurodevelopmental disorders such as ADHD and dyslexia. Single emission computed tomography has found that adults with ADHD exhibit increased striatal availability of a dopamine transporter [59], and medications used to treat ADHD commonly exert their effect via inhibition of this transporter [60]. Polymorphisms of both the dopamine receptor and dopamine transporter genes have been observed in ADHD [61], and ADHD has been linked to a variant of the serotonin-2A receptor gene [62]. However, dyslexia, which shows a high level of comorbidity with ADHD [63], has failed to show similar genetic associations [64, 65], and there is little evidence to support an association between neurotransmitter modulation and this disorder.

Neurotransmitters, particularly dopamine, have similarly been a focus of investigation in the study of schizophrenia. While it was previously thought that the symptoms of schizophrenia were primarily due to an excess of dopamine in the brain, in a recent re-evaluation of this hypothesis, Abi-Dargham [66] suggested that the brain of schizophrenic patients produces more dopamine than normal brains in the subcortical region and less dopamine than normal brains in the cortex. Considerable supportive evidence for the involvement of dopamine in schizophrenia comes from analysis of drugs that influence levels of this neurotransmitter in the brain. Anti-psychotic drugs, such as haloperidol and chlorpromazine, act by blocking dopamine receptors in the brain [67], whereas drugs such as methylphenidate that elevate dopamine in the brain have been shown to exacerbate symptoms [68]. Genetic polymorphisms of dopamine genes have been investigated quite extensively, and studies have yielded both positive and negative results [69–71], suggesting that in some patients genes may play a role in the disease.

In addition to dopamine, serotonin has also been a focus of schizophrenic research. In 1954, Wooley and Shaw [72] proposed that schizophrenia was related to alterations in serotonergic neurotransmission, since LSD, which shows structural similarity to serotonin, induces psychotic symptoms in normal individuals. In support of this theory, clozapine, which is a traditional anti-psychotic drug, is a serotonergic antagonist [73], and some new medications function as both serotonin and dopamine modulators [74]. As with dopamine, studies investigating a genetic link between serotonin genes and schizophrenia have produced both positive and negative findings [75–77], thus suggesting that variation of serotonin related genes may influence the disease.

Although they do not serve directly as substrates for the formation of serotonin and dopamine, n-3 polyunsaturated fatty acids have been shown to influence levels of these molecules in the brain. When piglets are fed a diet deficient in AA and DHA,

there is a decrease in both dopamine and serotonin concentration in the frontal cortex [78]. Conversely, when their diet was supplemented with AA and DHA, piglets showed an increase in the frontal cortex concentration of serotonin, possibly due to a decrease in degradation [79]. A similar situation has been found in rats, who when fed a diet deficient in n-3 fatty acids, displayed inadequate storage of newly synthesized dopamine [80], as well as an overall reduction in the dopaminergic vesicle pool [81]. Alternatively, when rats are fed fish oil, there is a 40% increase in frontal cortex dopamine concentrations as well as a greater binding to dopamine D₂ receptors [82]. Serotonergic neurotransmission has also been shown to be modulated by dietary n-3 polyunsaturated fatty acids, with dietary deficiency causing an increase in higher levels of basal serotonin but a decrease in the amount released during synaptic transmission [83].

Acetylcholine (Ach), another neurotransmitter found in the brain, is also modulated by dietary n-3 fatty acids. Acetylcholine has been implicated in the etiology of several neuropsychiatric disorders, including Alzheimer's disease [84], schizophrenia [85], and bipolar disorder [86]. Following a dietary induced reduction in brain phospholipid DHA, administration of a DHA enriched diet increases basal levels of brain Ach [87]. Moreover, an increase in cerebral Ach levels following administration of dietary DHA is correlated with an improved performance in passive avoidance tasks in a model of stroke-prone spontaneously hypertensive rats [88]. This could be because an n-3 deficient diet, which leads to a loss of DHA in both the hippocampus and frontal cortex, causes changes in cholinergic neurotransmission in the hippocampus only [89]. The hippocampus is a region of the brain that is closely associated with learning, attention, and memory [18].

The influence of n-3 fatty acids on neurotransmission may be related to the production of eicosanoids, since in addition to

their role in inflammation and immune responsiveness, eicosanoids also modify neurotransmitter release [90]. The eicosanoid prostaglandin (PG) E₂ appears to play a role in dopaminergic transmission in the brain [91], and is known to act on the receptor of the inhibitory neurotransmitter glycine to reduce synaptic transmission [92]. PGD₂ increases brain serotonin content and turnover [93], and PGE₁ and PGE₂ have an inhibitory effect on serotonin release [94]. Eicosanoids also affect levels of signal transducing molecules such as cyclic AMP [95]. Therefore, eicosanoids may act to affect neurotransmitter release and modify synaptic strength, thereby influencing various processes that are central to cognitive function.

3.4. Oxidative stress

Free radicals are generated under normal physiological conditions, and play important roles in a variety of biological processes. However, when these molecules are generated in excess, they can initiate spontaneous chain reactions that may have negative consequences, such as abnormal neurodevelopment and neuronal function [96]. Free radicals are considered unstable because they carry one or more unpaired electrons, which make them highly reactive. Examples of free radicals are superoxide radical, hydroxy radical, and nitric oxide, all of which are oxygen-containing species and are therefore referred to as oxyradicals. These oxyradicals can react with polyunsaturated fatty acids, and cell membranes of tissues exposed to high concentrations of oxygen, such as the brain, are susceptible to oxidation because of the presence of unsaturated fatty acids in their phospholipids [97]. Oxyradicals are eliminated by enzymes such as superoxide dismutase, glutathione peroxidase, and catalase, endogenous antioxidants such as glutathione and uric acid, and dietary antioxidants such as vitamins E and C [98].

While it is generally accepted that oxidative cell damage likely plays a role in many

neuropsychiatric conditions including Alzheimer's disease [99] neurodevelopmental disorders [100], and schizophrenia [101], there are several different methods of evaluating oxidative damage, and this must be considered when assessing the available research. For example, one study of depressive patients that looked at different measures of oxidative stress in both plasma and saliva found that while catalase and total peroxidase activity were increased in both body fluids, the activity of superoxide elimination was decreased in the plasma but increased in the saliva [102]. However, taken together the findings cumulatively suggest an increased level of oxidative stress in depression, and this is corroborated by the results of other studies [103–105]. Similarly, in children with ADHD, exhalant ethane, which is a non-invasive marker of oxidative damage to n-3 fatty acids, is increased, suggesting that some patients with the condition may show an increased breakdown of n-3 polyunsaturated fatty acids [106]. Moreover, schizophrenic patients have shown deficits in both non-enzymatic antioxidant [107] and enzymatic antioxidant [108, 109] function, and there is considerable evidence to suggest increased oxidative stress in patients with Alzheimer's disease [110–112]. It is unknown whether oxidative stress is the primary event in the pathophysiology of the aforementioned conditions, or whether it is a secondary contributor to deterioration and poor clinical outcome [98].

N-3 fatty acids may influence oxidative pathology via replacement of lost membrane phospholipid polyunsaturated fatty acids following attack by oxyradicals [96]. In animals, consumption of dietary n-3 fatty acids has been shown to modulate levels of these in the brain [113], and human serum and erythrocyte phospholipids are very responsive to dietary n-3 modulation [114–116]. Because of the vulnerability of lipids to attack by oxyradicals, it has been suggested that supplementation with n-3 polyunsaturated fatty acids should be accompanied by cotreatment with an antioxidant [96].

However, despite an often cited concern of an n-3 induced increase in oxidative stress with fatty acid supplementation, the available evidence does not appear to support this contention. In fact, there is evidence to the contrary demonstrating that EPA and DHA in fact reduce oxidative stress. Measurement of F2-isoprostanes, which reflect *in vivo* lipid production and oxidant stress, were shown to decrease following dietary supplementation with either EPA or DHA [117], as well as with a daily meal of fish [118]. N-3 fatty acids may do this by modifying the activity of antioxidant enzymes, since there is evidence demonstrating an increase in the activity of both xanthine oxidase [119] and superoxide dismutase [120] following consumption of an n-3 rich diet. The antioxidant effect of n-3 fatty acids has even been shown to extend to neonates following daily maternal fish oil supplementation [121]. Therefore, the long-chain n-3 fatty acids actually appear to exert protection against oxidative stress.

3.5. Ion channel and enzyme regulation

Proper physiological function requires coordinated integration of a number of different cellular components, including ion channels and enzymes. Sodium channels, which are glycoproteins that form pores in the cell membrane, open and close in response to changes in membrane potential thereby regulating the generation of action potentials. A similar process occurs with potassium channels, which are also found in the cell membrane. Enzymes such as the Na^+K^+ ATPase and Ca-ATPase perform the functions of ion transport, allowing for maintenance of proper intracellular ion concentration and cellular homeostasis, and the regulation of ion channels and enzymes is accomplished by molecules such as neurotransmitters and G proteins. Therefore, there are a multitude of levels at which neuronal functioning might be compromised, potentially resulting in pathology that could give rise to neuropsychiatric disorders.

Ion channel, enzyme, and regulatory molecule function may be influenced by polyunsaturated n-3 fatty acids. EPA has been found to inhibit voltage-activated Na^+ currents [122, 123], as has DHA [123, 124] and ALA [123, 125]. It appears that these n-3 polyunsaturated fatty acids modify the function of the Na^+ channel by binding directly to channel proteins [123]. DHA [126, 127] and EPA [126] have also been shown to inhibit voltage-activated K^+ current, and DHA has been observed to do this via binding to an external site on the channel structure [128]. Importantly, the opening of the K^+ channel TREK-1 by ALA and DHA appears to exert a neuroprotective effect against ischemia and epileptic damage in the brain [129, 130]. DHA [124, 131], EPA [131], and ALA [131] have further been shown to inhibit voltage-activated Ca^+ currents. The ion regulating enzyme Na^+K^+ ATPase appears to be strongly influenced by the presence of DHA in the surrounding cell membrane, in that high concentrations of DHA have been associated with high Na^+K^+ ATPase activity [132], and both Ca^+ ATPase and Na^+K^+ ATPase activity have been shown to be inhibited by both EPA and DHA [133]. While the effect of DHA on Na^+K^+ ATPase activity in [132] and [133] appears to be contradictory, the use of different methodologies precludes a direct comparison between the two, since Turner et al. [132] correlated the activity of the enzyme with pre-existing levels of DHA in various tissues while Kearns and Haag [133] added DHA to the enzymatic assay. Other cellular functions, such as the rate of glutamate uptake [134], the responsiveness of the NMDA receptor [135], and the activation of protein kinase C [136, 137] have also been shown to be affected by polyunsaturated n-3 fatty acids.

