Polyunsaturated Fatty Acids and Neurological Diseases

S. Salvati*, L. Attorri, R. Di Benedetto, A. Di Biase and F. Leonardi

Department of Food, Nutrition and Health, Istituto Superiore di Sanità, Rome, Italy

Abstract: This review summarizes the knowledge of the role of dietary PUFAs, especially ω-3, on normal brain function. Furthermore, it reports the evidence pointing to potential mechanisms of ω-3 fatty acids in development of neurological disorders and efficacy of their supplementation in terms of symptom management.

Key Words: Docosahexaenoic acid, eicosapentaenoic acid, arachidonic acid, neurodegenerative diseases, Alzheimer's disease, Multiple sclerosis, Depression, Parkinson's disease.

INTRODUCTION

Fatty acids are compounds that have a carboxyl head group attached to a long hydrocarbon chain. Different kinds of fatty acid exist and some have one or more double bonds in their hydrocarbon tail and are said to be unsaturated. Fatty acids are structurally classified by the number of carbons, double bonds, and proximity of the first double bond to the methyl (omega) terminal of the fatty acid acyl chain. Fatty acids other than the essential fatty acids (EFAs) can be synthesized endogenously; however, the major source is from dietary fat, which accounts for 25%-50% of the energy content of most diets. Triglycerides, which have three, usually different, fatty acid molecules esterified to a molecule of glycerol , are the major component of dietary fat. These are hydrolyzed in the intestinal lumen, the bulk of released fatty acids are reassembled within the enterocyte, and the reassembled triglycerides along with phospholipids, monoglycerides, diglycerides, and sterol esters are adsorbed into thoracic duct, eventually reaching the bloodstream, where they circulate primarily as components of the various lipoproteins. The remaining fatty acids circulate bound to albumen.

ESSENTIAL FATTY ACIDS

Two families of EFAs exist in nature: ω-3 (α-linolenic fatty acid; C18:3ω-3) and ω-6 (linoleic fatty acid; C18:2ω-6). Fatty acids of the ω-3 family contain a double bond at the third carbon; those of the ω-6 family contain a double bond at the sixth carbon. Since humans do not have the capacity for *de novo* biosynthesis of EFAs owing to the natural absence of Δ-15 and Δ-12 desaturase enzymes, adequate amounts of ω-3 and ω-6 fatty acids must be provided in the diets. Afterwards EFAs are desaturated (by the insertion of double bonds) and elongated (by the addition of 2-carbon units) to long-chain polyunsaturated fatty acids (LC-PUFAs). α-linolenic is the dietary precursors to eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) while linoleic acid to arachidonic acid (AA).

Fig. (**1**) displays biosynthetic pathways for the ω-3 and ω-6 families. As both EFAs families compete for the same bio-

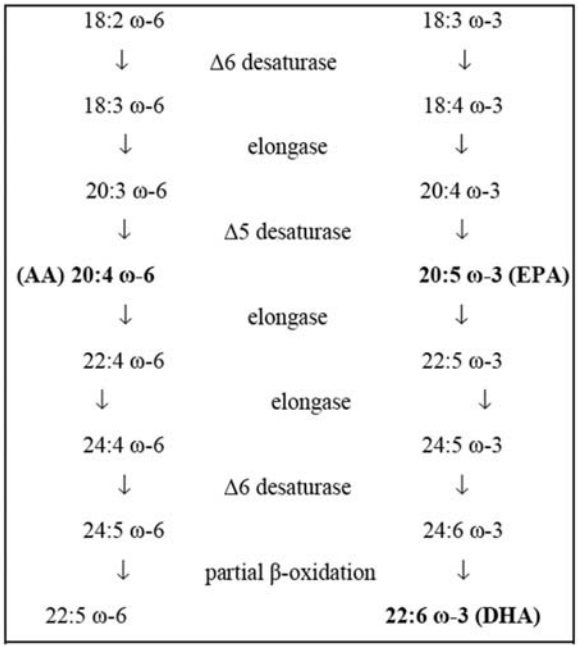

Fig. (1). Schematic representation of the desaturation and elongation of 18:2 ω-6 to AA and that of 18:3 ω-3 to EPA and DHA.

synthetic enzymes, dietary lipid balance and composition will affect production and tissue accretion of these nutrients.

C18:2ω-6 has been identified as an essential nutrient for the human species for almost 75 years [1,2]. Symptoms of deficiency include poor growth and scaly skin lesions. Although the essentiality of C18:3ω-3 was suspected for some time, it was identified as an essential nutrient about 20 years ago. In animals the deficiency of this fatty acid results in visual and neurological abnormalities [3-5]. Neurological abnormalities have been also observed in a human infant who had been maintained for several weeks on a parenteral nutrition regimen lacking C18:3ω-3 [6].

LC-PUFAs synthesized from EFAs are fatty acids of physiological significance:

- DHA with a molecular weight of 328 is found in higher concentration in the more metabolically active subcellular

*Address correspondence to this author at the Department of Food, Nutrition and Health, Istituto Superiore di Sanità, Rome, Italy;
E-mail: salvatis@iss.it

1389-5575/06 $50.00+.00

compartments of the brain, including the mi-tochondria, synaptosomes and synaptic vesicles [7,8].

- EPA is the other major dietary ω-3 PUFAs. This compound contains 5 double bonds and has a molecular weight of 302. EPA is present in blood components, but is not accreted in tissues in large amounts as it is quickly used in DHA or eicosanoid biosynthesis [9,10].
- AA is a ω-6 PUFAs with a 4 double bonds and a molecular weight of 304. AA is a major fatty acid of neural and vascular tissue of the retina and brain. The chemical structures of DHA, EPA and AA are represented in Fig. (**2**).

The ω-3 and ω-6 PUFAs acts as:

- Key structural constituents of phospholipids membrane. Fatty acid composition of membrane phospholipids determines the physic-chemical properties of the membrane bilayer and may thus influence the activity of membrane-associated proteins [11-13].
- Ligands to transcription factors influencing genes: a) cellular differentiation and growth; b) lipid, protein and carbohydrate metabolism. DHA, EPA and AA affect gene expression through the regulation of transcription factor activity and concentration within the nucleus. Transcription factors containing an LC-PUFA binding domain include peroxisome proliferators-activated receptor (PPAR), retinoid X receptor (RXR), nuclear-factor kappa B (NFκB), and sterol regulatory element binding proteins (SREBPs) [14-17].
- Effectors of signal transduction pathways regulating gene expression. These pathways include enzyme-based lipoxygenase, cyclooxygenase, protein kinase C and sphingomyelinase. LC-PUFAs may also regulate pathways affecting tyrosine kinase-linked- and G-protein receptors.
- Substrates for the formation of a family of hormone-like agents called eicosanoids involved in inter- and intracellular signalling cascades that influence vascular, neural, and immune function. [19-21]

LONG-CHAIN POLYUNSATURATED FATTY ACIDS AND THE BRAIN

Omega-3 and omega-6 fatty acids are crucial for normal brain structure and function. Structurally, AA and DHA are key components of neural membranes, making up 15-20% of the brain's dry mass and more than 30% of the retina. In the early life, both ω-6 and ω-3 LC-PUFAs are critical for supporting brain growth and maturation. During prenatal development, adequate supplies are so essential that the placenta doubles the levels circulating in maternal plasma [22], and severe deficits may have permanent effects if they occur during critical periods of early development. AA is crucial to brain growth, and mild deficiencies are associated with low birth weight and reduced head circumference. DHA is particularly concentrated in highly active membranes such as synapses and photoreceptors, and adequate supplies are essential for normal visual and cognitive development [23-24].

