Journal of Animal and Feed Sciences, 19, 2010, 511–524

The necessity of adequate nutrition with diets containing omega-3 and omega-6 fatty acids for proper brain development, function and delayed aging: Review

K. Kochman[1] and M. Czauderna

The Kielanowski Institute of Animal Physiology and Nutrition,
Polish Academy of Sciences
05-110 Jabłonna, Poland

(Received 1 June 2010; revised version 19 November 2010; accepted 26 November 2010)

ABSTRACT

The necessity of appropriate nutrition with diets containing omega-3 and omega-6 fatty acids for physiologically optimal brain and nervous tissue function has been demonstrated in numerous experiments conducted in very prestigious research laboratories worldwide. Complex mechanisms and dysfunctions in the area of developmental neurobiology and neurology are impossible to understand and describe in detail without the interdisciplinary study of diet and nutrition. Studies of human infants suggest that dietary docosahexaenoic acid plays an important role in cognitive development and, in cases of its deficit, in some neurodevelopmental disorders as well; this possibility has important public health implications.

Both omega-3 and omega-6 fatty acids are crucial elements in the structure and function of cellular membranes, determining their proper physiological activity in regards to fluidity, intracellular transport, and protection against intruders such as bacteria and viruses. These acids actively participate in the biosynthesis of such neurotransmitters as dopamine and serotonin, which are required in nerve cells for quick and efficient signal conductance.

The proper content of omega-3 fatty acids in diets increases and improves learning ability, problem-solving skills, concentration, memory, and communication between nerve cells. Omega-3 fatty acids also support positive mood and emotional balance, and are beneficial in the treatment of depression and Alzheimer's disease; they also help maintain good mental skills in aging people. Omega-3 fatty acids are derived from food; they are able to restore the proper flexibility of neuronal membranes, resulting in improved cell communication and physiologically optimal brain function in cases in which this flexibility was previously disordered.

[1] Corresponding author: e-mail: k.kochman@ifzz.pan.pl

KEY WORDS: brain, nutrition, omega-3 fatty acids, omega-6 fatty acids, neurodevelopment, brain function, aging

INTRODUCTION

Nutrition plays an important role in the functions of brain and nervous tissue. A number of mechanisms and dysfunctions based on developmental neurobiology and neurology can certainly not be understood without analysis of diet and nutrition. In recent years, significant conclusions reached on nutrition and neurodevelopment show that a number of cellular and molecular mechanisms are affected by our diet.

Scientific studies during the 1970s on the health of Inuit-Eskimos living in Greenland clearly showed that they were not only the most healthy population in the world, but their good health exceeded by far that of any other population in the world. Their diet consisted mainly of whale, salmon and seal. The incidence of such serious diseases as coronary heart disease, arthritis, diabetes and many others, was extraordinarily lower than in other populations. The main reason for this was the content of omega-3 fatty acids in the diet - the key factor determining the excellent health of Eskimos. Similar studies in Iceland gave the same result. It was shown that in Iceland, the incidence of such health problems as heart disease, stroke, and high blood pressure was minimal in comparison with other populations in Europe and elsewhere. They also had the lowest infant mortality rates in the world. Scientists attributed these positive facts concerning the health of these people to high intakes of fish oils rich in long-chain omega-3 fatty acids, particularly docosahexaenoic acid (DHA), docosapentaeneoic acid (DPA) and eicosapentaenoic acid (EPA) (Gordon and Joiner-Bey, 2004).

Longitudinal and epidemiological studies revealed positive correlations between the low DHA concentrations in plasma and blood cells and the risk of neural and visual disorders in infants and children and to a greater risk of cognitive deterioration and dementia in aging people (Dullemeijer et al., 2007; Horrocks and Yeo, 1999; Innis, 2008; Innis and Friesen, 2008). DHA is the most abundant omega-3 fatty acid in the central nervous system, being concentrated in particular in the membrane lipids of grey matter and visual elements of the retina (Horrocks and Yeo, 1999; Innis, 2008).