3.6. Gene expression

The regulation of genetic expression dictates the rate at which genes are transcribed to effect changes in the production of various gene products. Genes can either be up-

or down-regulated, resulting either in an increase or decrease in transcription. Up-regulation of a gene may lead to an increase in the synthesis of a particular protein, while down-regulation may have the opposite effect. Modulation of gene expression at the transcription level can be mediated by n-3 polyunsaturated fatty acids, and Wahle et al. [138] recently summarized the generally accepted mechanisms of this regulation. The first reported mechanism is activation of cell signal cascades which results in covalent modification of specific transcription factors, which can in turn then bind to promoter regions of a gene causing an up- or down-regulation of transcription. The second reported mechanism is by direct binding of the fatty acid (or its derivative) to specific transcription factors, which consequently has a positive or negative effect on its promoter binding capacity. The third reported mechanism is modification of transcription factor mRNA, or alteration of the stability of such mRNA and possibly its DNA-binding capacity. There are also likely indirect mechanisms of regulation of gene expression, such as modulation of the redox state of the cell. Among the transcription factors that are known to be activated by n-3 polyunsaturated fatty acids are peroxisome proliferated activated receptors (PPARs), liver X receptors α and β , hepatic nuclear factor-4, and sterol regulatory element binding proteins (SREBPs) [139].

The relationship between n-3 polyunsaturated fatty acids, gene expression, and neuropsychiatric disorders is suggested by research that shows that these lipids modulate the expression of a number of genes in the brain, including those involved in synaptic plasticity and signal transduction. For example, DNA microarray studies performed on rats following dietary manipulation of fatty acid content showed that the genes coding for α - and γ -synuclein and the D-cadherin gene were up-regulated with feeding of diets rich in ALA and DHA [140], and research suggests that these proteins are involved in neural plasticity [141, 142]. Similarly, the transcript levels of three genes

coding for calmodulin were up-regulated, albeit to a similar extent with diets containing either ALA, DHA, linoleic acid (LA; 18:2n-6) plus ALA, or LA plus DHA [140]. Calmodulin has also been shown to play an important role in synaptic plasticity [143, 144] as well as signal transduction [145, 146]. The expression of numerous other genes have been found to be affected by dietary manipulation of fatty acid content, and the reader is referred to [147] for a comprehensive review. Due to the association between n-3 polyunsaturated fatty acids and regulation of the expression of genes associated with neural function, this may be another mechanism by which these lipids are involved in the aetiology of neuropsychiatric disorders. Clearly, the effect of n-3 fatty acids on cellular physiology is widespread, and the relationship between impaired brain function and neuropsychiatric disorders necessitates that the n-3 fatty acids be considered as candidates for involvement in the aetiology of these conditions.

4. OMEGA-3 FATTY ACID STATUS OF BLOOD AND CELLS OF INDIVIDUALS WITH VARIOUS NEUROPSYCHIATRIC DISORDERS

Omega-3 fatty acid deficiencies are associated with a wide range of neuropsychiatric disorders, including, but not limited to, attention deficit hyperactivity disorder (ADHD), neurodevelopmental disorders such as dyslexia and autism, depression, aggression and dementia. This review will present available information on blood levels of omega-3 fatty acids in individuals with these and other neuropsychiatric disorders, as compared with healthy controls. We will also discuss available evidence as to the efficacy of omega-3 fatty acid supplementation in alleviating the symptoms of these conditions. The role of omega-3 fatty acids in retinitis pigmentosa and other retinal degenerative disorders, will not be discussed in this review. Neither will the

role of omega-3 fatty acids in peroxisomal disorders, disorders characterized by the absence of normal peroxisomes and thus difficulties in beta-oxidation of long chain fatty acids. The role of omega-3 fatty acids in these disorders has been discussed previously [148–151].

4.1. Attention deficit disorder and hyperactivity

Attention Deficit/Hyperactivity Disorder (ADHD), also known as Attention Deficit Disorder (ADD), is a condition characterized by disabling levels of inattention, impulsivity, and/or hyperactivity, which are inappropriate for the individual's level of development [152]. The prevalence of ADHD in North America is approximately 3–5% of the school age population [153], with a male to female ratio of around 4–6:1 [152]. Twenty to twenty five percent of children with ADHD show one or more specific learning disabilities in math, reading, or spelling. Hyperactive children have also been reported to experience increased thirst, eczema, asthma, and other allergies, which are known to be symptoms of essential fatty acid (EFA) deficiency, more often than normal children [154]. Although previously thought to be a condition of childhood, it is now recognized that in up to 60% of sufferers, ADHD persists into adulthood [155]. In adults, ADHD is manifest by disorganization, impulsivity, and poor work skills, and sufferers tend to be impatient and easily bored.

Since the 1980's, both n-3 and n-6 long chain polyunsaturated fatty acids (LCPU-FAs) have been suspected of being associated with ADHD. In one of the first investigative studies conducted, the serum levels of DHA, dihomo-gamma-linolenic acid (DGLA, 20:3n-6), and arachidonic acid (AA, 20:4n-6) were found to be significantly lower in hyperactive children than in controls [156]. Stevens et al. [157] found that plasma and red blood cell (RBC) levels of AA, EPA, and DHA were significantly lower in ADHD patients as compared to controls,

and that a subgroup of ADHD patients exhibiting symptoms of LCPUFA deficiency had even lower plasma concentrations of AA and DHA than did ADHD subjects with few LCPUFA-deficiency symptoms. Recently, Young et al. [158] demonstrated that adults with ADHD also have an altered phospholipid fatty acid status, specifically having lower levels of omega-6 fatty acids and DHA in serum and lower levels of omega-3 fatty acids, including DHA in red blood cells.

Low levels of these LCPUFA in blood could be related to marginal consumption, inefficient conversion of precursors (linoleic acid and ALA) to LCPUFA, or enhanced metabolism of LCPUFA [154]. Preliminary work suggests no difference in dietary intakes of fatty acids between children with ADHD and healthy children [157]. Recently, Ross et al. [100] demonstrated that children with ADHD exhaled increased levels of ethane, a non-invasive measure of oxidative damage to omega-3 fatty acids, indicating increased breakdown.

Based on this body of research, it has been hypothesized that supplementation with LCPUFAs, particularly of the n-3 fatty acid family, may result in an improvement in the learning and behavioral symptoms of ADHD. However, very few clinical trials have been conducted in this field. In 2001, Voigt et al. [159] supplemented 63 children with ADHD with either placebo or 345 mg DHA·day⁻¹ for 4 months. DHA levels in blood increased but there were no significant improvements in any measure of ADHD symptoms. However, Richardson and Puri [160] showed that supplementation with a mixture of EPA, DHA, gamma-linolenic acid (GLA, 18:3n-6), vitamin E, AA, LA and thyme oil for 12 weeks in children with specific learning disabilities, improved symptoms in 7 out of 14 symptoms of ADHD (although only 3 were significant) compared to none for placebo. Recently, Stevens et al. [161] supplemented children with ADHD with (per day) 480 mg DHA, 80 mg EPA, 40 mg AA, and 96 mg GLA for 4 months. There was an increase in both

EPA and DHA in plasma as well as improvement in parent-rated conduct, teacher-rated attention and oppositional defiant behaviour. Furthermore, there was a significant correlation between increased RBC EPA and DHA and a decrease in disruptive behaviour. Harding et al. [162] compared the effect of Ritalin and dietary supplements including, among other ingredients, omega-3 fatty acids (180 mg EPA, 120 mg DHA) and 45 mg GLA per day. Although small and non-randomized, this study suggested that dietary supplementation resulted in equivalent improvements in attention and self control as Ritalin. Finally, Hirayama et al. [163] examined the effect of DHA supplementation in food sources for 2 months on symptoms of ADHD. On average, children received 0.5 g DHA·day⁻¹ vs. control foods. There was no improvement of ADHD symptoms in this study. These findings seem to suggest that a combination of LCPUFAs is more likely to exert a positive effect on ADHD symptoms than omega-3 fatty acids alone.

4.2. Alzheimer's disease and dementia

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, intellectual decline and eventual global cognitive impairment. The incidence of dementia in western countries, of which AD is the major cause, is estimated to be approximately 10% of the population over the age of 65 y and 47% of the population over 80 y of age [164].

It has long been suggested that AD is associated with brain lipid defects [165–170]. More recently, epidemiological studies [171–177] have suggested that high fish and/or omega-3 fatty acid consumption is inversely associated with cognitive impairment, cognitive decline, and/or development of dementia or AD.

Blood levels of omega-3 fatty acids of individuals with existing AD have also been investigated and compared with control subjects. One study suggests an inverse

association between cognitive decline and ratio of n-3/n-6 fatty acids in RBC membranes [178]. Furthermore, serum cholesteryl ester (CE) EPA and DHA levels have been shown to be lower in AD patients [179]. This study also suggested that CE-DHA is an important determinant of minimal state examination (MMSE) score across the population. Another study by ourselves [180] suggests that phospholipid-(PL) and phosphatidylcholine-(PC) EPA, DHA and total omega-3 fatty acid levels are decreased in cognitively impaired and demented (including AD) individuals. Only one study [181] found no significant difference in plasma PL omega-3 fatty acid levels between controls and cognitively impaired/demented individuals.

The reason for potential decreased blood levels of omega-3 fatty acids in individuals with AD is unclear. Studies have suggested an increased omega-6 and/or decreased omega-3 fatty acid consumption in individuals with AD [182, 183] and at least one of these studies [183] suggests that this altered fatty acid intake precedes the development of AD. Furthermore, Kyle et al. [184] suggests that decreased blood levels of plasma DHA is a risk factor for the development of AD. Although decreased omega-3 fatty acid consumption prior to the development of AD is one possibility to explain the decreased omega-3 fatty acids in the blood of individuals with AD, increased omega-3 oxidation is also possible. For example, F4-isoprostane (peroxidized DHA) production is increased in certain brain cortex regions of AD brains [185] as well as in cerebrospinal fluid from individuals with AD [185, 186].

There are only three known studies in which individuals with AD or dementia have been supplemented with long chain omega-3 fatty acids. In the first [187], by Terano et al., individuals with dementia were supplemented with 0.72 g DHA per day for 1 year. Blood levels of omega-3 fatty acids increased and scores on dementia rating scales improved. In the second study, by

Otsuka [183], individuals with AD were supplemented with 900 mg EPA per day for 6 months. MMSE scores increased maximally by 3 months and remained higher for 6 months. In the third study, by Suzuki et al. [188], adults with dementia showed both an increase in intelligence and an improvement in visual acuity following supplementation with an oil containing DHA (15%) and EPA (3%). Non-demented elderly also showed improvements in both intelligence and visual acuity in this study.

4.3. Schizophrenia

Schizophrenia is a severe mental illness characterized by positive (hallucinations and delusions) and negative (lack of emotional responsiveness and drive) symptoms. The global distribution of schizophrenia is even, despite environmental factors across countries and cultures. Schizophrenic outcome, however, has been suggested to be inversely related to the consumption of saturated fats and directly related to consumption of omega-3 fatty acids [189, 190]. Furthermore, blood omega-3 fatty acid levels have been shown to be correlated with positive schizotypal trait measures [191], and this suggests that these fatty acids may offer protection against psychotic breakdown. The reader is referred to Section 3.1. for a discussion of the membrane hypothesis of schizophrenia, as proposed by Horrobin [23] as evidence of increased catabolism of phospholipids in this pathology.