Throughout life, adequate supply of LC-PUFAs remains crucial for optimal brain function. They increase the fluidity of neuronal membranes, essential for efficient signal transduction, and some act as second messengers in chemical neurotransmitter system as well as contributing to many other aspects of cell signalling [25]. AA and EPA are substrates for the eicosanoids (Fig. **3**) that play key roles in regulating endocrine and immune function and in modulating ion channels, neurotransmitter uptake, synaptic transmission and apoptosis [26-28].

AA is the precursor of a group of eicosanoids that include series-2 prostaglandins and tromboxane (Figs. **4, 5**) and serie-4 leukotrienes (Fig. **6**) whereas EPA is the precursor of a group of eicosanoids that include serie-3 prostaglandins and tromboxane (Figs. **7, 8**) and serie-5 leukotrienes (Fig. **9**) [19-21]. The AA-derived series-2 prostaglandins and series-4 leukotrienes are often synthesized in response to some emergency such as injury or stress, whereas the EPA-derived series-3 prostaglandins and series-5 leukotrienes appear to modulate the effects of the series-2 prostaglandins and series-4 leukotrienes. More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate the effects of excessive levels of series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins seems to prevent stroke as well as certain inflammatory diseases.

EPA also affects lipoprotein metabolism and decreases the production of some cytokines like interleukin 1β (IL-1 β) and tumor necrosis factor α (TNF-α) that have pro-inflammatory effects. DHA is the precursor to a newly described

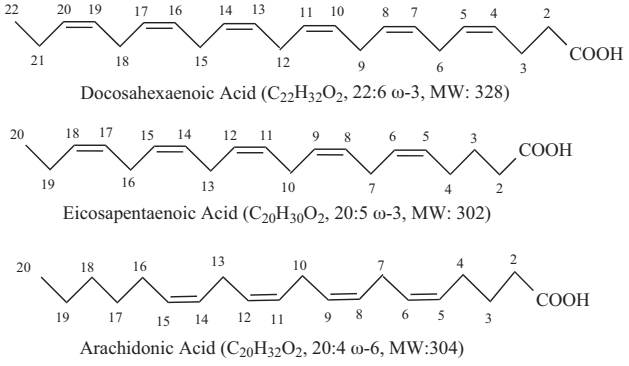

Fig. (2). Chemical structures of DHA, EPA and AA. Molecules are oriented with methyl (omega) terminal shown above left.

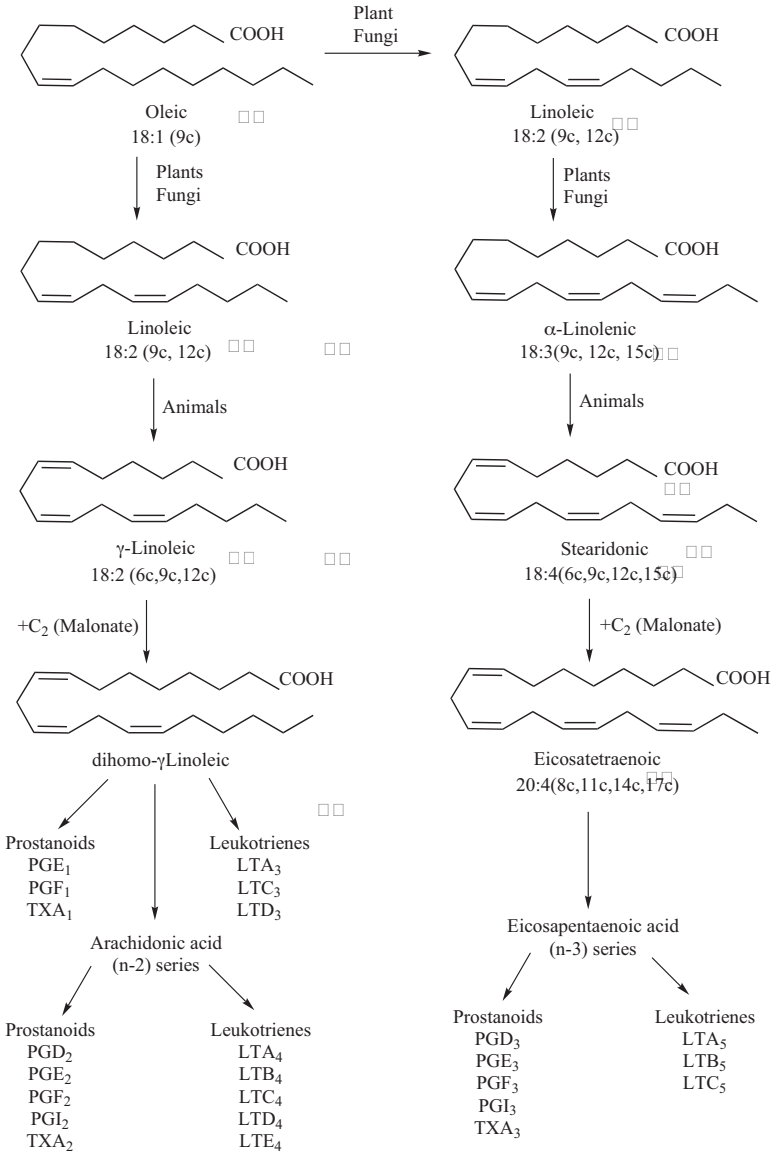

Fig. (3). Thromboxane, leucotriene and prostaglandin structures representative of the 1-, 2-, and 3- series elaborated from dihomo-gamma linolenic acid, AA, and EPA.

metabolite called 10,17S-docosatriene or neuroprotectin D1, which is part of a family of compounds called 'resolvins' (Fig. **10**). They are in the brain in response to an ischemic insult and counteract the pro-inflammatory actions of infiltrating leukocyte by blocking IL-1 β-induced NF-κB activation and cyclooxygenase-2 expression [29].

An adequate and an appropriately balanced supply of LC-PUFAs is thus required for normal brain function, both during the early development and throughout life. Unfortunately, there are many possible reasons why their availability may be less than optimal, particularly in the case of ω-3 PUFAs such as EPA and DHA. These PUFAs are scarce in the modern diet, which are found in appreciable quantities only in fish and other seafood. Their precursor, α-linolenic acid, is found in green vegetables and some nuts and seeds, but *in vivo* studies indicate that its conversion to EPA and DHA is not very efficient in humans [30].

LONG-CHAIN POLYUNSATURATED FATTY ACIDS IN NEUROLOGICAL DISORDERS

Deficiencies in ω-3 fatty acids and/or an imbalance in the ratio of ω-6 FA to ω-3 FA have been implicated in many diseases affecting CNS, including Alzheimer's disease, Parkinson's disease, multiple sclerosis etc. Studies on animals and humans have suggested several possible biological mechanisms for the role of LC-PUFAs in the disease process. Furthermore, several trials in human infants have inves-

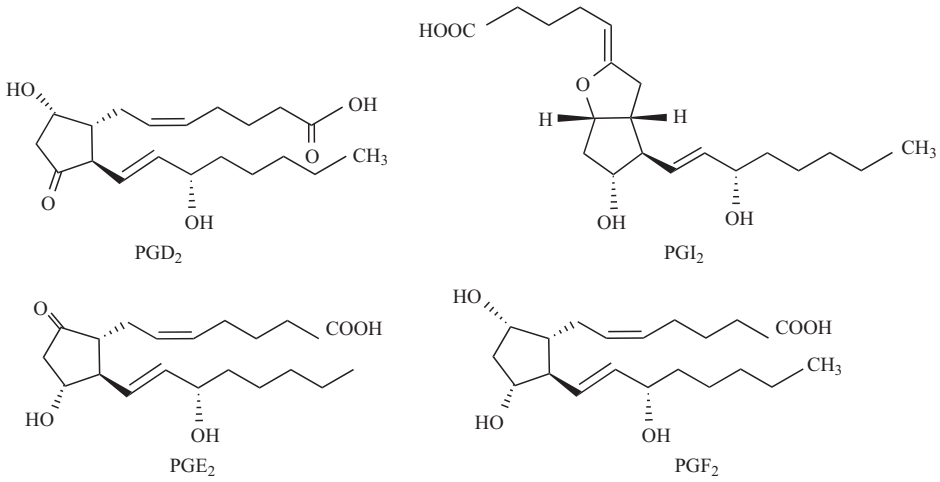

Fig. (4) Molecular structure of series-2 prostaglandins.

tigated the effects of ω-3 PUFAs on cognitive development. Controlled trials have also suggested that the LC-PUFAs supplements may be of some value in the management of some neurological conditions.