Omega-3 α-linolenic acid belongs to a group of essential nutrients and is necessary for humans and animals alike. It is not synthesized in the body, but rather should be supplied in adequate amounts through the diet. Sources of these fatty acids include: salmon, mackerel, vegetables, vegetable oils, linseed, and, in smaller quantities, the oils of other plants. Of utter importance is maintaining a diet

that provides a specific fatty acid, which has 22 carbon chain and 6 double bonds, known as DHA. Its role is imperative for the development and function of nervous tissue, especially the human brain, whose mass being more than 50% fat, contains an abundance of omega-3 fatty acids. Epidemiological and interventional studies have linked low plasma and blood cell lipid DHA to increased risk of insufficient visual and neutral development in embryos, babies and children (Bouwstra et al., 2003; Helland et al., 2003; Dunstan et al., 2006; Hibbeln et al., 2007; Innis, 2008; Innis and Friesen, 2008). Other noteworthy omega-3 acids include α-linolenic acid (α-LNA), EPA. Fatty acids are essential building blocks of the brain (in neurons and cellular membranes), but they also function in improving learning and memory, augmenting suboptimally functioning synapses. Large amounts of DHA as well as selenium (Se) are stored in the retina; DHA ensures smooth transmission of visual stimuli to the brain.

Another series of unsaturated fatty acids is the omega-6 fatty acids. They are also important for the body and can be found in diets rich in sunflower oil, soyabeans, rapeseed oil, and black currants. The most important omega-6 fatty acids for human health are γ-linolenic acid (γ-LNA) and arachidonic acid (AA; C20:4n-6) (Innis, 2008; Xie and Innis, 2008).

Both omega-3 and omega-6 fatty acids are important components in the building of cellular membrane structures, which in turn determine the physiologically essential, smooth functioning of membranes in regards to their fluidity, intracellular and extracellular transport, protection against intruders such as bacteria and viruses. They participate in the biosynthesis of such neurotransmitters as dopamine and serotonin, which are necessary in nerve cell bodies for quick and unhindered signal conductance.

Many studies have shown that diets rich in omega-3 fatty acids resulted in increased and improved learning ability, problem-solving skills, concentration, memory, and communication between nerve cells. Omega-3 fatty acids participate in improving mood and emotional balance, and support the maintenance of good mental ability in the people as they age (Whelan, 2008).

Prostaglandins biosynthesized from AA play central roles in the regulation of brain development, synaptic plasticity, spatial learning, and long-term potentiation (Bazan, 2003). It is important to note that DHA may regulate AA release from neural membranes, affecting prostaglandin biosynthesis in this way (Corey et al., 1983; Chen and Bazan, 2005; Bazan, 2006; Strokin et al., 2007; Tassoni et al., 2008).

Membranes in brain neurons are composed, among the others, of phospholipids, mostly glycero-phospholipids enriched in PUFAs, where DHA comprises a major portion of acyl chains; taken together, omega-3 fatty acids are the most essential in their structure.

For proper functional communication among neurons and signal transmission, these membranes need to be appropriately flexible to permit vital molecules to pass through. Age or diets abundant in cholesterol and saturated fatty acids can cause these membranes to stiffen and become less pliable. This stiffness does not permit the needed molecules to pass through the neurons correctly and can result in mood imbalances, difficulties in learning, difficulties in recalling information, and other perturbations in brain function. When omega-3 fatty acids are ingested with food, they are able to restore the flexibility and pliable nature of neuronal membranes, resulting in increased cell communication and physiologically normal brain function.