Decreased red blood cell omega-3 fatty acids levels have been shown in first episode psychotic patients (medication-free) [192–194], as well as in medicated schizophrenic patients [195–198], as compared with control subjects. Furthermore, levels of total omega-3 fatty acids and DHA are decreased in cultured skin fibroblasts from schizophrenic patients as compared with controls [199]. Some studies also suggest decreased levels of certain omega-6 fatty acids, mainly AA, accompanies the modification of omega-3 fatty acid levels in these individuals [196]. Medication itself may

influence the levels of omega-3 fatty acids in red blood cells of schizophrenic patients in either a positive [193, 194] or negative [200] manner. Interestingly, Hibbeln et al. [201], suggests that schizophrenic smokers have decreased blood levels of DHA and EPA as compared with schizophrenic non-smokers. In schizophrenic individuals there may be an increased breakdown of these omega-3 and omega-6 fatty acids, as suggested by various authors [192, 196] and/or there is a decreased activity in one or more of the enzymes, responsible for the synthesis of the long chain omega-3 and omega-6 fatty acids [199, 202]. Consistent with alteration in fatty acid metabolism in schizophrenic individuals is the finding that there may also be abnormalities in retinal photoreceptor function [203].

The findings involving supplementation of schizophrenic individuals with omega-3 fatty acids have been reviewed by various authors [204–206]. There is evidence to suggest positive benefits for omega-3 fatty acid supplementation in schizophrenic individuals but more well designed studies are still needed before definite conclusions can be made. Most studies have investigated the ability of ethyl-EPA to modify positive and negative schizophrenic symptoms in individuals with residual symptoms despite medication. Most of these studies have shown improvements in Positive and Negative Syndrome Scale (PANSS) scores after at least 12 weeks of supplementation [34, 200, 207]. Levels of ethyl-EPA used range from 1–4 g·day⁻¹ with 2–3 g·day⁻¹ being the most common, and this level appears to have the most benefit. Benefits have also been noted in dyskinesia scores after 12 weeks of supplementation [34]. Interestingly Peet et al. [208] suggests that EPA supplementation is preferable to DHA supplementation, which performed no better than placebo on symptoms in schizophrenic individuals. One study in the USA [209] found no differences in symptoms, mood or cognition after supplementation with 3 g ethyl-EPA for 16 weeks.

At least two studies have been conducted with EPA and DHA combinations in fish oil, investigating changes in omega-3 fatty acid levels of red blood cells and improvement in symptoms. One of these studies investigated the combined supplementation of omega-3 fatty acids (EPA plus DHA) and antioxidant vitamins (E and C) [210], and the other [34], investigated the effect of 10 g·day⁻¹ MaxEPA (EPA plus DHA) in an open study. Both studies had positive results.

Additionally, two authors have presented results of findings in individual patients. In one, a 30 year old woman with exacerbation of symptoms during pregnancy, was supplemented with omega-3 fatty acids [211]. This resulted in an increase in omega-3 levels of RBC and improvement in positive and negative symptoms. In a second study, a drug-naïve patient was supplemented with 2 g EPA·day⁻¹ for 6 months [212–214]. Improvements were noted in PANSS scores, RBC omega-3 levels, cerebral atrophy and hemispheric imbalance.

4.4. Depression and post-partum depression

Major depression is defined as at least 2 weeks of predominantly low mood or diminished interests in one's usual activities in combination with 4 or more of the following: increased or decreased sleep patterns, inappropriate guilt or loss of self-esteem, increased or decreased appetite, low energy, difficulty concentrating, agitation or retardation, and suicidal thoughts [215]. During the past century, there has been a dramatic increase in the rates of depression among cohorts [216], and it is thought that there is a causative environmental factor involved [217]. Several observational studies have provided evidence that supports the theory that decreased fish and/or omega-3 fatty acid consumption may be involved with increased incidence of depression and this has been reviewed by various authors [218, 219].

Societies consuming large amounts of fish and n-3 fatty acids appear to have lower

rates of major depression and bipolar disorders [216, 220, 221] and the likelihood of having depressive symptoms increases among infrequent fish consumers versus frequent fish consumers [222]. Studies have also suggested that depression associated with disease diagnosis is also associated with decreased dietary intake of total omega-3 fatty acids [223, 224]. Seasonal variation of serum long chain PUFA, including EPA and DHA, correlates negatively with the number of violent suicidal deaths in Belgium [225]. However, one study found no associations between dietary intakes of omega-3 fatty acids and depressed mood or major depressive episodes [226].

Total n-3 PUFA, EPA, and DHA are depleted in red blood cell membranes of depressive patients and/or individuals at risk for the recurrent form of the major depressive disorder [217, 227, 228], and there is a negative correlation between levels of blood and adipose tissue n-3 PUFA and depressive symptoms [227, 229–231]. A study by Mamalakis et al. [232] suggests that while there is no relation between adipose tissue n-3 PUFA and depression, increased ratios of longer chain n-3 and n-6 fatty acids are noted and this suggests increased fatty acid elongation in general. N-3 fatty acids are also depleted in the serum PL and CE of depressed and bipolar patients [233–235], and an increase in the AA to EPA ratio has repeatedly been positively correlated with depression [233, 234, 236].

Post-partum depression (PPD) also appears to be associated with omega-3 fatty acid levels. Higher concentrations of DHA in breast milk and higher seafood consumption predicts lower prevalence of post-partum depression in society [237]. Higher plasma DHA of the mother is associated with a reduction in depressive symptom reporting in the immediate post-partum period [238]. Plasma DHA was influenced by maternal education and smoking, however, so these results should be interpreted with caution. Another study suggested that the

post-partum normalisation of DHA status was lower in individuals who were “possibly depressed” versus the non-depressed group [239]. In mothers who developed PPD, DHA and total omega-3 fatty acids (PL and CE) were decreased and the omega-6:omega-3 ratio was increased as compared with mothers who did not develop PPD [240].

As with the other neurological disorders mentioned in this review, there are a few studies investigating the effect of omega-3 fatty acid supplementation on symptoms of depression. At least four studies have investigated the potential efficacy of omega-3 fatty acid supplementation in depressive individuals. Most of these studies involved individuals who were on standard medications. Three of these studies investigated the effects of ethyl-EPA and found improvements in scores on depressive rating scales as well as suicidal thoughts and social phobia [241–243], with maximum benefits observed with the 1 g·day⁻¹ dose [241]. In another study, individuals were supplemented with 6.6 g of omega-3 fatty acids or placebo for 8 weeks [244]. A decreased score in the Hamilton rating scale was noted in the omega-3 supplemented group. One study investigated the effect of supplementation with DHA alone (2 g·day⁻¹) versus placebo for 6 weeks and found no difference in rating scale scores between the groups [245]. In bipolar patients on medication, Stoll et al. [35] determined that 9.6 g·day⁻¹ omega-3 fatty acids for 4 months, as compared with placebo, resulted in improved outcome and longer remission.

At least two studies have been conducted on individuals with PPD. In the first study, mothers with a history of PPD were supplemented with approximately 3 g fish oil from the 34th–36th week of pregnancy to 12 weeks post-partum [246]. There were no dropouts but there was also no evidence of benefit based on the number of individuals who had depressive episodes during the study. In the second study, individuals were supplemented with 200 mg DHA·day⁻¹ or placebo for

4 months following delivery [247]. Increased plasma DHA was noted in the supplemented group, whereas there was a decrease in the placebo group. There was no difference in self-rating or diagnostic measures of depression. It is still unclear whether there are potential benefits of omega-3 fatty acid supplementation from earlier on in pregnancy and/or prior to conception.

4.5. Other disorders

The role of omega-3 fatty acids has also been investigated in other neurological disorders, although the information is scarce. These include dyslexia, autistic spectrum disorders, dyspraxia, borderline personality (BPD) disorder and obsessive compulsive disorder (OCD), as well as in aggression and hostility.

In adults and children with dyslexia, signs of fatty acid deficiencies are correlated with the severity of dyslexic signs and symptoms [248, 249]. Cerebral P-31 magnetic resonance in dyslexics indicate increased membrane PL turnover [250]. Increased PLA2 activity has also been suggested [251]. Supplementation with PUFA from the omega-3 and omega-6 series (186 mg EPA, 480 mg DHA, 96 mg GLA, 864 mg LA and 42 mg AA per day) improved ADHD symptoms in children with learning disabilities (mainly dyslexia) [160] and supplementation with DHA for 1 month improved dark adaptation in dyslexic young adults [252].

Decreased DHA and total omega-3 fatty acids have been shown in blood of autistic children versus mentally retarded children [253]. Furthermore, there is also decreased PUFA in RBC membranes of autistic children which has been shown to break down faster than control samples when stored at -20°C versus -80°C [254]. There do not appear to be any published trials in which individuals with autistic spectrum disorder are supplemented with omega-3 fatty acids.

Two supplementation trials have been conducted in children with dyspraxia. These trials suggest improvement in movement

skills with high DHA fish oil plus evening primrose oil for 4 months [252] and improvement in reading and spelling, with a decrease in ADHD symptoms after supplementation with fish oil and evening primrose oil for 12 weeks [255].

Supplementation with 1 g of E-EPA per day for 8 weeks was investigated in individuals with BPD. Improvement was noted in aggression and severity of symptoms [256].

Omega-3 fatty acid supplementation has also been investigated in individuals with OCD on traditional selective serotonin reuptake inhibitors (SSRI's). Individuals were supplemented with 2 g EPA·day⁻¹ or placebo for 6 weeks. Scores on the Yale Brown Obsessive Compulsive Scale decreased in both groups [257].

Cross-nationally, it has been observed that rates of death from homicide are lower in countries with high n-3 consumption [258]. In a 5 year prospective interventional study, an increase in dietary n-3 fatty acids caused a significant decrease in hostility [259].

Omega-3 supplementation has been investigated in terms of aggression and hostility. Supplementation with 1.5 g DHA·day⁻¹ versus placebo for 2 months resulted in decreased aggression in educated University workers but not uneducated villagers after a videotape stressor [260]. When aggression was measured during exam time, after three months of supplementation with 1.5 g DHA·day⁻¹, there was an increase in aggression in the control group, but no change in the DHA group [261]. This same dose appeared to decrease the level of norepinephrine (NE), but not other catecholamines, in medical students during exams [262]. Interestingly, when aggression was determined during a non-stressful time, there was no change in aggression in the DHA group and a slight decrease in the control group [263]. It is possible DHA supplementation is offering protection during stressful conditions.

In cocaine addicts admitted to hospital, aggressive patients were shown to have decreased levels of total omega-3 fatty acids

and DHA as well as an increased n-6:n-3 ratio in blood [264].

5. CONCLUSION

It is obvious that there is a limited amount of work in the field of omega-3 fatty acids and neuropsychiatric disorders, and thus there are exciting opportunities for researchers. Evidence suggests decreased blood levels of omega-3 fatty acids in individuals with various psychiatric conditions. The reasons for this are not clear; they include a decreased biosynthesis and/or increased breakdown. Both would increase dietary requirements in this population. Alterations in the levels of minerals such as zinc, as observed in individuals with ADHD, would also play a role in LCPUFA synthesis. Epidemiological evidence suggests that either a decreased intake of omega-3 PUFA, or decreased levels of omega-3 PUFA in plasma or RBC are risk factors for the development of at least some of these conditions. This suggests that they may play a role in the actual development of the disorder as opposed to being a consequence of the disorder.