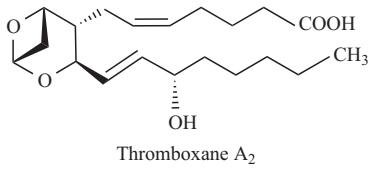

Fig. (5) Molecular structure of serie-2 tromboxane.

In this report we will analyze the role of LC-PUFAs in different neurological diseases.

Alzheimer's Diseases

One of the more exciting impacts of ω-3 fatty acids is their potential to reduce the risk of chronic neurodegenerative diseases, such as Alzheimer's disease (AD). This pathology is most common disease of late life that derives from pathogenic processes underlying abnormal accumulation of amyloid-β (Aβ) peptides (neurite plaques), neurofibrillary tangles, synaptic deficit and extensive neurodegeneration [31-33]. AD represents a significant and growing public health burden since affects more than 10 million people worldwide [34]. AD is expected to increase dramatically from the current prevalence of 12.4% of the population in individuals 65 years and older to almost 20% by 2030 [35]. The aetiology is complex and multifactorial and environmental factors appear to modify genetic risk [36,37]. However, no specific environmental factor has been definitively identified as being associated with AD. There is evidence that dietary factors may have a role in the pathogenesis of AD [38].

Attention was focused on dietary fat and particularly on ω-3PUFAs. The interest developed because different studies showed lower blood levels of ω3-PUFAs in patients with AD or cognitive decline compared to controls [39,40]. More interestingly, some authors found a very low DHA level in the brain membranes of AD patients [41,42].

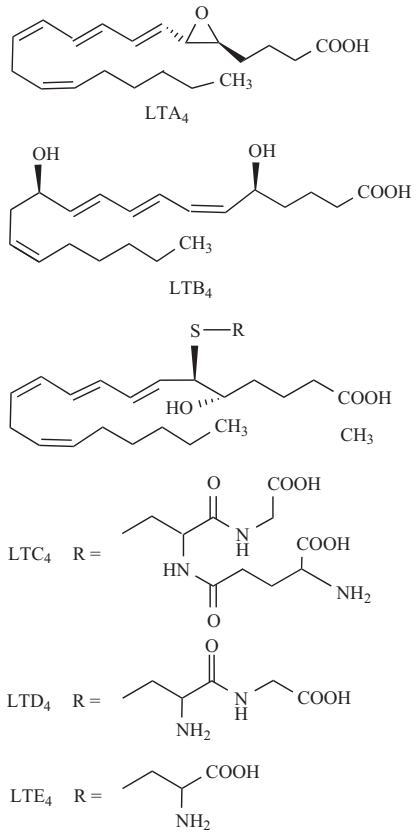

Fig. (6) Molecular structure of series-4 leukotrienes.

In animal studies it has been shown that chronic administration of DHA enhances long-term memory in both young and old rats [43]. However, the mechanism of action of ω-3 PUFAs on cognitive processes is still unclear.

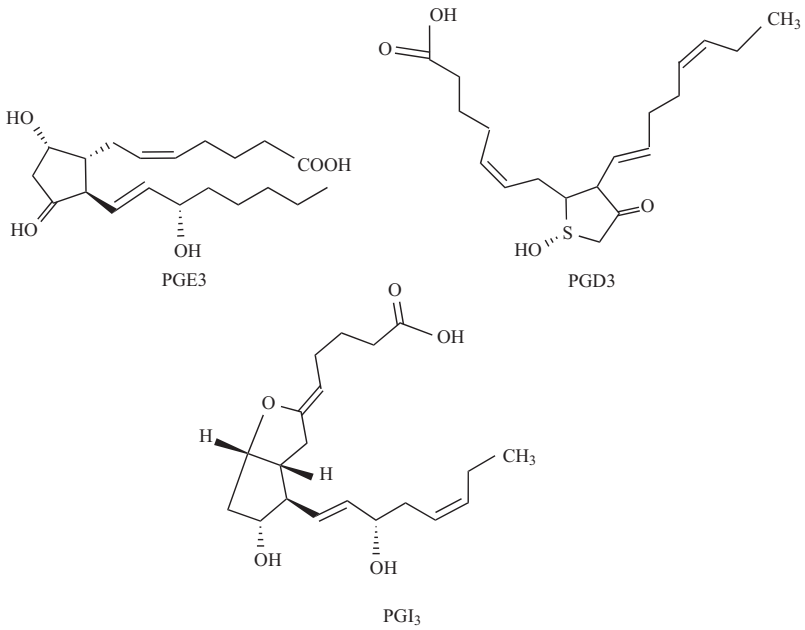

Fig. (7) Molecular structure of series n-3 prostaglandins.

In the AD transgenic mouse model (Tg2576) expressing amyloid precursor protein (APP) within neurons, Calon *et al*. [44] have shown that a diet deficient in DHA lead to massive loss of the p85α subunit of phosphatidyl-inositol 3 kinase (PI-3K) and the postsynaptic actin-regulating protein drebrin as in AD brain. The loss of postsynaptic proteins was associated with increased oxidation, without concomitant neuron or presynaptic protein loss. Treatment with DHA provided protection against these effects and subsequently behavioural changes. Since ω-3 PUFAs are essential for p85-mediated central nervous system insulin signalling and selective protection of postsynaptic proteins, these findings may have an application for neurodegenerative diseases where synaptic loss is critical as AD. Further data [45-49] obtained in the Tg2576 mouse highlighted that DHA deficiency results in an inflammation or excessive oxidation stress, two conditions present in AD patients. Recently [50], it has been also reported that adequate DHA intake can significantly reduce amyloid precursor protein processing pathways and amyloid burden. Furthermore, it has also been shown that DHA is important regulator of NMDA receptors in the cerebral cortex and in hippocampus [47]. NMDA receptors are ionotropic glutamate receptors playing a key role in cognitive processes [51,52].

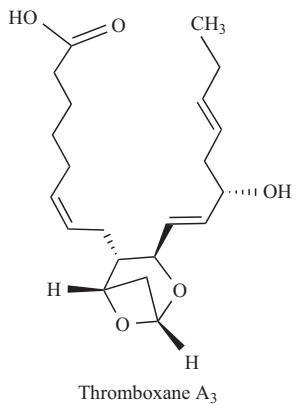

Fig. (8) Molecular structure of serie n-3 tromboxane.

The epidemiological data on ω-3 PUFAs and the risk of AD are interesting: two prospective studies found that fish consumption was inversely associated with risk of incident of AD [53]. A recent prospective study [54] on the risk of AD in a biracial community of 815 individuals (aged 65-94 years, 3.9 years of follow-up) in Chicago (ILL), found the largest potential impact of ω-3 PUFAs to date, especially with DHA. Morris *et al*. [54] found that subjects who ate fish once a week or more had 60% lower risk for developing AD than those who consumed fish less frequently. The data were statistically adjusted to correct for the effects of age, sex, ethnicity, education, stroke, hypertension, heart disease, apolipoprotein E (apo E) genotype, total caloric intake, and consumption of other fats or vitamin E. The intake of ω-3 PUFAs and DHA was associated with a reduced risk of developing AD over the 4 years of the study for the general population, whereas the intake of α-linolenic acid and eicosapentaenoic acid was not. Intake of α-linolenic acid was protective only in people with the apoE ε 4 allele, and total ω-3 PUFAs intake was protective only in women. The non protective effect of EPA could be ascribed to its low-content in main edible fishes. Further studies might be carried out with high concentration of EPA to establish its role in the AD. The impact of apo E genotype on the inherited risk of AD is an important reminder that normal lipid balances are critical because apo E protein functions in lipid transport [55,56].