STRUCTURAL AND FUNCTIONAL ROLES OF OMEGA-3 AND OMEGA-6 FATTY ACIDS IN THE BRAIN

Lipids are essential constituents of brain nervous tissue and show a relatively high content of docosahexaenoic acid (C22:6n-3, DHA), which is particularly enriched in aminophospholipids, ethanolamine and serine phosphoglycerides (Sastry, 1985). DHA is the most essential omega-3 PUFA and is highly enriched in fish oils but is also synthetized via elongation and Δ4-desaturation of the 20-carbon eicosapentaenoic acid (EPA; C20:5n-3) or metabolism comprising elongation, β-oxidation, Δ5-, Δ4- and Δ6-desaturation of the 18-carbon omega-3 fatty acid, α-linolenic acid (α-LNA, C18:3n-3), which is present in a high concentration in linseed, walnut, chia, and other photosynthesizing terrestrial plants (Lukiw and Bazan, 2008). The omega-3 polyunsaturated fatty acids, including DHA, occupy the sn-2 position of phospholipids, and it has been established that brain tissues need specific molecular species for its function (Salem and Niebylski, 1995; Kitajka et al., 2002). These lipids are of primary importance in building structural integrity and efficient function of biological membranes (Murphy, 1990), which is highlighted by the property of DHA that it is depleted slowly from the brain (Holman and Mohrhauer, 1963; Mohrhauer and Holman, 1963); usually two generations are necessary to reduce its level significantly (Abe et al., 1989; Bourre et al., 1992).

In growing nerve cells, the small membrane protein syntaxin 3 (STX3) has been identified as the target for the action of omega-3 and omega-6 fatty acids (Darios and Davietov, 2006). These fatty acids activate syntaxin 3, allowing growth of neuronal extensions, an essential process in brain development. This discovery is, in perspective, a good preview of further identification of other potent compounds that will be able to accelerate neuronal repair following injury (Darios and Davietov, 2006). Fatty acid imbalance as well as specific fatty acid deficiencies can adversely affect brain development, including the ability to respond to environmental stimuli.

Although the impaired water-maze performance of mice fed a diet rich in saturated fatty acids improved in response to early environmental enrichment, the brains of these animals showed less complex patterns of dendritic branching. Omega-3 fatty acid deficiency negatively influences specific neurotransmitter systems. Studies of human infants suggest that dietary DHA may play a crucial role in cognitive development as well as in some neurodevelopmental disorders; this possibility has very important implications for public health (Wainwright, 2002).

The critical period during neuronal development is growth and achieving the final structure of processes from the nerve cell body, leading to an enormous increase in cell membrane surface area. AA-releasing phospholipases are highly abundant in nerve growth cones and are also precedentially active in neurite outgrowth. Cell membrane expansion occurs through the fusion of transporting organelles with the plasma membrane (Wainwright, 2002; Darios and Davietov, 2006). Importantly, syntaxin 3 participates in the growth of neurites and is also a direct target for omega-6 arachidonic acid. Dietary omega-3 linolenic and docosahexaenoic acids are efficiently able to substitute for the AA in activating syntaxin 3. These findings provide a molecular basis for the action of omega-3 and omega-6 PUFA in membrane expansion at growth cones, and are the first evidence for the presence of a single effector molecule for these important fatty acids (Wainwright, 2002). The absence of syntaxin 3 has a profound effect on embryonic neurons, confirming the physiological relevance of this syntaxin isoform in cells that were co-treated with AA and NGF. Downregulation of syntaxin 3 had a potent inhibitory influence on neurite outgrowth (Marszalek and Lodish, 2005; Darios and Davietov, 2006).

DHA is a compound of basic importance for the life and function of brain neurons and synapses. In the brain, DHA is present particularly in all excitable cell membranes and in the synaptic junctions between neurons, where neurotransmission processes are intense. It has also been found in non-neuronal cells such as glia, in retinal pigment epithelial cells, and in the photoreceptor cells that make up most of the retina. DHA is present mainly in the phospholipids of cellular membranes. The highest content of DHA is in CNS synapses and retinal photoreceptors; DHA accounts for about 60% of all fatty acids in the phospholipids of the neuronal plasma membrane (Neuringer and Connor, 1989; Scott and Bazan, 1989; Lukiw and Bazan, 2008). Studies on mice during postnatal development showed that dietary linolenic acid is first taken up by the liver, where elongation and desaturation to DHA takes place and then DHA is supplied through the bloodstream to the brain and retina. Brain and retinal cells have a readily accessible supply of DHA through highly regulated phospholipase-mediated exoprotease activity that releases membrane-bound DHA for neuroprotective and signaling activities (Lukiw and Bazan, 2008). A deficiency of DHA and/or excess of AA are