Thus far, the benefits of supplementation, in terms of decreasing disease risk and/or aiding in symptom management are not clear and more research is needed. Timing of dietary changes and/or supplementation use as well as levels and specific types of omega-3 fatty acids are still in the process of being investigated.

REFERENCES

- [1] Voss A, Reinhart M, Sankarappa S, Sprecher H. The metabolism of 7,10,13,16,19-docosapentaenoic acid to 4,7,10,13,16,19-docosahexaenoic acid in rat liver is independent of a 4-desaturase. *J Biol Chem* 1991, 266: 19995–20000.
- [2] Emken EA, Adolf RO, Gulley RM. Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. *Biochim Biophys Acta* 1994, 1213: 277–288.
- [3] Salem N Jr, Wegher B, Mena P, Uauy R. Arachidonic acid and docosahexaenoic acid are biosynthesized from their 18-carbon precursors in human infants. *Proc Natl Acad Sci USA* 1996, 93: 49–54.
- [4] Burdge G. Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. *Curr Opin Clin Nutr* 2004, 7: 137–144.
- [5] Conquer JA, Holub BJ. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. *J Nutr* 1996, 126: 3032–3039.
- [6] Conquer JA, Holub BJ. Dietary docosahexaenoic acid as a source of eicosapentaenoic acid in vegetarians and omnivores. *Lipids* 1997, 32: 341–345.
- [7] Simopolous AP. Essential fatty acids in health and chronic disease. *Am J Clin Nutr* 1999, 70: S560–S569.
- [8] Simopolous AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991, 54: 438–463.
- [9] Kris-Etherton PM, Shaffer D, Yu-Poth S, Huth P, Moriarty K, Fishell V, Hargrove RL, Zhao G, Etherton TD. Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr* 2000, 71: S179–S188.
- [10] Howe PR, Meyer BJ, Record S, Baghurst K. Contribution of red meat to very long chain omega-3 fatty acid (VLCOmega3) intake. *Asia Pac J Clin Nutr* 2003, 12 (Suppl): S27.
- [11] Institute of Medicine (IOM). *Dietary References Intakes for Energy and Macronutrients*. National Academy Press, Washington, 2002.
- [12] British Nutrition Foundation. *Task Force on Unsaturated Fatty Acids*. Chapman and Hall, London, 1992.
- [13] Sugano M, Hirahara F. Polyunsaturated fatty acids in the food chain in Japan. *Am J Clin Nutr* 2000, 71: 189S–196S.
- [14] Sastry PS. Lipids of nervous tissue: composition and metabolism. *Prog Lipid Res* 1985, 24: 69–176.
- [15] Dennis EA. Diversity of group types, regulation, and function of phospholipase A2. *J Biol Chem* 1994, 269: 13057–13060.
- [16] Balboa MA, Varela-Nieto I, Killermann Lucas K, Dennis EA. Expression and function of phospholipase A(2) in brain. *FEBS Lett* 2002, 531: 12–17.
- [17] Molloy GY, Rattray M, Williams RJ. Genes encoding multiple forms of phospholipase A2

- are expressed in rat brain. *Neurosci Lett* 1998, 258: 139–142.
- [18] Jarrard LE. On the role of the hippocampus in learning and memory in the rat. *Behav Neural Biol* 1993, 60: 9–26.
- [19] Farooqui AA, Yang HC, Rosenberger TA, Horrocks LA. Phospholipase A2 and its role in brain tissue. *J Neurochem* 1997, 69: 889–901.
- [20] Farooqui AA, Horrocks LA. Brain phospholipase A2: a perspective on the history. *Prostaglandins Leukot Essent Fatty Acids* 2004, 71: 161–169.
- [21] Gattaz WF, Hubner CV, Nevalainen TJ, Thuren T, Kinnunen PK. Increased serum phospholipase A2 activity in schizophrenia: a replication study. *Biol Psychiatry* 1990, 28: 495–501.
- [22] Pettegrew JW, Keshavan MS, Panchalingam K, Strychor S, Kaplan DB, Tretta MG, Allen M. Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naïve schizophrenics. A pilot study of the dorsal prefrontal cortex by in vivo phosphorus 31 nuclear magnetic resonance spectroscopy. *Arch Gen Psychiatry* 1991, 48: 563–568.
- [23] Horrobin DF, Glen AI, Vaddadi K. The membrane hypothesis of schizophrenia. *Schizophr Res* 1994, 13: 195–207.
- [24] Wei J, Hemmings GP. A study of a genetic association between the PTGS2/PA2G4A locus and schizophrenia. *Prostaglandins Leukot Essent Fatty Acids* 2004, 70: 413–415.
- [25] MacDonell LE, Skinner FK, Ward PE, Glen AI, Glen AC, Macdonald DJ, Boyle RM, Horrobin DF. Increased levels of cytosolic phospholipase A2 in dyslexics. *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 37–39.
- [26] Noponen M, Sanfilippo M, Samanich K, Ryer H, Ko G, Angrist B, Wolkin A, Duncan E, Rotrosen J. Elevated PLA2 activity in schizophrenics and other psychiatric patients. *Biol Psychiatry* 1993, 34: 641–649.
- [27] Chang MC, Jones CR. Chronic lithium treatment decreases brain phospholipase A(2) activity. *Neurochem Res* 1998, 23: 887–892.
- [28] Horrobin DF, Bennett CN. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis. *Prostaglandins Leukot Essent Fatty Acids* 1999, 60: 217–234.
- [29] Ghelardoni S, Tomita YA, Bell JM, Rapoport SI, Bosetti F. Chronic carbamazepine selectively downregulates cytosolic phospholipase A2 expression and cyclooxygenase activity in rat brain. *Psychiatry* 2004, 56: 248–254.
- [30] Papadimitriou GN, Dikeos DG, Souery D, Del-Favero J, Massat I, Avramopoulos D, Blairy S, Cichon S, Ivezic S, Kaneva R, Karadima G, Lilli R, Milanova V, Nothen M, Oruc L, Rietschel M, Serretti A, Van Broeckhoven C, Stefanis CN, Mendlewicz J. Genetic association between the phospholipase A2 gene and unipolar affective disorder: a multicentre case-control study. *Psychiatr Genet* 2003, 13: 211–220.
- [31] Meira-Lima I, Jardim D, Junqueira R, Ikenaga E, Vallada H. Allelic association study between phospholipase A2 genes and bipolar affective disorder. *Bipolar Disord* 2003, 5: 295–299.
- [32] Ross BM, Turenne S, Moszczynska A, Warsh JJ, Kish SJ. Differential alteration of phospholipase A2 activities in brain of patients with schizophrenia. *Brain Res* 1999, 821: 407–413.
- [33] Finnen MJ, Lovell CR. Purification and characterization of phospholipase A2 from human epidermis. *Biochem Soc Trans* 1991, 19: 91S.
- [34] Emsley R, Myburgh C, Oosthuizen P, van Rensburg SJ. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. *Am J Psychiatry* 2002, 159: 1596–1598.
- [35] Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB. Omega-3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999, 56: 407–412.
- [36] Christensen O, Christensen E. Fat consumption and schizophrenia. *Acta Psychiatr Scand* 1988, 78: 587–592.
- [37] Mellor JE, Laugharne JD, Peet M. Omega-3 fatty acid supplementation in schizophrenia patients. *Hum Psychopharmacol* 1996, 11: 39–46.
- [38] Maes M, Stevens WJ, Declercq LS, Bridts CH, Peeters D, Schotte C, Cosyns P. Significantly increased expression of T-cell activation markers (interleukin-2 and HLA-DR) in depression: further evidence for an inflammatory process during that illness. *Prog Neuropsychopharmacol Biol Psychiatry* 1993, 17: 241–255.
- [39] Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. *J Psychiatr Res* 1995, 29: 141–152.
- [40] Maes M, Delange J, Ranjan R, Meltzer HY, Desnyder R, Cooremans W, Scharpe S. Acute

- phase proteins in schizophrenia, mania and major depression: modulation by psychotropic drugs. *Psychiatry Res* 1997, 66: 1–11.
- [41] Segman RH, Meltzer A, Gross-Tsur V, Kosov A, Frisch A, Inbar E, Darvasi A, Levy S, Goltser T, Weizman A, Galili-Weisstub E. Preferential transmission of interleukin-1 receptor antagonist alleles in attention deficit hyperactivity disorder. *Mol Psychiatry* 2002, 7: 72–74.
- [42] Jyonouchi H, Sun S, Le H. Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. *J Neuroimmunol* 2001, 120: 170–179.
- [43] Croonenberghs J, Bosmans E, Deboutte D, Kenis G, Maes M. Activation of the inflammatory response system in autism. *Neuropsychobiology* 2002, 45: 1–6.
- [44] Bousserouel S, Brouillet A, Bereziat G, Raymondjean M, Andreani M. Different effects of n-6 and n-3 polyunsaturated fatty acids on the activation of rat smooth muscle cells by interleukin-1 beta. *J Lipid Res* 2003, 44: 601–611.
- [45] Hardardottir I, Kinsella JE. Tumor necrosis factor production by murine resident peritoneal macrophages is enhanced by dietary n-3 polyunsaturated fatty acids. *Biochim Biophys Acta* 1991, 1095: 187–195.
- [46] Song C, Leonard BE, Horrobin DF. Dietary ethyl-eicosapentaenoic acid but not soybean oil reverses central interleukin-1-induced changes in behavior, corticosterone and immune response in rats. *Stress* 2004, 7: 43–54.
- [47] Song C, Horrobin D. Omega-3 fatty acid ethyl-eicosapentaenoate, but not soybean oil, attenuates memory impairment induced by central IL-1 beta administration. *Lipid Res* 2004, 45: 1112–1121.
- [48] Kinsella JE, Broughton KS, Whelan JW. Dietary unsaturated fatty acids: interactions and possible needs in relation to eicosanoid synthesis. *J Nutr Biochem* 1990, 1: 123–141.
- [49] Youdim KA, Martin A, Joseph JA. Essential fatty acids and the brain: possible health implications. *Int J Dev Neuroscience* 2000, 28: 383–399.
- [50] Guyton AC, Hall JE. *Textbook of Medical Physiology*. 9th ed. WB Saunders CO, PN, 1996, 569 p.
- [51] Wise RA. Dopamine, learning and motivation. *Nat Rev Neurosci* 2004, 5: 483–494.
- [52] Baldwin D, Rudge S. The role of serotonin in depression and anxiety. *Int Clin Psychopharmacol* 1995, 9: S41–S45.
- [53] Fernstrom JD. Dietary amino acids and brain function. *Am Diet Assoc* 1994, 94: 71–77.
- [54] Paez X, Hernandez L. Simultaneous brain and blood microdialysis study with a new removable venous probe. Serotonin and 5-hydroxy indolacetic acid changes after D-norfenfluramine or fluoxetine. *Life Sci* 1996, 58: 1209–1221.
- [55] Post RM, Jimerson DC, Bunney WE Jr, Goodwin FK. Dopamine and mania: behavioral and biochemical effects of the dopamine receptor blocker pimozide. *Psychopharmacology (Berl)* 1980, 67: 297–305.
- [56] Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N, Baldwin RM, Seibyl JP, Innis RB, Charney DS. Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. *Biol Psychiatry* 1998, 44: 1090–1098.
- [57] Ogilvie AD, Battersby S, Bubb VJ, Fink G, Harmar AJ, Goodwin GM, Smith CA. Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet* 1996, 347: 731–733.
- [58] Mundo E, Walker M, Cate T, Macciardi F, Kennedy JL. The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder: preliminary findings. *Arch Gen Psychiatry* 2001, 58: 539–544.
- [59] Elliot H. Attention deficit hyperactivity disorder in adults: a guide for the primary care physician. *South Med J* 2002, 95: 736–742.
- [60] Cook EH, Stein MA, Krasowski MD, Cox NJ, Olkon DM, Kieffer JE, Leventhal BL. Association of attention-deficit disorder and the dopamine transporter gene. *Am J Hum Genet* 1995, 56: 993–998.
- [61] Qian Q, Wang Y, Zhou R, Yang L, Faraone SV. Family-based and case-control association studies of DRD4 and DAT1 polymorphisms in Chinese attention deficit hyperactivity disorder patients suggest long repeats contribute to genetic risk for the disorder. *Am J Med Genet* 2004, 128B: 84–89.
- [62] Levitan RD, Masellis M, Basile VS, Lam RW, Jain U, Kaplan AS, Kennedy SH, Siegel G, Walker ML, Vaccarino FJ, Kennedy JL. Polymorphism of the serotonin-2A receptor gene (HTR2A) associated with childhood attention deficit hyperactivity disorder (ADHD) in adult women with seasonal affective disorder. *J Affect Disord* 2002, 71: 229–233.
- [63] Richardson AJ, Ross MA. Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 1–9.