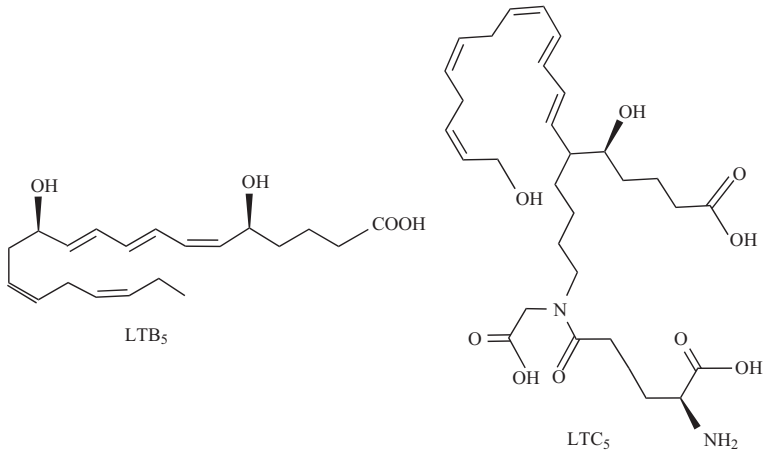

Fig. (9) Molecular structure of series-5 leukotrienes.

Appropriate dietary changes and the higher consumption of ω-3 PUFAs might open new ways for the prevention and management of cognitive diseases and dementia.

Depression and Other Conditions in Psychiatry

Recent and past observational and preliminary clinical studies support the thought that one of most intriguing areas of benefit for ω-3 PUFAs is the potential for the reduction in risk of depression and other conditions in psychiatry, such as schizophrenia [57-59].

Mood disorders, including major depression, are recurrent, debilitating, and potentially life-threatening illnesses. In the last 100 years, the age of onset of major depression has decreased and its incidence has increased in Western coun-

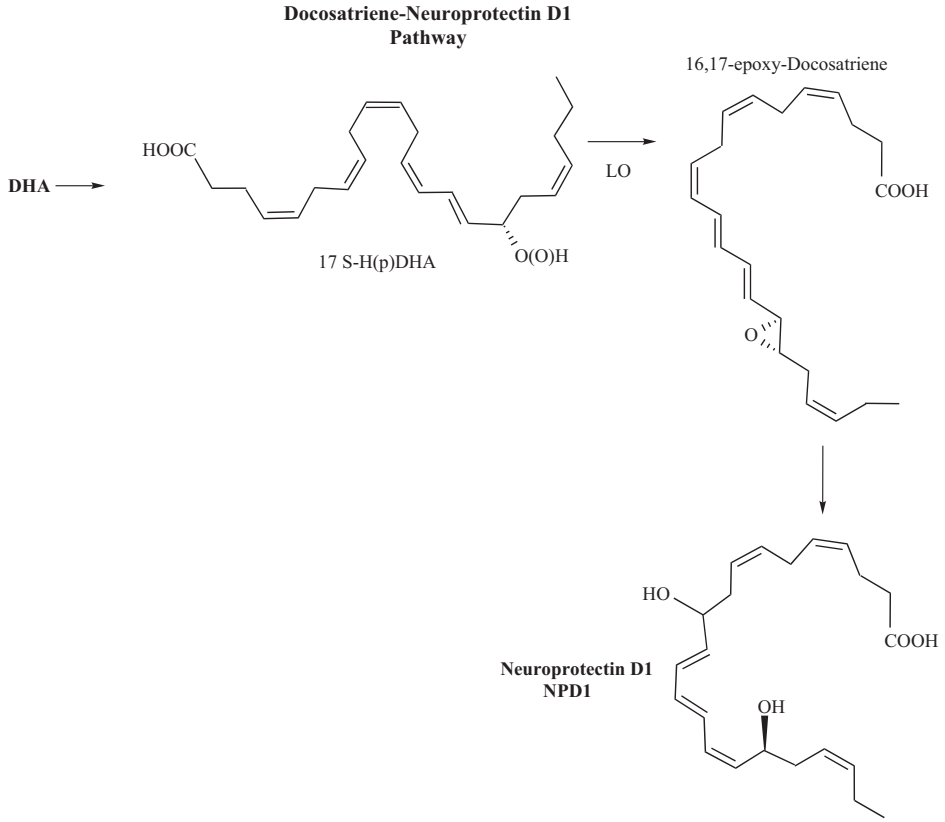

Fig. (10) Docosatriene formation and neuroprotectin D1 pathway.

tries [60]. In contrast to the increased incidence of depression, the dietary intake of ω-3 PUFAs is dramatically decreased. The ideal ratio of ω-3 to ω-6 is approximately 1:1, according to the conclusion of an international panel of lipid experts [61]. Indeed, Western diets have replaced ω-3 fatty acids from fish and leaves with ω-6 oils from seeds and currently the ratio is 1: 20 [62]. This dietary fatty acid alterations result in high levels of ω-6 PUFAs in serum and membranes of the Western population [63].

If ω-3 PUFAs play a role in depressive disorders, countries consuming low amounts of these fatty acids would be expected to have higher prevalence of depression. Hibbeln [64] found a strong inverse relationship between the consumption of ω-3 fatty acids and the prevalence of both major depression and postpartum depression. Furthermore, many studies have reported reduced levels of ω-3 PUFAs in plasma and cell membranes from depressed patients [65-67].

The exact mechanisms involved in the pathogenesis of depression, is still unknown. It has been discussed that changes in serotonin (5-HT) receptor number and function caused by changes in polyunsaturated fatty acids provide the theoretical rationale connecting fatty acids with the current receptor and neurotransmitter theories of depression [68].

The involvement of changes in fatty acid composition in the pathogenesis of major depression also revolves around its role in immune function and production of cytokines. There is some evidence that depression is accompanied by an increased secretion of eicosanoids; such as prostaglandins, and by excessive secretion of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α. Increased C20:4 ω-6/ C20:5 ω-3 and ω-6/ ω-3 ratios could be related to increased production of proinflammatory cytokines. Both changes in fatty acids and immune activation may interact with 5-HT functioning to cause depression. This may be consistent with the hypothesis of a combined deregulation of 5HT, fatty acids, immune-inflammatory functioning, and HPA-axis hyperactivity as an integral component of depression [69].

Clinical trials support an antidepressive effect of ω-3PUFAs and among the ω-3, EPA would be responsible of the therapeutic effect. The available studies are summarized in Table **1**.

In three of the reported studies, EPA or fish oil was given in addition to antidepressant treatment to patients who were treatment non responders. All three studies in unipolar depression gave strong positive results. Peet and Horrobin [71] have reported a dose-finding study in which 1,2 or 4g per day of ethyl-EPA or placebo were added to the treatment of patients who had failed to respond to initial antidepressant treatment. An effect was seen at a 1g/day dosage, but not at higher dosage. High doses of EPA, which overwhelms normal dietary intake can unbalance the physiological cellular state. The loss of therapeutic response can be due to the increase in ω-3 fatty acids that causes a depletion of ω-6 fatty acids with a consequent alteration in the balance between ω-3 and ω-6. These findings were supported by an eight-week, double bind, placebo controlled trial in women with borderline personality disorder. The researchers reported 1g of EPA led to a reduction in scores assessing both depression and aggressive symptoms [72].