observed in persons suffering from Alzheimer disease. The neuroprotective activity of DHA and NPD1 (a DHA metabolite discovered by researchers from Louisiana State University, who named it neuroprotectin D1 or NPD1) is mediated through their functional ability to upregulate the expression of genes that code a number of beneficial proteins, and to suppress the expression of genes that code other proteins that are deleterious to the brain. This beneficial activity of NPD1 takes place not only in the brain but also in DHA-rich retina and nerve cells (Jeong and Ikeda, 2000), where NPD1 promotes the survival of retinal pigment epithelial cells. This protective action is a particularly important because damage to or apoptosis of these cells impairs the survival of the underlying photoreceptor cells; this is a dominant factor in age-related macular degeneration, an incurable disease that gradually destroys central vision. In the case of Alzheimer's disease, the expression of the genes that code for the enzymes responsible for the synthesis of a DHA-derived mediator, neuroprotectin D1 (NPD1) from DHA is impaired (Kim et al., 2000; Salem et al., 2001; Bazan, 2005). This explains, at least partially, why NPD1 levels in the hippocampus of Alzheimer's brains are reduced to only one-tenth of those in healthy, age-matched controls. DHA levels are reduced by about half. This results in the effective loss of NPD1's neuroprotective action during the brain cell degeneration for which the disease is so notorious (Lukiw et al., 2005).

Neuroprotectin D1 (NPD1) induces a positive molecular programme in cells leading to the expression of antiapoptotic and neuroprotective genes that regulate the secretion of amyloid-beta peptides, resulting in the modulation of inflammatory signaling, neuronal survival, and, in consequence, the protection of brain cell function. Transmembrane glycoprotein βAPP increases the synthesis of neurotoxic Aβ peptides, one of which, Aβ40, is associated with neurovascular deposition and vascular pathology, while another highly amyloidogenic Aβ42 dimer is estimated to be particularly detrimental to neuronal activity through its promotion of oxidative stress and synaptotoxic effects (Lukiw and Bazan, 2006; Osenkowski et al., 2008). Alternatively, βAPP is processed *via* a membrane-associated disintegrin metalloprotein α-secretase into a soluble form of APP (sAPPα), which is known as to be neuritogenic, neurotrophic, and to promote neuronal survival. Both DHA and APD1 promote the synthesis of sAPPα *via* stimulation of α-secretase activity (Lukiw and Bazan, 2006; Osenkowski et al., 2008). DHA is a potent inhibitor of amyloid-beta formation in aging human neuronal cell cultures under oxidative stress (Lukiw et al., 2005). Stimulators of NPD1 biosynthesis or NPD1 analogs may be useful in future research on new therapeutic strategies for both Alzheimer's and similar neurodegenerative diseases (Bazan, 2005; Lukiw et al., 2005; Lukiw and Bazan, 2008).

A low intake of a DHA precursor, α-linolenic acid (α-LNA), as well as low capacity of elongase and/or Δ5-, Δ4-, Δ6-desaturases results in the lower transfer

of DHA to the brain from the liver, where a substantial amount of DHA is formed from α-LNA *via* the bloodstream. It should be mentioned and stressed that this synthesis does not supply a sufficient quantity of DHA for normal brain function. Therefore, its delivery to the brain is more efficient by consumption of food containing sufficient amounts of both DHA and EPA.

Another important function of DHA is its role in cognitive processes. When the DHA content in the brain was diminished, animals underperformed in learning tests and showed evidence of other disordered mental processes (Bourre et al., 1989; Greiner et al., 1999), which were reversed when they received a diet enriched in DHA (the best way) or other omega-3 polyunsaturated fatty acids (precursors), such as α-linolenic acid (C18:3n-3, α-LNA) (Bourre et al., 1989).