- [64] Marino C, Giorda R, Vanzin L, Molteni M, Lorusso ML, Nobile M, Baschiroto C, Alda M, Battaglia M. No evidence for association and linkage disequilibrium between dyslexia and markers of four dopamine-related genes. *Eur Child Adolesc Psychiatry* 2003, 12: 198–202.
- [65] Nopola-Hemmi J, Myllyluoma B, Haltia T, Taipale M, Ollikainen V, Ahonen T, Voutilainen A, Kere J, Widen E. A dominant gene for developmental dyslexia on chromosome 3. *J Med Genet* 2001, 38: 658–664.
- [66] Abi-Dargham A. Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int J Neuropsychopharmacol* 2004, 7: S1–S5.
- [67] Carlsson A, Lindqvist M. Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol* 1963, 20: 140–144.
- [68] Lieberman JA, Kane JM, Gadaleta D, Brenner R, Lesser MS, Kinon B. Methylphenidate challenge as a predictor of relapse in schizophrenia. *Am J Psychiatry* 1984, 141: 633–638.
- [69] Glatt SJ, Faraone SV, Tsuang MT. Meta-analysis identifies an association between the dopamine D2 receptor gene and schizophrenia. *Mol Psychiatry* 2003, 8: 911–915.
- [70] Ambrosio AM, Kennedy JL, Macciardi F, Macedo A, Valente J, Dourado A, Oliveira CR, Pato C. Family association study between DRD2 and DRD3 gene polymorphisms and schizophrenia in a Portuguese population. *Psychiatry Res* 2004, 125: 185–191.
- [71] Glatt SJ, Faraone SV, Tsuang MT. DRD2 – 141C insertion/deletion polymorphism is not associated with schizophrenia: results of a meta-analysis. *Am J Med Genet B* 2004, 128: 21–23.
- [72] Wooley D, Shaw E. A biochemical and pharmacological suggestion about certain mental disorders. *Proc Natl Acad Sci USA* 1954, 40: 228–231.
- [73] Fink H, Morgenstern R, Oelssner W. Clozapine-A serotonin antagonist? *Pharmacol Biochem Behav* 1984, 20: 513–517.
- [74] DeLeon A, Patel NC, Lynn Crismon M. Aripiprazole: A comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clin Ther* 2004, 26: 649–666.
- [75] Castensson A, Emilsson L, Sundberg R, Jazin E. Decrease of serotonin receptor 2C in schizophrenia brains identified by high-resolution mRNA expression analysis. *Biol Psychiatry* 2003, 54: 1212–1221.
- [76] Dubertret C, Hanoun N, Ades J, Hamon M, Gorwood P. Family-based association study of the serotonin-6 receptor gene (C267T polymorphism) in schizophrenia. *Am J Med Genet B* 2004, 126: 10–15.
- [77] Ellingrod VL, Miller D, Ringold JC, Perry PJ. Distribution of the serotonin 2C (5HT2C) receptor gene -759C/T polymorphism in patients with schizophrenia and normal controls. *Psychiatr Genet* 2004, 14: 93–95.
- [78] De la Presa Owens S, Innis SM. Docosahexaenoic acid and arachidonic acid prevent a decrease in dopaminergic and serotonergic neurotransmitters in frontal cortex caused by a linoleic and alpha-linolenic acid deficient diet in formula-fed piglets. *J Nutr* 1999, 129: 2088–2093.
- [79] Austead N, Innis SM, de la Presa Owens S. Auditory evoked response and brain phospholipid fatty acids and monoamines in rats fed formula with and without arachidonic acid (AA) and/or docosahexaenoic acid (DHA). In: Watkins P, Spector A, Hamilton J, Katz R (Eds), *Brain uptake and utilization of fatty acids: applications to peroxisomal biogenesis disorders*, Maryland: National Institutes of Health Conference, 2000, p 3.
- [80] Zimmer L, Durand G, Guilloteau D, Chalons S. n-3 polyunsaturated fatty acid deficiency and dopamine metabolism in the rat frontal cortex. *Lipids* 1999, 34: S251.
- [81] Zimmer L, Delpal S, Guilloteau D, Aioun J, Durand G, Chalons S. Chronic n-3 polyunsaturated fatty acid deficiency alters dopamine vesicle density in the rat frontal cortex. *Neurosci Lett* 2000, 284: 25–28.
- [82] Chalons S, Delion-Vancassel S, Belzung C, Guilloteau D, Leguisquet A, Besnard JC, Durand G. Dietary fish oil affects monoaminergic neurotransmission and behavior in rats. *J Nutr* 1998, 128: 2512–2519.
- [83] Kodas E, Galineau L, Bodard S, Vancassel S, Guilloteau D, Besnard JC, Chalons S. Serotonergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. *Neurochem* 2004, 89: 695–702.
- [84] Sirvio J. Strategies that support declining cholinergic neurotransmission in Alzheimer's disease patients. *Gerontology* 1999, 45 (Suppl 1): 3–14.
- [85] Raedler TJ, Knable MB, Jones DW, Urbina RA, Gorey JG, Lee KS, Egan MF, Coppola R, Weinberger DR. In vivo determination of muscarinic acetylcholine receptor availability in schizophrenia. *Am J Psychiatry* 2003, 160: 118–127.
- [86] Leiva DB. The neurochemistry of mania: a hypothesis of etiology and rationale for treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 1990, 14: 423–429.

- [87] Favreliere S, Perault MC, Huguot F, De Javel D, Bertrand N, Piriou A, Durand G. DHA-enriched phospholipid diets modulate age-related alterations in rat hippocampus. *Neurobiol Aging* 2003, 24: 233–243.
- [88] Minami M, Kimura S, Endo T, Hamaue N, Hirafuji M, Togashi H, Matsumoto M, Yoshioka M, Saito H, Watanabe S, Kobayashi T, Okuyama H. Dietary docosahexaenoic acid increases cerebral acetylcholine levels and improves passive avoidance performance in stroke-prone spontaneously hypertensive rats. *Pharmacol Biochem Behav* 1997, 58: 1123–1129.
- [89] Aid S, Vancassel S, Pomes-Ballihaut C, Chalou S, Guesnet P, Lavialle M. Effect of a diet-induced n-3 PUFA depletion on cholinergic parameters in the rat hippocampus. *Lipid Res* 2003, 44: 1545–1551.
- [90] Piomelli D. Eicosanoids in synaptic transmission. *Crit Rev Neurobiology* 1994, 8: 65–82.
- [91] Di Marzo V, Piomelli D. Participation of prostaglandin E2 in dopamine D2 receptor-dependent potentiation of arachidonic acid release. *J Neurochem* 1992, 59: 379–382.
- [92] Ahmadi S, Lippross S, Neuhuber WL, Zeilhofer HU. PGE(2) selectively blocks inhibitory glycinergic neurotransmission onto rat superficial dorsal horn neurons. *Nat Neurosci* 2002, 5: 34–40.
- [93] Wolfe L, Horrocks L. Eicosanoids. In: Seigel GJ, Agranoff BW, Albers RW, Molinoff PB (Eds), *Basic Neurochemistry: Molecular, Cellular, and Medical Aspects*, 5th ed, Raven Press, New York, 1994, p 475–490.
- [94] Schlicker E, Fink K, Gothert M. Influence of eicosanoids on serotonin release in the rat brain: inhibition by prostaglandins E1 and E2. *Naunyn Schmiedeberg's Arch Pharmacol* 1987, 335: 646–651.
- [95] Rettori V, Gimeno M, Lyson K, McCann SM. Nitric oxide mediates norepinephrine-induced prostaglandin E2 release from the hypothalamus. *Proc Natl Acad Sci USA* 1992, 89: 11543–11546.
- [96] Mahadik SP, Mukherjee S. Free radical pathology and antioxidant defense in schizophrenia: a review. *Schizophr Res* 1996, 19: 1–17.
- [97] Groff JL, Gropper SS, Hunt SM. *Advanced Nutrition and Human Metabolism*. 2nd ed. West Publishing Co, MN, 1995.
- [98] Mahadik SP, Evans D, Lal H. Oxidative stress and role of antioxidant and ω -3 essential fatty acid supplementation in schizophrenia. *Prog Neuro Psychopharmacol Biol Psychiatr* 2001, 25: 463–493.
- [99] Rosler M, Retz W, Thome J, Riederer P. Free radicals in Alzheimer's dementia: currently available therapeutic strategies. *J Neural Transm Suppl* 1998, 54: 211–219.
- [100] Ross MA. Could oxidative stress be a factor in neurodevelopmental disorders? *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 61–63.
- [101] Dakhale G, Khanzode S, Khanzode S, Saoji A, Khobragade L, Turankar A. Oxidative damage and schizophrenia: the potential benefit by atypical antipsychotics. *Neuropsychobiology* 2004, 49: 205–209.
- [102] Lukash AI, Zaika VG, Kucherenko AO, Miliutina NP. Free radical processes and antioxidant system in depression and treatment efficiency. *Zh Nevrol Psikhiatr Im S S Korsakova* 2002, 102: 41–44.
- [103] Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. *Redox Rep* 2003, 8: 365–370.
- [104] Ozcan ME, Gulec M, Ozerol E, Polat R, Akyol O. Antioxidant enzyme activities and oxidative stress in affective disorders. *Int Clin Psychopharmacol* 2004, 19: 89–95.
- [105] Tsuboi H, Shimoi K, Kinai N, Oguni I, Hori R, Kobayashi F. Depressive symptoms are independently correlated with lipid peroxidation in a female population: comparison with vitamins and carotenoids. *J Psychosom Res* 2004, 56: 53–58.
- [106] Ross BM, McKenzie I, Glen I, Bennett CP. Increased levels of ethane, a non-invasive marker of n-3 fatty acid oxidation, in breath of children with attention deficit hyperactivity disorder. *Nutr Neurosci* 2003, 6: 277–281.
- [107] Yao JK, Reddy R, van Kammen DP. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia. *Psychiatry Res* 2000, 97: 137–151.
- [108] Stokiasova A, Zapletalek M, Kudrnova K, Randova Z. Glutathione peroxidase activity of blood in chronic schizophrenics. *Sb Ved Pr Lek Fak Karlovi University Hradci Kralove* 1986, 20: 103–108.
- [109] Reddy R, Mahadik SP, Mukherjee S, Murthy JN. Enzymes of the antioxidant defense system in chronic schizophrenic patients. *Biol Psychiatry* 1991, 20: 409–412.
- [110] Cecchi C, Fiorillo C, Sorbi S, Latorraca S, Nacmias B, Bagnoli S, Nassi P, Liguri G. Oxidative stress and reduced antioxidant defenses in peripheral cells from familial Alzheimer's patients. *Free Radic Biol Med* 2002, 33: 1372–1379.