Studies in bipolar depression have produced conflicting results. Keck *et al*. [74] have reported no benefit from high daily of EPA added to existing treatment. On the other hand, in a dose-response study in unipolar depression a positive effect was only observed at a lower dosage. In contrast, other studies reported a significant positive effect from 1 to 2g/day of EPA relative to placebo as an add-on treatment.

In addition, a population study in Finland showed that the likelihood of having depressive symptoms was significantly higher among infrequent fish consumers. Those who consumed large quantities of ω-6 PUFAs by cooking with vegetable oils had an increased rate of depression [77].

Conflicting results have been reported by Hakkarainen *et al*. [78] in a cohort of male smokers. The Authors failed to find an association between baseline intake of fish or dietary ω3 PUFAs. The use of tobacco induces an oxidative stress with a decrease of PUFAs and increased lipoperoxidation products [79]. Consequently, the loss of therapeutic effect could be due to the intake of fish oil not sufficient to increase the EPA levels in inducing pharmacological effects.

Although some studies can be limited both by the small sample size and by the experimental design, the results ob-

Table 1. Omega-3 Fatty Acids in the Treatment of Depression: Double-Bind, Placebo-Controlled Trials

Study	Dosage regimen	Outcome
Nemetes *et al*. [70]	Add-on; EPA 2g/day	EPA>placebo
Peet and Horrobin [71]	Add-on; EPA 1,2 and 4g/day	EPA 1g/day>placebo
Zanarini and Frankenburg [72]	Mono; EPA 1g/day	EPA>placebo
Su *et al*. [59]	Add-on; fish oil 9,6g/day	Fish oil>placebo
Marangell *et al*. [73]	Mono; DHA 2g/day	DHA= placebo
Keck *et al*. [74]	Add-on; EPA 6g/day	EPA = placebo
Frangou and Lewis [75]	Add-on; EPA 1 or 2g/day	EPA> placebo
Osher *et al*. [76]	Add-on; EPA 1,5 to 2g/day	EPA> placebo

Add-on=added to existing medication; **DHA**=docosahexaenoic acid; **EPA**= eicosapentaenoic acid; **Mono**=monotherapy

tained on the usefulness of EPA in depression are encouraging and prompted further studies for its therapeutic use.

Placebo-controlled trials on ω-3 fatty acids treatment have been also conducted in schizophrenic patients. Schizophrenia is one of the most severe mental illnesses and it is characterized by a combination of 'positive' symptoms such as hallucinations and negative symptoms such as lack of drive and motivation.

It was suggested that people already on antipsychotics when given EPA-supplementation had an improved mental state compared to those receiving a placebo supplementation [80,81]. However, it must be remembered that these studies used several grams or more per day and whether or not the use of such large doses in a clinical setting is practical and realistic needs to be determined. Furthermore, other issues that need to be resolved are the potential for these fatty acids to impact more on women than on men.

It is possible that mechanisms underlying the therapeutic effect of EPA are different for schizophrenia and depression. Some evidence suggests that the benefits of EPA in schizophrenia may depend on an indirect effect on arachidonic acid [82]. Elevated levels of phospholipase A_2 (PLA_2) has been observed in brain, plasma and red cells of schizophrenic subjects [83-85] PLA_2 is involved in the release of arachidonic acid with its consequent loss in membrane and abnormalities in phospholipids-AA signalling. EPA may be effective in the treatment of schizophrenia because it can inhibit PLA_2 [86]. It has been suggested that schizophrenia is a proinflammatory condition because of the increased levels of proinflammatory cytokines in schizophrenic patients [87]. Thus, EPA could be acting through an anti-inflammatory effect. In support of this concept a recent study has shown that celecoxib, a cyclooxygenase-2 inhibitor, is of therapeutic benefit in schizophrenia [88]. However, at the present time the true mode of action of EPA is unknown.

Multiple Sclerosis: Incidence and Progression

Multiple sclerosis (MS) is a chronic and disabling disease of the central nervous system with unknown aetiology. It has been hypothesized that diets high in meat and dairy products and low in fish increase the risk of MS [89-91]. This hypothesis was supported by ecologic studies. In fact since 1950, Swank *et al*. [89] analysing the incidence of MS in different regions of Norway, found a higher incidence in the inland farming communities with high consumption of animal fat and dairy products than in the coastal communities where the consumption of fish was high. However, no association between animal fat or saturated fat and the risk of MS was found in most case-control studies [92,93]. Recently, in a prospective cohort study Zhang *et al*. [94] have supported the findings that the amount and type of dietary fat did not affect the risk of developing MS. However, these authors observed that among ω-3 PUFAs α-linolenic acid was associated with a reduced risk of MS even though that did not reach statistical significance.

No significant association between fish consumption and MS risk was also demonstrated in one case-control study. However, fish consumption was significantly associated with a reduced risk of MS in women only [95].

Other studies have evaluated the effect of ω-3-PUFAs on the treatment and progression of MS. Nordvik *et al*. [96] found that newly diagnosed MS patients had a lower plasma total lipid concentration of EPA and DHA, and lower ratio of total ω-3 to ω-6 fatty acids compared to controls. With this background, they evaluated the effect of fish-oil supplementation on the progression of disease in 16 newly diagnosed patients and observed in treated subjects a significant reduction in the relapse rate and an improved Expanded Disability Status Scale (EDSS). Recently, Weinstock-Guttman *et al*. [97] supported this finding since they showed that a low fat diet supplemented with ω-3 PUFAs can have moderate benefits in relapsing-remitting MS patients even though the potential therapeutic effects related to a low fat diet can not be clearly excluded in this study.

The ω-3PUFAs may be beneficial in MS through immune modulation. Due to the competition between ω-3 and ω-6 fatty acids, an increased intake of ω-3 fatty acids will reduce the synthesis of pro-inflammatory leukotriene B_4 and prostaglandin E_2 [98,99] which are known to be increased in MS patients [100]. This speculation is supported by Gallai *et al*. [101] who found in MS patients supplemented with ω-3 fatty acids, a reduced levels of several pro-inflammatory cytokines as well as the production of prostaglandin E_2 and leukotriene B_4.

The PUFAs could also modulate MS course stimulating myelin synthesis. Our previous papers [102,103] have shown an accelerated development of reflexes linked to myelination in offspring of rats and mice fed during pregnancy and lactation diets rich in odd-chain fatty acids compared to controls fed a diet containing margarine. In 1972 Schlenk [104] included odd-chain fatty acids of the ω-5 series, with essential fatty acids. These occur in several natural dietary sources like fish and milk, but their concentration is very low, generally not exceeding 1-3% of total fatty acids, with the exception of mullet in which their concentration reaches about 20%. Subsequent studies [105] have shown that the expression of myelin proteins is higher in rats fed odd-chain fatty acids than in control animals, but the mechanism of the action of fatty acids is still unknown.

In our experimental *in vitro* model [106] we have shown that EPA up-regulates proteolipid lipid protein (PLP) gene expression whereas no effect was induced by DHA supplementation. On the other hand, Haubner *et al*. [107] demonstrated that maternal diet supplemented with high levels of DHA negatively affects the rat pup auditory system potentially through the effects on myelin. The discrepancies observed in previous studies on the effect of fish oil, rich in both DHA and EPA, on MS course could be ascribed to high DHA/EPA ratio in the tested oil.

These data can give a new insight in the therapeutical approaches involved to promote repair in demyelinating diseases.