A substantial amount of DHA is supplied to the brain from the liver during pregnancy (Nouvelot et al., 1986; Scott and Bazan, 1989) and by breast feeding after delivery (Farquharson et al., 1995; Kitajka et al., 2002). The mechanisms of functional involvement of DHA-containing phospholipids in cognitive processes are under intensive study; it has been shown that there is a close relationship between their effect on the blood-brain barrier (Hussain and Roots, 1994) and activity of certain brain enzymes (Bourre et al., 1989; Gerbi et al., 1994), neural signaling (Kim and Edsall, 1999), ionic channels (Vreugdenhil et al., 1996), or growth factor regulation (Ikemoto et al., 2000). Brain cells and synapses require EPA, DHA and other omega-3 fatty acids to be supplied in an adequate amount for the normal and efficient functioning of these structures. These fatty acids greatly affect the composition of different membrane phospholipids and the incorporation of specific fatty acid into complex molecules in the nervous system. Their structural presence modifies the physical properties of cell membranes (Neuringer and Connor, 1989; Gerbi et al., 1994), including membrane fluidity (Salem and Niebylsky, 1992), and alters the functioning of many cellular systems (Stubbs and Smith, 1985). It should be also pointed out that these fatty acids modify the activities of membrane-associated functional proteins (Fernstrom, 1999). It is well known that dietary omega-3 fatty acids influence such mental functions as learning, memory, and other functional abilities and performances through the activation of gene expression in combination with membrane effects (Kitajka et al., 2002).

The results of intensive research provide strong evidence documenting that an elevated ratio of omega-6 to omega-3 fatty acids in diets is a major risk of many disorders, so this ratio should be much lower than in presently consumed diets in many developed western countries (Innis, 2008). Considering the above, the Japan Society for Lipid Nutrition recommended that the ratio of omega-6 to omega-3 fatty acids in diets should be less than 4:1 for healthy adults and less than 2:1 for the prevention of chronic diseases in aging people (Horrocks and Yeo, 1999).

Similarly, the World Health Organization and many other health institutions (like the British Nutrition Foundation or FAO) are currently recommending an omega-6 to omega-3 ratio between 3:1 and 4:1 in diets (Horrocks and Yeo, 1999).

It has been shown that in omega-3 fatty acid-deficient hamsters, the induced changes in pineal PUFA membrane phospholipid composition were associated with a reduction in the nocturnal peak level of melatonin, which was 52% lower than in control animals. Omega-3 PUFA-deficient hamsters also had significantly higher diurnal and nocturnal locomotor activity than control animals, in parallel with activation of a striatal dopaminergic function (Lavialle et al., 2008). Omega-3 fatty acid-deficient hamsters exhibited several symptoms: chronic locomotor hyperactivity, a disturbance in melatonin rhythm, and striatal hyperdopaminergia. Investigations showed that an omega-3 fatty acid-deficient diet lessens the melatonin rhythm and weakens the endogenous functioning of the circadian clock, which plays an important role in nocturnal sleep disturbances as described in attention deficit/hyperactivity disorder (Lavialle et al., 2008).

DHA-rich phospholipids optimize G-protein-coupled signaling. A large number of experiments indicate that a high content of C22:6n-3 (DHA) in membrane phospholipids is necessary for efficient functioning of many different signaling pathways. The common characteristics of these processes are the central position of G-protein-coupled signaling. The conformational membrane modification accompanying receptor activation is dependent on the physical properties of the membrane lipid bilayer. The degree of unsaturation of the acyl chains of fatty acids and the cholesterol level in a membrane significantly affect metarhodopsin II (MII) formation, MII-G1 coupling efficiency, and the rate of phosphodiesterase (PDE) activity. The earliest events in G-protein-coupled signaling (receptor conformation change, receptor-G-protein binding, and PDE activity) are reduced in membranes lacking omega-3 acyl chains. Efficient and rapid propagation of G-protein-coupled signaling requires omega-3 polyunsaturated phospholipid acyl chains that optimize this process (Mitchell et al., 2003).

Changes in the composition of membrane phospholipids in nerve cells affect not only important intracellular and intercellular signaling, but also modify the physical properties of a membrane, its fluidity, phase transition temperature, bilayer thickness, and lateral domains (Horrocks and Farooqui, 2004). PUFA deficiency markedly influences neurotransmission, membrane-bound enzyme and ion channel performance, and synaptic plasticity. Its intake from the diet restores membrane fluidity and gene expression, decreases inflammation, and modulates neurotransmission (Tapiero et al., 2002; Yehuda et al., 2002; Stillwell and Wassall, 2003; Fukaya et al., 2007). Long-term dietary supplementation of arachidonic acid enables the preservation of proper membrane fluidity and hippocampal plasticity (Fukaya et al., 2007).