- [111] Perry G, Castellani RJ, Smith MA, Harris PL, Kubat Z, Ghanbari K, Jones PK, Cordone G, Tabaton M, Wolozin B, Ghanbari H. Oxidative damage in the olfactory system in Alzheimer's disease. *Acta Neuropathol (Berl)* 2003, 106: 552–556.
- [112] Montine KS, Quinn JF, Zhang J, Fessel JP, Roberts LJ 2nd, Morrow JD, Montine TJ. Isoprostanes and related products of lipid peroxidation in neurodegenerative diseases. *Chem Phys Lipids* 2004, 28: 117–124.
- [113] Hargreaves KM, Clandinin MT. Dietary control of diacylphosphatidylethanolamine species in brain. *Biochim Biophys Acta* 1998, 962: 98–104.
- [114] Bjerve KS, Brubakk AM, Fougner KJ, Johnsen H, Midthjell K, Vik T. Omega-3 fatty acids: essential fatty acids with important biological effects, and serum phospholipid fatty acids as markers of dietary omega 3-fatty acid intake. *Am J Clin Nutr* 1993, 57: 801S–805S.
- [115] Godley PA, Campbell MK, Miller C, Gallagher P, Martinson FE, Mohler JL, Sandler RS. Correlation between biomarkers of omega-3 fatty acid consumption and questionnaire data in African American and Caucasian United States males with and without prostatic carcinoma. *Cancer Epidemiol Biomarkers Prev* 1996, 5: 115–119.
- [116] Hjartaker J, Lund E, Bjerve KS. Serum phospholipid fatty acid composition and habitual intake of marine foods registered by a semi-quantitative food frequency questionnaire. *Eur J Clin Nutr* 1997, 51: 736–742.
- [117] Mori TA, Woodman RJ, Burke V, Puddey IB, Croft KD, Beilin LJ. Effect of eicosapentaenoic acid and docosahexaenoic acid on oxidative stress and inflammatory markers in treated-hypertensive type 2 diabetic subjects. *Free Radic Biol Med* 2003, 35: 772–781.
- [118] Mori TA, Puddey IB, Burke V, Croft KD, Dunstan DW, Rivera JH, Beilin LJ. Effect of omega-3 fatty acids on oxidative stress in humans: GC-MS measurement of urinary F2-isoprostane excretion. *Redox Rep* 2000, 5: 45–46.
- [119] Songur A, Sarsilmaz M, Sogut S, Ozyurt B, Zararsiz I, Turkoglu AO. Hypothalamic superoxide dismutase, xanthine oxidase, nitric oxide, and malondialdehyde in rats fed with fish omega-3 fatty acids. *Prog Neuropsychopharmacol Biol Psychiatry* 2004, 28: 693–698.
- [120] Barbosa DS, Cecchini R, El Kadri MZ, Rodriguez MA, Burini RC, Dichi I. Decreased oxidative stress in patients with ulcerative colitis supplemented with fish oil omega-3 fatty acids. *Nutrition* 2003, 19: 837–842.
- [121] Barden AE, Mori TA, Dunstan JA, Taylor AL, Thornton CA, Croft KD, Beilin LJ, Prescott SL. Fish oil supplementation in pregnancy lowers F2-isoprostanes in neonates at high risk of atopy. *Free Radic Res* 2004, 38: 233–239.
- [122] Xiao YF, Kang JX, Morgan JP, Leaf A. Blocking effects of polyunsaturated fatty acids on Na⁺ channels of neonatal rat ventricular myocytes. *Proc Natl Acad Sci USA* 1995, 92: 11000–11004.
- [123] Kang JX, Leaf A. Evidence that free polyunsaturated fatty acids modify Na⁺ channels by directly binding to the channel proteins. *Proc Natl Acad Sci USA* 1996, 93: 3542–3546.
- [124] Vreugdenhil M, Bruehl C, Voskuyl RA, Kang JX, Leaf A, Wadman WJ. Polyunsaturated fatty acids modulate sodium and calcium currents in CA1 neurons. *Proc Natl Acad Sci USA* 1996, 93: 12559–12563.
- [125] Renganathan M, Godoy CM, Cukierman S. Direct modulation of Na⁺ currents by protein kinase C activators in mouse neuroblastoma cells. *J Membr Biol* 1995, 144: 59–69.
- [126] Bogdanov KY, Spurgeon HA, Vinogradova TM, Lakatta EG. Modulation of the transient outward current in adult rat ventricular myocytes by polyunsaturated fatty acids. *Am J Physiol* 1998, 274: H571–H579.
- [127] Seebungert B, Lynch JW. Effects of polyunsaturated fatty acids on voltage-gated K⁺ and Na⁺ channels in rat olfactory receptor neurons. *Eur J Neurosci* 2002, 16: 2085–2094.
- [128] Honore E, Barhanin J, Attali B, Lesage F, Lazdunski M. External blockade of the major cardiac delayed-rectifier K⁺ channel (Kv1.5) by polyunsaturated fatty acids. *Proc Natl Acad Sci USA* 1994, 91: 1937–1944.
- [129] Lauritzen I, Blondeau N, Heurteaux C, Widmann C, Romey G, Lazdunski M. Polyunsaturated fatty acids are potent neuroprotectors. *EMBO* 2000, 19: 1784–1793.
- [130] Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M, Lang-Lazdunski L, Widmann C, Zanzouri M, Romey G, Lazdunski M. TREK-1, a K⁺ channel involved in neuroprotection and general anesthesia. *EMBO* 2004, 23: 2684–2695.
- [131] Xiao YF, Gomez AM, Morgan JP, Lederer WJ, Leaf A. Suppression of voltage-gated L-type Ca²⁺ currents by polyunsaturated fatty acids in adult and neonatal rat ventricular myocytes. *Proc Natl Acad Sci USA* 1997, 94: 4182–4187.

- [132] Turner N, Else PL, Hulbert AJ. Docosahexaenoic acid (DHA) content of membranes determines molecular activity of the sodium pump: implications for disease states and metabolism. *Naturwissenschaften* 2003, 90: 521–523.
- [133] Kearns SD, Haag M. The effect of omega-3 fatty acids on Ca-ATPase in rat cerebral cortex. *Prostaglandins Leukot Essent Fatty Acids* 2002, 67: 303–308.
- [134] Gegelashvili G, Schousboe A. High affinity glutamate transporters: regulation of expression and activity. *Mol Pharmacol* 1997, 52: 6–15.
- [135] Nishikawa M, Kimura S, Akaike N. Facilitatory effect of docosahexaenoic acid on N-methyl-D-aspartate response in pyramidal neurons of rat cerebral cortex. *J Physiol* 1994, 475: 83–93.
- [136] Graber R, Sumida C, Nunez EA. Fatty acids and cell signal transduction. *J Lipid Mediat Cell Signal* 1994, 9: 91–116.
- [137] Kogteva GS, Bezuglov VV. Unsaturated fatty acids as endogenous bioregulators. *Biochemistry (Moscow)* 1998, 63: 6–15.
- [138] Wahle KW, Rotondo D, Heys SD. Polyunsaturated fatty acids and gene expression in mammalian systems. *Proc Nutr Soc* 2003, 62: 349–360.
- [139] Horrocks LA, Farooqui AA. Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. *Prostaglandins Leukot Essent Fatty Acids* 2004, 70: 361–372.
- [140] Kitajka K, Puskas LG, Zvara A, Hackler L Jr, Barcelo-Coblijn G, Yeo YK, Farkas T. The role of n-3 polyunsaturated fatty acids in brain: modulation of rat brain gene expression by dietary n-3 fatty acids. *Proc Natl Acad Sci USA* 2002, 99: 2619–2624.
- [141] George JM, Jin H, Woods WS, Clayton DF. Characterization of a novel protein regulated during the critical period for song learning in the zebra finch. *Neuron* 1995, 15: 361–372.
- [142] Huntley GW, Gil O, Bozdagi O. The cadherin family of cell adhesion molecules: multiple roles in synaptic plasticity. *Neuroscientist* 2002, 8: 221–233.
- [143] Junge HJ, Rhee JS, Jahn O, Varoqueaux F, Spiess J, Waxham MN, Rosenmund C, Brose N. Calmodulin and Munc13 form a Ca²⁺ sensor/effector complex that controls short-term synaptic plasticity. *Cell* 2004, 118: 389–401.
- [144] Colbran RJ, Brown AM. Calcium/calmodulin-dependent protein kinase II and synaptic plasticity. *Curr Opin Neurobiol* 2004, 14: 318–327.
- [145] Li H, Sanchez-Torres J, Del Carpio A, Salas V, Villalobo A. The ErbB2/Neu/HER2 receptor is a new calmodulin-binding protein. *Biochem J* 2004, 381: 257–266.
- [146] Schmitt JM, Wayman GA, Nozaki N, Soderling TR. Calcium activation of ERK mediated by calmodulin kinase I. *J Biol Chem* 2004, 279: 24064–24072.
- [147] Kitajka K, Sinclair AJ, Weisinger RS, Weisinger HS, Mathai M, Jayasooriya AP, Halver JE, Puskas LG. Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. *Proc Natl Acad Sci USA* 2004, 101: 10931–10936.
- [148] Martinez M. Polyunsaturated fatty acids in the developing human brain, erythrocytes and plasma in peroxisomal disease: therapeutic implications. *J Inher Metab Dis* 1995, 18 (Suppl 1): 61–75.
- [149] Uauy R, Peirano P, Hoffman D, Mena P, Birch D, Birch E. Role of essential fatty acids in the function of the developing nervous system. *Lipids* 1996, 31 (Suppl): S167–S176.
- [150] Hoffman DR, Birch DG. Omega-3 fatty acid status in patients with retinitis pigmentosa 1998, 83: 52–60.
- [151] Martinez M. Restoring the DHA levels in the brains of Zellweger patients. *J Mol Neurosci* 2001, 16: 309–316.
- [152] Pary R, Lewis S, Matuschka PR, Lippmann S. Attention-deficit/hyperactivity disorder: an update. *South Med* 2002, 95: 743–749.
- [153] Richardson AJ, Puri BK. The potential role of fatty acids in attention-deficit/hyperactivity disorder. *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 79–87.
- [154] Burgess JR, Stevens L, Zhang W, Peck L. Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *Am J Clin Nutr* 2000, 71: 327–330.
- [155] Spencer T, Biederman J, Wilens TE, Faraone SV. Is attention deficit hyperactivity disorder in adults a valid disorder? *Harv Rev Psychiatry* 1994, 1: 326–335.
- [156] Mitchell EA, Aman MG, Turbott SH, Manku M. Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clin Pediatr* 1987, 26: 406–411.
- [157] Stevens LJ, Zentall SS, Deck JL, Abate ML, Watkins BA, Lipp SR, Burgess JR. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *Am J Clin Nutr* 1995, 62: 761–768.