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, caused by a selective degeneration of dopaminergic cells in the substantia nigra. The exact mechanism underlying this process is unclear, but oxidative

stress, mitochondrial dysfunction and inflammation are thought to play an important role. However, there are several reasons why dietary intake of unsaturated fatty acids might influence the risk of PD. Unsaturated fatty acids may be protective against the pathogenetic processes of oxidative damage and inflammation supposedly involved in PD [108,109]. PUFAs are shown to inhibit neuronal apoptosis [110], which is thought to play a role in the pathogenesis of PD [111]. Furthermore, PUFAs are precursors for endogenous cannabinoids, which play a role in the control of movement by modulating dopaminergic activity in the basal ganglia [112,113]. Animal studies have shown that endocannabinoid levels can be modified by the amount of PUFAs in the diet. [114]. Interestingly, the increasing evidence that genes involved in lipid metabolism may also regulate toxicity of α-synuclein, the major component of the inclusion bodies found in the brain of patients with PD.

Previous epidemiological studies of the association between dietary fat intake and the risk of PD have shown inconsistent results [115-117]. Most of these studies were case-control or only investigated the total fat intake. Recently [118], in a large, prospective population-based Rotterdam study, de Lau *et al*. found that a higher dietary intake of unsaturated fatty acids was associated with a decreased risk of PD. These observations were in line with the Honolulu-Asia Aging Study, a prospective cohort study among men of Japanese ancestry, in which a significant reduction of PD risk was observed with higher intake of PUFAs [119]. On the other hand, Chen *et al*. [117] did not find a significant association between PUFAs and PD, although the results have suggested a possible adverse effect of replacing polyunsaturated fatty acids with saturated fat for men and a potential beneficial effect of arachidonic acid intake. The discrepancies can be due to the different experimental designs because the study of Chen *et al*. [117] had a longer follow-up and repeated dietary assessments and therefore probably less misclassification with regard to life-time cumulative dietary exposure than the Rotterdam Study. On the other hand, it could be possible that the later-life dietary exposure rather than average life-time intake is related to the occurrence of PD. Additional prospective studies and a longer follow-up period are needed to confirm the beneficial role of PUFAs in PD.

CONCLUSION

The evidence suggests a possible association between ω-3 fatty acids and reduced risk of neurological diseases. The ratio of ω-3 to ω-6 dietary EFAs has profound effects on the balance of pro-inflammatory and anti-inflammatory eicosanoid metabolism, and the degree of saturation of lipids within cellular membranes has profound effects on the function, fluidity and oxidative susceptibility of neurological membranes. Although, there are insufficient data to draw definite conclusions, dietary ω-3 PUFAs interventions show great promise in prevention and improvement of neurological diseases.

ABBREVIATIONS

AA = Arachidonic acid

AD = Azheimer's disease

DHA = Docosahexaenoic acid

EFA = Essential fatty acids

EPA = Eicosapentaenoic acid

LC-PUFA = Long-chain polyunsaturated fatty acid

LT = Leukotriene

MS = Multiple sclerosis

PD = Parkinson's disease

PG = Prostaglandin

PLA_2 = Phospholipase A_2

TX = Tromboxane

REFERENCES

[1] Burr, G.O.; Burr, M.M. *J. Biol. Chem*. **1929**, *82*, 345.

[2] Hansen, A.E.; Steward, R.A.; Hughes, G.; Soderhejelm, L. *Acta Paediatr*., **1962**, *51*(S137), 1.

[3] Benolken, R.M.; Anderson, R.E.; Wheeler, T.G. *Science,* **1973**, *182,* 1253.

[4] Neuringer, M.; Connor, W.E.; Van Patten, C.; Barstad, L. *J. Clin. Invest*., **1984**, *73*, 272.

[5] Neuringer, M.; Connor, W.E.; Lin, D.S.; Barstad, L.; Luck, S. *Proc. Natl. Acad. Sci. USA,* **1986**, *83*, 4021.

[6] Holman, R.T.; Johnson, S.B.; Hatch, R.F. *Am. J. Clin. Nutr*., **1982**, *35*, 617.

[7] Carrie, I.; Clement, M.; de Javel, D.; Frances, H.; Bourre, J.M. *J. Lipid Res*., **2000**, *41*, 465.

[8] Gamoh, S.; Hashimoto, M.; Sugioka, K.; Shahdat Hossain, M.; Hata, N.; Misawa, Y.; Masumura, S. *Neuroscience,* **1999**, *93*, 237.

[9] Nelson, G.J. In *Fatty acids in foods and their health implications*, 2nd ed. Chow KC Ed. Marcel Dekker, Inc., New York, **2000**; pp. 481-516.

[10] San Giovanni, E.P. and Chew, E.Y. *Prog. Retinal Eye Res.,* **2005**, *24*, 87.

[11] Leaf, A. *J. Nutr. Health Aging,* **2001**, *5*, 173.

[12] Pound, E.M.; Kang, J.X.; and Leaf, A. *J. Lipid Res*., **2001**, *42*, 346.

[13] Marcheselli, V.L.; Hong, S.; Lukiw, W.J.; Tian, X.H.; Gronert, K.; Musto, A.; Hardy, M.; Gimenez, J.M.; Chiang, N.; Serhan, C.N.; Bazan, N.G. *J. Biol. Chem*., **2003**, *278*, 51974.

[14] Jump, D.B. and Clarke, S.D. *Ann. Rev. Nutr*., **1999**, *19*, 63.

[15] Lin, Q.; Ruuska, S.E.; Shaw, N.S.; Dong, D.; Noy, N. *Biochemistry,* **1999**, *38*, 185.

[16] de Urquiza, A.M.; Liu, S.; Sjoberg, M.; Zetterstrom, R.H.; Griffiths, W.; Sjovall, J.; Perlmann, T. *Science,* **2000**, *290*, 2140.

[17] Serhan, C.N. *Curr. Opin. Clin. Nutr. Metab. Care,* **2005**, *8*, 115.

[18] Chen, C.; Bazan, N.G. *Prostaglandins other Lipid Mediat.,* **2005,** *77*, 65.

[19] Venkatraman, J. and Meksawan, K. *J. Nutr. Biochem*., **2002**, *13*, 479.

[20] Purasiri, P.; Mckechnie, A.; Heys, S.D.; Eremin, O. *Immunology,* **1997**, *92*, 166.

[21] Jump, D.B. *J. Biol. Chem*., **2002**, *277*, 8755.

[22] Crawford, M.A. *Am. J. Clin. Nutr*., **2000**, *71*(S1), S275.

[23] Neuringer, M.; Reisbick, S. and Janowsky, J. *J. Pediatr*., **1994**, *125*(5 Pt 2), S39.

[24] Uauy, R.; Hoffman, D.R.; Peirano, P.; Birch, D.G.; Birch, E.E. *Lipids,* **2001**, *36*, 885.

[25] Yehuda, S.; Rabinovitz, S. and Mostofsky, D.I. *J. Neurosci. Res*., **1999**, *56*, 565.

[26] Jones, C.R.; Arai, T.; Rapoport , S.I. *Neurochem. Res*., **1997**, *22*, 663.

[27] Piomelli, D. *Crit. Rev. Neurobiol*., **1994**, *8*, 65.

[28] Piomelli, D.; Wang, J.K.; Sihra, T.S.; Nairn, A.C.; Czernik, A.J.; Greengard, P. *Proc. Natl. Acad. Sci. USA,* **1989**, *86*, 8550.

[29] Serhan, C.N.; Gotlinger, K.; Hong, S.; Arita, M. *Prostaglandins Other Lipid Mediat.,* **2004,** *73*, 155.

[30] Pawlosky, R.J.; Hibbeln, J.R.; Novotny, J.A.; Salem, N. Jr. *J. Lipid Res*., **2001**, *42*, 1257.