The development of dysfunction of cholinergic neurons arising from the basal forebrain and terminating in the cortex and hippocampus is possibly the cause of cognitive deterioration that occurs during aging and Alzheimer's disease (Willis et al., 2009). Intensive research on this problem has concentrated on pharmacological interventions in treating or forestalling the development of Alzheimer's disease, primarily by focusing on enhancing cholinergic transmission, either through increasing acetylcholine (ACh) synthesis or inhibition of the acetylcholinesterase responsible for ACh hydrolysis. Recent studies have shown, however, that dietary supplementation can impact the cholinergic system, which is most visible during aging (Willis et al., 2009). Results of several studies indicate that the presence of adequate amounts of PUFAs in the diet improves cholinergic transmission in the aged brain, leading in consequence to significant improvement in cognitive functioning (Willis et al., 2009).

A gene expression pattern resulting from the feeding of omega-3 fatty acids in the rat brain was also intensively studied. Using cDNA microarrays, it was found that in different dietary regiments, 55 genes were found to be overexpressed and 47 were suppressed in comparison with controls. The altered genes included those controlling synaptic plasticity, cytoskeleton and membrane association, signal transduction, ion channel formation, energy metabolism, and regulatory proteins. This effect seems to be independent of the chain length of fatty acids, but the omega-3 structure appears to be very important. Because omega-3 fatty acids were shown to participate in proper and optimal maintenance of normal mental functions, docosahexaenoic acid-containing ethanolamine phosphoglyceride molecules are accumulated in response to dietary omega-3 fatty acids (as indicated by, i.e. the ratio of C18:0/C22:6n-3); a casual relationship between the two events can be surmised (Kitajka et al., 2002).

Bioactive lipids control neuronal excitability by acting on G-protein-coupled receptors (such as CB1) but also directly modulate the conductance of various ions, including voltage-activated T-type calcium channels (T-channels) (Chemin et al., 2007).

Anandamide, originally described as an endocannabinoid, is an important molecule of newly recognized lipids participating in signaling, including endocannabinoids and N-acyl-related molecules, eicosanoids, and fatty acids.

Therefore, the original natural (food-supplied) and endogenous fatty acids including γ-linolenic acid, mead acid, and arachidonic acid, as well as all omega-3 fatty acids (i.e. long-chain omega-3 PUFAs) that are present in fish oil (e.g., eicosapentaenoic and docosahexaenoic acids), are strong inhibitors of T-type Ca^{2+} currents, which possibly contribute to their physiological functions (Chemin et al., 2007).

Polyunsaturated fatty acids and N-acyl ethanolamine signaling are implicated in a multitude of physiological and pathophysiological signaling events, including

cardiac and neuronal excitability (Abe et al., 1989; Siesjo et al., 1989; Piomelli, 1994; van der Vusse et al., 1997; Bazan, 2003; Leaf et al., 2003), cardioprotection and neuroprotection from ischemic and epileptic episodes (Bazan, 2003; Chen and Bazan, 2005), inflammation, and pain (Julius and Basbaum, 2001).

Studying the role of T-channels in the cardiac and neuronal pacemaker (Hagarivara et al., 1988; Huguenard, 1996; Perez-Reyes, 2003; Mangoni et al., 2006), cardiac hypertrophy (Nuss and Houser, 1993), neuroprotection and absence of epilepsy (Tsakiridou et al., 1995; Kim et al., 2001; Nikonenko et al., 2005), perception (Todorovic et al., 2001; Kim et al., 2003; Bourinet et al., 2005), it can be concluded that T-channel inhibition may have a connection with fatty acid and N-acyl ethanolamide effects. It is important to note that both anandamide (AEA) and arachidonic acid also function as intracellular second messengers (Axelrod, 1990; van der Stelt et al., 2005) and therefore could potentially participate in the signal transduction chains in the cell and messenger cascades by which neurotransmitters inhibit T-currents (Perez-Reyes, 2003).