- [158] Young GS, Maharaj NJ, Conquer JA. Blood phospholipid fatty acid analysis of adults with and without attention deficit/hyperactivity disorder. *Lipids* 2004, 39: 117–123.
- [159] Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr* 2001, 139: 189–196.
- [160] Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Prog Neuro-Psychopharmacol Biol Psychiatry* 2002, 26: 233–239.
- [161] Stevens L, Zhang W, Peck L, Kuczek T, Grevsted N, Mahon A, Zentall SS, Arnold E, Burgess JR. EPA supplementation in children with inattention, hyperactivity, and other disruptive behaviours. *Lipids* 2003, 38: 1007–1021.
- [162] Harding KL, Judah RD, Gant CE. Outcome-based comparison of ritalin versus food-supplement treated children with AD/HD. *Altern Med Rev* 2003, 8: 319–330.
- [163] Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder—a placebo-controlled double-blind study. *Eur J Clin Nutr* 2004, 58: 467–473.
- [164] Evans DA, Funkenstein HH, Alber M, Scherr PA, Cook NR, Chown M, Herbert L, Hennekens C, Taylor J. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. *J Am Med Assoc* 1989, 262: 2551–2556.
- [165] Nitsch R, Pittas A, Blustztajn JK, Slock BE, Growdon J. Alterations of phospholipid metabolites in post-mortem brains from patients with Alzheimer's disease. *Ann NY Acad Sci* 1991, 640: 110–113.
- [166] Soderberg M, Edlund C, Kristensson K, Dallner G. Fatty acid composition of brain phospholipids in aging and Alzheimer's disease. *Lipids* 1991, 26: 421–428.
- [167] Soderberg M, Edlund C, Kristensson K, Alafuzoff I, Dallner G. Lipid composition in different regions of the brain in Alzheimer's disease/senile dementia of Alzheimer's type. *J Neurochem* 1992, 59: 1646–1653.
- [168] Coorigan FM, Horrobin DF, Skinner ER, Besson JA, Cooper MB. Abnormal content of n-6 and n-3 long-chain unsaturated fatty acids in the phosphoglycerides and cholesterol esters of parahippocampus cortex from Alzheimer's disease patients and its relationship to acetyl CoA content. *Int J Biochem Cell Biol* 1998, 30: 197–207.
- [169] Mulder M, Ravid R, Swaab DF, deLoet ER, Haasdijk ED, Julk J, van der Bloom J, Havekes LM. Reduced levels of cholesterol, phospholipids, and fatty acids in CSF of Alzheimer's disease patients are not related to Apo E4. *Alzheimer Dis Assoc Disord* 1998, 12: 198–203.
- [170] Prasad MR, Lovell MA, Yatin M, Dhillon H, Markesbery WR. Regional membrane phospholipid alterations in Alzheimer's disease. *Neurochem Res* 1998, 23: 81–88.
- [171] Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF. Fish, meat, and risk of dementia: cohort study. *Br Med J* 2002, 325: 932–933.
- [172] Larrieu S, Letenneur L, Helmer, C, Dartigues JF, Barberger-Gateau P. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. *J. Nutr Health Aging* 2004, 8: 150–154.
- [173] Grant WB. Dietary Links to Alzheimer's Disease. *Alzheimer Dis Rev* 1997, 2: 42–55.
- [174] Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am J Epidemiol* 1997, 145: 33–41.
- [175] Grant WB. Diet and risk of dementia: Does fat matter? The Rotterdam study. *Neurology* 2003, 60: 2020–2021.
- [176] Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol* 2003, 60: 940–946.
- [177] Kalmijn S, van Boxtel MPJ, Ocke M, Verschuren WMM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology* 2004, 62: 275–280.
- [178] Heude B, Ducimetiere P, Berr C. Cognitive decline and fatty acid composition of erythrocyte membranes. The EVA study 2003, 77: 803–808.
- [179] Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, Coakley D, Gibney MJ. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. *Br J Nutr* 2003, 89: 483–489.
- [180] Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's Disease, other types of dementia and cognitive impairment. *Lipids* 2000, 35: 1305–1312.

- [181] Laurin D, Verreault R, Lindsay J, Dewailly E, Holub BJ. Omega-3 fatty acids and risk of cognitive impairment and dementia. *J Alzheimer Dis* 2003, 5: 315–322.
- [182] Otsuka M, Yamaguchi K, Ueki A. Similarities and differences between Alzheimer's disease and vascular dementia from the viewpoint of nutrition. *Ann NY Acad Sci* 2002, 977: 155–161.
- [183] Otsuka M. Analysis of dietary factors in Alzheimer's disease: clinical use of nutritional intervention for prevention and treatment of dementia. *Nippon Ronen Igakkai Zasshi* 2000, 37: 970–973.
- [184] Kyle DJ, Schaefer E, Patton G, Beiser A. Low serum docosahexaenoic acid is a significant risk factor for Alzheimer's dementia. *Lipids* 1999, 34 (Suppl): S245.
- [185] Nourooz-Zadeh J, Liu EH, Yhlen B, Anggard EE, Halliwell B. F4-isoprostanes as specific marker of docosahexaenoic acid peroxidation in Alzheimer's disease. *J Neurochem* 1999, 72: 734–740.
- [186] Montine TJ, Beal MF, Cudkowicz ME, O'Donnell H, Margolin RA, McFarland L, Bachrach AF, Zackert WE, Roberts LJ, Morrow JD. Increased CSF F2-isoprostane concentration in probable AD. *Neurology* 1999, 52: 562–565.
- [187] Terano T, Fujishiro S, Ban T, Yamamoto K, Tanaka T, Noguchi Y, Tamura Y, Yazawa K, Hirayama T. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids* 1999, 34: S345–S346.
- [188] Suzuki H, Morikawa Y, Takahashi H. Effect of DHA oil supplementation on intelligence and visual acuity in the elderly. *World Rev Nutr* 2001, 88: 68–71.
- [189] Christensen O, Christensen E. Fat consumption and schizophrenia. *Acta Psychiatr Scand* 1988, 78: 587–591.
- [190] Mellor JE, Laugharne JDE, Peet M. Omega-3 fatty acid supplementation in schizophrenia patients. *Hum Psychopharmacol* 1996, 11: 39–46.
- [191] Richardson AJ, Cyhlarova E, Ross MA. Omega-3 and omega-6 fatty acid concentrations in red blood cell membranes relate to schizotypal traits in healthy adults. *Prostaglandins Leukot Essent Fatty Acids* 2003, 69: 461–466.
- [192] Evans DR, Parikh VV, Khan MM, Coussons C, Buckley PF, Mahadik SP. Red blood cell membrane essential fatty acid metabolism in early psychotic patients following antipsychotic drug treatment. *Prostaglandins Leukot Essent Fatty Acids* 2003, 69: 393–399.
- [193] Arvindakshan M, Sitasawad S, Debsikdar V, Ghate M, Evans D, Horrobin DF, Bennett C, Ranjekar PK, Mahadik SP. Essential polyunsaturated fatty acid and lipid peroxide levels in never-medicated and medicated schizophrenia patients. *Biol Psychiatry* 2003, 53: 56–64.
- [194] Khan MM, Evands DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. *Schizophr Res* 2002, 58: 1–10.
- [195] Assies J, Lieverse R, Vreken P, Wanders RJ, Dingemans PM, Linszen DH. Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. *Biol Psychiatry* 2001, 49: 510–522.
- [196] Peet M, Laugharne J, Rangarajan N, Horrobin D, Reynolds G. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. *J Psychiatr Res* 1995, 29: 227–232.
- [197] Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP. Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Res* 2003, 121: 109–122.
- [198] Laugharne JD, Mellor JE, Peet M. Fatty acids and schizophrenia. *Lipids* 1996, 31 (Suppl): S163–S165.
- [199] Mahadik SP, Mukherjee S, Horrobin DF, Jenkins K, Correnti EE, Scheffer RE. Plasma membrane phospholipid fatty acid composition of cultured skin fibroblasts from schizophrenic patients: comparison with bipolar patients and normal subjects. *Psychiatry Res* 1996, 63: 133–142.
- [200] Fischer S, Kissling W, Kuss HJ. Schizophrenic patients treated with high dose phenothiazine or thioxanthene become deficient in polyunsaturated fatty acids in their thrombocytes. *Biochem Pharmacol* 1992, 44: 317–323.
- [201] Hibbeln JR, Makino KK, Martin CE, Dickerson F, Boronow J, Fenton WS. Smoking, gender, and dietary influences on erythrocyte essential fatty acid composition among patients with schizophrenia or schizoaffective disorder. *Biol Psychiatry* 2003, 53: 431–441.
- [202] Mahadik SP, Shendarkar NS, Scheffer RE, Mukherjee S, Correnti EE. Utilization of precursor essential fatty acids in culture by skin