[31] Selkoe, D.J. *Physiol. Rev*., **2001**, *81*, 741.
[32] Cummings, J.L.; Cole, G. *JAMA,* **2002**, *287*, 2335.
[33] Ingelsson, M.; Fukumoto, H.; Newell, K.L.; Growdon, J.H.; Hedley-Whyte, E.T.; Frosch, M.P.; Albert, M.S.; Hyman, B.T.; Irizarry, M.C. *Neurology,* **2004**, *62*, 925.
[34] Evans, D.A. *Milbank Q,* **1990**, *68*, 267.
[35] Friedland, R.P. *Arch. Neurol*., **2003**, *60*, 923.
[36] Ashford, J.W. and Mortimer, J.A. *J. Alzheimer's Dis.,* **2002**, *4*, 169.
[37] Grant, W.B.; Campbell, A.; Itzhaki, R.F. and Savory J. *J. Alzheimer's Dis.,* **2002,** *4*, 179.
[38] Luchsinger, J.A and Mayeux, R. *Lancet Neurol*. **2004**, *3*, 579.
[39] Heude, B.; Ducimetiere, P.; and Berr C. *Am. J. Clin. Nutr*., **2003**, *77*, 803.
[40] Tully, A.M.; Roche, H.M.; Doyle, R.; Fallon, C.; Bruce, I.; Lawlor, B.; Coakley, D.; Gibney, M.J. *Br. J. Nutr*., **2003**, *89*, 483.
[41] Soderberg, M.; Edlund, C.; Kristensson, K. and Dallner, G. *Lipids,* **1991**, *26*, 421.
[42] Lavell, M.A.; Yatin, M.; Dhillan, H.; Markesbery, W.R. *Neurochem. Res*., **1998**, *23*, 81.
[43] Gamoh, S.; Hashimoto, M.; Hossain, S.; Masumura, S. *Clin. Exp. Pharmacol. Physiol*., **2001**, *28*, 266.
[44] Calon, F.; Lim, G.P.; Yang, F.; Morihara, T.; Teter, B.; Ubeda, O.; Rostaing, P.; Triller, A.; Salem, N. Jr.; Ashe, K.H.; Frautschy, S.A.; Cole, G.M. *Neuron,* **2004**, *43*, 633.
[45] Lim, G.P.; Chu, T.; Yang, F.; Beech, W.; Frautschy, S.A. and. Cole, G.M. *J. Neurosci*., **2001**, *21*, 8370.
[46] Praticò, D.; Uryu, K.; Leight, S.; Trojanoswki, J.Q. and Lee, V.M.Y *J. Neurosci*., **2001**, *21*, 4183.
[47] Calon, F.; Lim, G.P.; Morihara, T.; Yang, F.; Ubeda, O.; Salem, N. Jr; Frautschy, S.A., Cole, G.M. *Eur. J. Neurosci*., **2005**, *22*, 617.
[48] Montine, T.J. and Morrow, J.D. *Am. J. Pathology,* **2005**, *166*, 1283.
[49] Cull-Candy, S.; Brickley, S.; Farrant, M. *Curr. Opin. Neurobiol*., **2001**, *11*, 327.
[50] Lim, G.P.; Calon, F.; Morihara, T.; Yang, F.; Teter, B.; Ubeda, O.; Salem, N. Jr; Frautschy, S.A. and Cole, G.M. *J. Neurosci.,* **2005**, *25*, 3032.
[51] Newcomer, J.W. and Krystal, J.H. *Hippocampus,* **2001**, *11*, 529.
[52] Barberger-Gateau, P.; Letenneur, L.; Deschamps, V.; Peres, K.; Dartigues, J.F.; Renaud, S. *BMJ,* **2002**, *325*, 932.
[53] Kalmijn, S.; Launer, L.J.; Ott, A.; Witteman, J.C.; Hofman, A.; Breteler, M.M. *Ann. Neurol*., **1997**, *42*, 776.
[54] Morris, M.C.; Evans, D.A.; Bienias, J.L.; Tangney, C.C.; Bennett, D.A.; Wilson, R.S.; Aggarwal, N.; Schneider, J. *Arch. Neurol*., **2003**, *60*, 940.
[55] Petot, G.J.; Traore, F.; Debanne, S.M.; Lerner, A.J.; Smyth, K.A.; Friedland, R.P. *Metabolism,* **2003**, *52*, 279.
[56] Petot, G.J. and Friedland, R.P. *J. Neurol. Sci.,* **2004**, *226*, 31.
[57] Peet, M. *Prostaglandins Leukot. Essent. Fatty Acids,* **2003**, *69*, 477.
[58] Mamalakis, G. ; Kiriakakis, M.; Tsibinos, G.; Kafatos A. *Prostaglandins Leukot. Essent. Fatty Acids,* **2004**, *70*, 495.
[59] Su, K.P.; Huang, S.Y. ; Chin, C.C. ; Shen, W.W. *Eur. Neuropsychopharmacol*., **2004**, *14*, 173.
[60] Logan, A.C. *Alternative Med. Rev*., **2003**, *8*, 410.
[61] Simopoulos, A.P. ; Leaf, A. ; Salem, N.Jr. *J. Am. Coll. Nutr*., **1999**, 18, 487.
[62] Simopoulos, A.P. *World Rev. Nutr. Diet,* **2001**, *88*, 18.
[63] Sinclair, A.J.; Johnson, L.; O'Dea, K.; Holman, R.T. *Lipids,* **1994**, *29*, 337.
[64] Hilben, J.R. *Lancet,* **1998**, *351*, 1213.
[65] Peet, M.; Murphy, B.; Shay, J.; Horrobin, D. *Biol. Psychiatry,* **1998**, *43*, 315.
[66] Maes, M.; Christophe, A.; Delanghe, J.; Altamura, C.; Neels, H.; Meltzer, H.Y. *Psychiatric Res.,* **1999**, *85*, 275.
[67] Tiemeier, H.; van Tuijl, H.R.; Hofman, A.; Kiliaan, A.J.; Breteler, M.M. *Am. J. Clin. Nutr*., **2003**, *78*, 40.
[68] Maes, M.; Smith, R.; Christophe, A.; Cosyns, P.; Desnyder, R.; Meltzer, H. *J. Affect. Disord*., **1996**, *38*, 35.
[69] Maes, M.; Smith, R. *Biol. Psychiatry,* **1998**, *43*, 313.
[70] Nemetes, B.; Sthal, Z.; Belmaker, R.H. *Am. J. Psychiatry,* **2002,** *159*, 477.
[71] Peet, M. and Horrobin, D. *Arch. Gen. Psychiatry,* **2002**, *59*, 913.
[72] Zanarini, M.C. and Frankenburg, F.R. *Am. J. Psychiatry,* **2003**, *160*, 167.
[73] Marangell, L.B.; Martinez, J.M.; Zboyan, H.A.; Kertz, B.; Kim, H.F.; Puryear, L.J. *Am. J. Psychiatry,* **2003**, *160*, 996.
[74] Keck, P.E. Jr.; McElroy, S.L.; Freeman, M.P.; Altshuler, L.L.; Frye, M.A.; Kupka, R.; Nolen, W.; Grunze, H.; Walden, J.; Denicoff, K.D.; Leverich, G.S.; Post, R.M. *Bipolar Disord*., **2003**, *5*, 58.
[75] Frangou, S.; Lewis, M. *Bipolar Disord.,* **2002**, *1*, 123.
[76] Osher, Y.; Bersudsky, Y.; Belmaker, R.H. *J. Clin. Psychiatry,* **2005**, *66*, 726.
[77] Tanskanen, A.; Hibbeln, J.R.; Tuomilehto, J.; Uutela, A.; Haukkala, A.; Viinamaki, H.; Lehtonen, J.; Vartianen, E. *Psychiatr. Serv*., **2001**, *52*, 529.
[78] Hakkarainen, R.; Partonen, T.; Haukka, J.; Virtamo, J.; Albanes, D.; Lonnqvist, J. *Am. J. Psychiatry,* **2004**, *161*, 567.
[79] Brown, K.M.; Morrice, P.C.; Duthie, G.G. *Eur. J. Clin. Nutr*., **1998**, *52*, 145.
[80] Peet, M.; Brind, J.; Ramchand, C.N.; Shah, S.; Vankar, G.K. *Schizophr. Res*., **2001**, *49*, 243.
[81] Emsley, R.; Myburgh, C.; Oosthuizen, P.; van Rensburg, S.J. *Am. J. Psychiatry,* **2002**, *159*, 1596.
[82] Peet, M. and Horrobin, D. *J. Psychiatry Res*., **2002**, *36*, 7.
[83] Gattaz, W.F.; Hubner, C.V.; Nevalainen, T.J.; Thuren, T.; Kinnunen, P.K. *Biol. Psychiatry,* **1990**, *28*, 495.
[84] Ross, B.M.; Hudson, C.; Erlich, J.; Warsh, J.J.; Kish, S.J. *Arch. Gen. Psychiatry,* **1997**, *54*, 487.
[85] Macdonald, D.J.; Boyle, R.M.; Glen, A.C.; Ross, B.M.; Glen, A.I.; Ward, P.E.; McKinney, S.B.; Peterkin, M.A. *Prostaglandins Leukot. Essent. Fatty Acids*, **2004**, *70*, 377-81.
[86] Finnen, M.J.; Lovell, C.R. *Biochem.Soc. Trans*., **1991**, *19*, S91.
[87] Gaughran, F. *Int. Rev. Neurobiol*., **2002,** *52*, 275.
[88] Muller, N.; Riedel, M.; Scheppach, C.; Brandstatter, B.; Sokullu, S.; Krampe, K.; Ulmschneider, M.; Engel, R.R.; Moller, H.J.; Schwarz, M.J. *Am. J. Psychiatry,* **2002**, *159*, 1029.
[89] Swank, R.L.; Lerstad, O.; Strom, P.; Barker, J. *N. Engl. J. Med*., **1952**, *246*, 721.
[90] Alter, M.; Yamoor, M.; Harshe, M. *Arch. Neurol*., **1974**, *31*, 267.
[91] Lauer, K. *Neurology,* **1997**, *49,* S55.
[92] Antonovsky, A.; Leibowitz, U.; Smith, H.A.; Medalie, J.M.; Balogh, M.; Kats, R.; Halpern, L.; Alter, M. *Arch. Neurol*., **1965**, *13*, 183.
[93] Berr, C.; Puel, J.; Clanet, M.; Ruidavets, J.B.; Mas, J.L.; Alperovitch, A. *Acta Neurol. Scand*., **1989**, *80*, 46.
[94] Zhang, S.M.; Willett, W.C.; Hernan, M.A.; Olek, M.J.; Ascherio, A. *Am. J. Epidemiol*., **2000**, *152*, 1056.
[95] Ghadirian, P.; Jain, M.; Ducic, S.; Shatenstein, B.; Morisset, R. *Int. J. Epidemiol*., **1998**, *27*, 845.
[96] Nordvik, I.; Myhr, K.M.; Nyland, H.; Bjerve, K.S. *Acta Neurol. Scand*., **2000**, *102*, 143.
[97] Weinstock-Guttman, B.; Baier, M.; Park, Y.; Feichter, J.; Lee-Kwen, P.; Gallagher, E.; Venkatraman, J.; Meksawan, K.; Deinehert, S.; Pendergast, D.; Awad, A.B.; Ramanathan, M.; Munschauer, F.; Rudick, R. *Prostaglandins Leukot. Essent. Fatty Acids*, **2005**, *73*, 397.
[98] Calder, P.C. *Trends Immunol. Today,* **1998**, *6*, 244.
[99] James, M.J.; Gibson, R.A.; Cleland, L.G. *Am. J. Clin. Nutr*., **2000**, *71*, 343S.
[100] Neu, I.; Mallinger, J.; Wildfeuer, A.; Mehlber, L. *Acta Neurol. Scand*., **1992**, *86*, 586.
[101] Gallai, V.; Sarchielli, P.; Trequattrini, A.; Franceschini, M.; Floridi, A.; Firenze, C.; Alberti, A.; Di Benedetto, D.; Stragliotto, E. *J. Neuroimmunol*., **1995**, *56*, 143.
[102] Gozzo, S.; Oliverio, A.; Salvati, S.; Serlupi Crescenzi, G.; Tagliamone, B. and Tomassi, G. *Nutr. Rep. Inter.,* **1978**, *17*, 357.
[103] Gozzo, S.; Oliverio, A.; Salvati, S.; Serlupi Crescenzi, G.; Tagliamone, B. and Tomassi, G. *Food Chem.Toxicol*., **1982**, *20*, 153.
[104] Schlenk, H. *Fed. Proc.,* **1972**, *31*, 1430.
[105] Salvati, S.; Sanchez, M.; Malvezzi Campeggi, L.; Suchanek, G.; Breitschop H.; Lassman, H. *J. Neurochem*., **1996**, *67*, 1744.
[106] Salvati, S.; Natali, F.; Attorri, L.; Raggi, C.; Di Biase, A.; Sanchez, M. *Neurochem. Inter.,* **2004**, *44*, 331.
[107] Haubner, L.Y.; Stockard, J.E.; Saste, M.D.; Benford, V.J.; Phelps, C.P.; Chen, L.T.; Barness, L.; Wiener, D.; Carver, J.D. *Brain Res. Bull*., **2002**, *58*, 1.
[108] Jenner, P. *Ann. Neurol*., **2003**, *53*, S26.
[109] Wullner, U.; Klockgether, T. *J Neurol*., **2003**, *250*(Suppl. 1), I35.
[110] Kim, H.Y.; Akbar, M.; Kim, K.Y. *J. Mol. Neurosci*., **2001**, *16*, 223.

[111] Lev, N.; Melamed, E.; Offen, D. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2003**, *27*, 245.
[112] Giuffrida, A.; Piomelli, D. *Chem. Phys. Lipids*, **2000**, *108*, 151.
[113] Fernandez-Ruiz, J.; Lastres-Becker, I.; Cabranes, A.; Gonzalez, S.; Ramos, J.A. *Prostaglandins Leukot. Essent. Fatty Acids,* **2002**, *66*, 257.
[114] Watanabe, S.; Doshi, M.; Hamazaki, T. *Prostaglandins Leukot. Essent. Fatty Acids*, **2003**, *69*, 51.
[115] Johnson, C.C.; Gorell, J.M.; Rybicki, B.A.; Sanders, K.; Peterson, E.L. *Int. J. Epidemiol*., **1999**, *28*, 1102.
[116] Powers, K.M.; Smith-Weller, T.; Franklin, G.M.; Longstreth, W.T. Jr.; Swanson, P.D.; Checkoway, H. *Neurology,* **2003**, *60*, 1761.
[117] Chen, H.; Zhang, S.M.; Hernan, M.A.; Willett, W.C.; Ascherio, A. *Am. J. Epidemiol*., **2003**,*157*, 1007.
[118] de Lau, L.M.; Bornebroek, M.; Witteman, J.C.; Hofman, A.; Koudstaal, P.J.; Breteler, M.M. *Neurology,* **2005**, *64*, 2040.
[119] Abbott, R.D.; Ross, G.W.; White, L.R.; Sanderson, W.T.; Burchfiel, C.M.; Kashon, M.; Sharp, D.S.; Masaki, K.H.; Curb, J.D.; Petrovitch, H. *J. Neurol*., **2003**, *250* (Suppl. 3), III30.

Received: February 10, 2006 **Revised: April 13, 2006** **Accepted: April 14, 2006**