- fibroblasts from schizophrenic patients and normal controls. *Prostaglandins Leukot Essent Fatty Acids* 1996, 55: 65–70.
- [203] Warner R, Laugharne J, Peet M, Brown L, Rogers N. Retinal function as a marker for cell membrane omega-3 fatty acid depletion in schizophrenia: a pilot study. *Biol Psychiatry* 1999, 45: 1138–1142.
- [204] Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid supplementation for schizophrenia. *Cochrane Database Syst Rev* 2003, CD001257.
- [205] Peet M. Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. *Prostaglandins Leukot Essent Fatty Acids* 2003, 69: 477–485.
- [206] Peet M. Nutrition and schizophrenia: beyond omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids* 2004, 70: 417–422.
- [207] Peet M, Horrobin DF, E-E Muticentre group. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *J Psychiatr Res* 2002, 36: 7–18.
- [208] Peet M, Brind-J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001, 49: 243–251.
- [209] Fenton WS, Dickerson F, Boronow J, Hibbeln JR, Knable M. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Psychiatry* 2001, 158: 2071–2074.
- [210] Arvindakshan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP. Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. *Schizophr Res* 2003, 62: 195–204.
- [211] Su KP, Shen WW, Huang SY. Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient. *Eur Neuropsychopharmacol* 2001, 11: 295–299.
- [212] Richardson AJ, Easton T, Puri BK. Red cell and plasma fatty acid changes accompanying symptom remission in a patient with schizophrenia treated with eicosapentaenoic acid. *Eur Neuropsychopharmacol* 2000, 10: 189–193.
- [213] Puri BK, Richardson AJ, Horrobin DF, Easton T, Saeed N, Oatridge A, Hajnal JV, Bydder GM. Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalisation of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. *Int J Clin Pract* 2000, 54: 57–63.
- [214] Richardson AJ, Easton T, Gruzeliier JH, Puri BK. Laterality changes accompanying symptom remission in schizophrenia following treatment with eicosapentaenoic acid. *Int J Psychophysiol* 1999, 34: 333–339.
- [215] American Psychiatric Association. *Diagnostic and statistical manual for mental disorders (DSM-IV)*. Washington DC, APA, 1994.
- [216] Hibbeln JR, Salem N. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr* 1995, 62: 1–9.
- [217] Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry* 1998, 43: 315–319.
- [218] Logan AC. Neurobehavioural aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. *Altern Med Rev* 2003, 8: 410–425.
- [219] Mischoulon D, Fava M. Docosahexaenoic acid and omega-3 fatty acids in depression. *Psychiatr Clin North Am* 2000, 23: 785–794.
- [220] Noaghiul S, Hibbeln JR. Cross national relationship of seafood consumption and rates of bipolar disorders. *Am J Psychiatry* 2003, 160: 2222–2227.
- [221] Hibbeln JR. Fish consumption and major depression. *Lancet* 1998, 351: 1213.
- [222] Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamaki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv* 2001, 52: 529–531.
- [223] Suzuki S, Akechi T, Kobayashi M, Taniguchi K, Goto K, Sasaki S, Tsugane S, Nishiwaki Y, Miyaoka H, Uchitomi Y. Daily omega-3 fatty acid intake and depression in Japanese patients with newly diagnosed lung cancer. *Br J Cancer* 2004, 90: 787–793.
- [224] Frasare-Smith N, Lesperance F, Julien P. Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol Psychiatry* 2004, 55: 891–896.
- [225] De Vriese SR, Christophe AB, Maes M. In humans, the seasonal variation in polyunsaturated fatty acids is related to the seasonal variation in violent suicide and serotonergic markers of violent suicide. *Prostaglandins Leukot Essent Fatty Acids* 2004, 71: 13–18.

- [226] Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry* 2004, 161: 567–569.
- [227] Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord* 1998, 48: 149–155.
- [228] Assies J, Lok A, Bockting CL, Weverling GJ, Lieveise R, Visser I, Abeling NGGM, Duran M, Schene AH. Fatty acids and homocysteine levels in patients with recurrent depression: an explorative pilot study. *Prostaglandins Leukot Essent Fatty Acids* 2004, 70: 349–356.
- [229] Mamalakis G, Kiriakakis M, Tsibinos G, Kafatos A. Depression and adipose polyunsaturated fatty acids in the survivors of the Seven Countries Study population of Crete. *Prostaglandins Leukot Essent Fatty Acids* 2004, 70: 495–501.
- [230] Tiemeier H, van Tuijl HR, Hofman A, Kiliaan AJ, Breteler MM. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam study. *Am J Clin Nutr* 2003, 78: 40–46.
- [231] Mamalakis G, Tornaritis M, Kafatos A. Depression and adipose essential polyunsaturated fatty acids. *Prostaglandins Leukot Essent Fatty Acids* 2002, 67: 311–318.
- [232] Mamalakis G, Kiriakakis M, Tsibinos G, Kafatos A. Depression and adipose polyunsaturated fatty acids in an adolescent group. *Prostaglandins Leukot Essent Fatty Acids* 2004, 71: 289–294.
- [233] Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H. Fatty acid composition in major depression: decreased ω 3 fractions in cholesteryl esters and increased C20:4 ω 6/C20:5 ω 3 ration in cholesteryl esters and phospholipids. *J Affect Disord* 1996, 38: 35–46.
- [234] Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer HY. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res* 1999, 85: 275–291.
- [235] Ranjekar PK, Hinge A, Hegde MV, Ghate M, Kale A, Sitasawad S, Wagh UV, Debsikdar VB, Mahadik SP. Decreased antioxidant enzymes and membrane essential polyunsaturated fatty acids in schizophrenic and bipolar mood disorder patients. *Psychiatry Res* 2003, 121: 109–122.
- [236] Adams PB, Lawson S, Sanigorski A, Sinclair AJ. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 1996, 31 (Suppl): S157–S161.
- [237] Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect. Disord.* 2002, 69: 15–29.
- [238] Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. Docosahexaenoic acid and post-partum depression-is there a link? *Asia Pac J Clin Nutr* 2003, 12 (Suppl): S37.
- [239] Otto SJ, de Groot RH, Hornstra G. Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic status. *Prostaglandins Leukot Essent Fatty Acids* 2003, 69: 237–243.
- [240] De Vriese SR, Christophe AB, Maes M. Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered n-3 PUFAs are related to major depression. *Life Sci* 2003, 73: 3181–3187.
- [241] Peet M, Horrobin DF. A dose-ranging study of the effects ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* 2002, 59: 913–919.
- [242] Puri BK, Counsell SJ, Hamilton G, Richardson AJ, Horrobin DF. Eicosapentaenoic acid in treatment resistant depression associated with symptom remission, structural brain changes and reduced neuronal phospholipid turnover. *Int J Clin Pract* 2001, 55: 560–563.
- [243] Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* 2002, 159: 477–479.
- [244] Su KP, Huang SY, Chiu CC, Shen WW. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol* 2003, 13: 267–271.
- [245] Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HF, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry* 2003, 160: 996–998.
- [246] Marangell LB, Martinez JM, Zboyan HA, Chong H, Puryear LJ. Omega-3 fatty acids

- for prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depress Anxiety* 2004, 19: 20–23.
- [247] Llorente AM, Jensen CL, Voigt RG, Fraley JK, Berretta MC, Heird WC. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am J Obstet Gynecol* 2003, 188: 1348–1353.
- [248] Taylor KE, Higgins CJ, Calvin CM, Hall JA, Easton T, McDaid AM, Richardson AJ. Dyslexia in adults is associated with clinical signs of fatty acid deficiency. *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 75–78.
- [249] Richardson AJ, Calvin CM, Clisby C, Schoenheimer DR, Montgomery P, Hall JA, Hebb G, Westwood E, Talcott JB, Stein JF. Fatty acid deficiency signs predict the severity of reading and related difficulties in dyslexic children. *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 69–74.
- [250] Richardson AJ, Cox IJ, Sargentoni J, Puri BK. Abnormal cerebral phospholipid metabolism in dyslexia indicated by phosphorus-31 magnetic resonance spectroscopy. *NMR Biomed* 1997, 10: 309–314.
- [251] MacDonnell LEF, Skinner FK, Ward PE, Glen AI, Glen AC, Macdonald DJ, Boyle RM, Horrobin DF. Increased levels of cytosolic phospholipase A2 in dyslexics. *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 95–100.
- [252] Stordy BY. Dark adaptation, motor skills, docosahexaenoic acid, and dyslexia. *Am J Clin Nutr* 2000, 71 (Suppl 1): 323S–326S.
- [253] Vancassel S, Durand G, Barthelemy C, Lejeune B, Martineau J, Guilloteau D, Andres C, Chalon S. Plasma fatty acid levels in autistic children. *Prostaglandins Leukot Essent Fatty Acids* 2001, 65: 1–7.
- [254] Bell JG, Sargent JR, Tocher DR, Dick JR. Red blood cell fatty acid compositions in a patient with autistic spectrum disorder: a characteristic abnormality in neurodevelopmental disorders? *Prostaglandins Leukot Essent Fatty Acids* 2000, 63: 21–25.
- [255] Richardson AJ. Clinical trials of fatty acid treatment in ADHD, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot Essent Fatty Acids* 2004, 70: 383–390.
- [256] Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* 2003, 160: 167–169.
- [257] Fux M, Benjamin J, Nemets B. A placebo-controlled cross-over trial of adjunctive EPA in OCD. *J Psychiatr Res* 2004, 38: 323–325.
- [258] Hibbeln JR. Seafood consumption and homicide mortality. *World Rev Nutr Diet* 2001, 88: 41–46.
- [259] Iribarren C, Markovitz JH, Jacobs DR Jr, Schreiner PJ, Daviglius M, Hibbeln JR. Dietary intake of n-3, n-6 fatty acids and fish: relationship with hostility in young adults – the CARDIA study. *Eur J Clin Nutr* 2004, 58: 24–31.
- [260] Hamazaki T, Thienprasert A, Kheovichai K, Samuhaseneetoo S, Nagasawa T, Watanabe S. The effect of docosahexaenoic acid on aggression in elderly Thai subjects – a placebo controlled double blind study. *Nutr Neurosci* 2002, 5: 37–41.
- [261] Hamazaki T, Sawazaki S, Itomura M, Asaoka E, Nagao Y, Nishimura N, Yazawa K, Kuwamori T, Kobayashi M. The effect of docosahexaenoic acid on aggression in young adults. A placebo-controlled double-blind study. *J Clin Invest* 1996, 97: 1129–1133.
- [262] Sawazaki S, Hamazaki T, Yazawa K, Kobayashi M. The effect of docosahexaenoic acid on plasma catecholamine concentrations and glucose tolerance during long-lasting psychological stress: a double-blind placebo-controlled study. *J Nutr Sci Vitaminol* 1999, 45: 655–665.
- [263] Hamazaki T, Sawazaki S, Nagao Y, Kuwamori T, Yazawa K, Mizushima Y, Kobayashi M. Docosahexaenoic acid does not affect aggression of normal volunteers under nonstressful conditions. A randomized, placebo-controlled, double-blind study. *Lipids* 1998, 33: 663–667.
- [264] Buydens-Branchey L, Branchey M, McMakin DL, Hibbeln JR. Polyunsaturated fatty acid status and aggression in cocaine addicts. *Drug Alcohol Depend* 2003, 71: 319–323.
- [265] Available from URL: <http://www.ahrq.gov/downloads/pub/evidence/pdf/o3asthma/tbls.pdf> [consulted: 13 Sept 2004].
- [266] Nutrition Facts “Omega 3” eggs, Gray Ridge Egg Farms, RR#7, Strathroy, ONN7G 3H8.
- [267] Available from URL: <http://www.dairy-oh.com/nutrition.htm> [consulted: 13 Sept 2004].
- [268] Available from URL: <http://www.tiptop.com.au/driver.asp?page=main/brands/bread/up+omega+3+dha> [consulted: 13 Sept 2004].