PUFA act by participating in the control of many various metabolic mechanisms like regulation of calcium levels in astrocytes (Sergeeva et al., 2005). It has also been shown that phospholipases A2, C, and D are important participants in the signaling and interplay of different metabolic and signal pathways in LA-N-1 cell nuclei (Farooqui and Horrocks, 2005).

CONCLUSIONS

It has been observed that sometimes small benefits as well as minor health problems, stem from the consumption of diets containing inappropriate ratios of omega-3 fatty acids, omega-6 fatty acids, saturated fatty acids, and *trans*-fatty acids. It was also found that excessive intake of omega-6 fatty acids relative to omega-3 fatty acids causes a variety of health problems. On the other hand, results of many studies clearly confirm the positive effects of an appropriate level of omega-3 fatty acids in diets on the improvement of health in many diseases and disorders. It should also be noted that the extraction methods used to obtain different vegetable fats and oils have greatly evolved during the past 40-years. Extraction at temperatures ranging between 160-200^{o}C has both doubled extraction efficiency, but also introduced negative changes in unsaturated fatty acids. At such temperatures, positional isomers of linolenic acid, for example, are transformed from the *cis* geometrical form to their biologically inactive forms of *cis-trans*/*trans-cis* (C18:3) and are essentially rendered biologically inactive (Salminen et al., 1998; Flak et al., 2008).

All these aforementioned aspects concerning the merits of polyunsaturated fatty acids (omega-3 and omega-6) are crucial both from a purely theoretical point

of view as well as the practical incorporation of such knowledge in day-to-day nutrition.

REFERENCES

Abe K., Yoshidomi M., Kogure K., 1989. Arachidonic acid metabolism in ischemic neuronal damage. Ann. NY Acad. Sci. 559, 259-268

Axelrod J., 1990. Receptor mediated activation of phospholipase A2 and arachidonic acid release in signal transduction. Biochem. Soc. Trans. 18, 503-507

Bazan N.G., 2003. Synaptic lipid signaling significance of polyunsaturated fatty acids and platelet-activating factor. J. Lipid Res. 44, 2221-2233

Bazan N.G., 2005. Neuroprotectin D1 (NPD1): a DHA-derived mediator that protects brain and retina against cell injury-induced oxidative stress. Brain Pathol. 15, 159-166

Bazan N.G., 2006. Cell survival matters: docosahexaenoic acid signaling, neuroprotectional photoreceptors. Trends Neurosci. 29, 263-271.

Bourinet E., Alloui A., Monteil A., Barrere C., Couette B., Poirot O., Pages A., McRoy J., Snutch T.P., Eschalier A., Nargeot J., 2005. Silencing of Cav3.2 T-type calcium channel gene in sensory neurons demonstrates its major role in nociception. EMBO J. 24, 315-324

Bourre J.M., Dumont O.S., Piciotti M., Ga P., Durand G.A., 1992. Dietary alpha-linolenic acid deficiency in adult rats for 7 months does not alter brain docosahexaenoic acid content, in contrast to liver, heart and testes. Biochim. Biophys. Acta 1124, 119-122

Bourre J.M., Francois M., Youyou A., Dumont O.S., Piciott M., Pascal G., Durand G., 1989. The effects of dietary [alpha]-linolenic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats. J. Nutr. 119, 1880-1892

Bouwstra H., Dijck-Brouwer D.A., Wildeman J.A., Tjoonk H.M., van der Heide J.C., Boersma E.R., Muskiet F.A., Hadders-Algra M., 2003. Long-chain polyunsaturated fatty acids have a positive effect on the quality of general movements of healthy term infants. Amer. J. Clin. Nutr. 78, 313-318

Chemin J., Nargeot J., Lory P., 2007. Chemical determinants involved in anandamide-induced inhibition of T-type calcium channels. J. Biol. Chem. 282, 2314-2323

Chemin J., Traboulsie A., Lory P., 2006. Molecular pathways underlying the modulation of T-type calcium channels by neurotransmitters and hormones. Cell Calcium 40, 121-134

Chen C., Bazan N.G., 2005. Lipid signaling: sleep, synaptic plasticity and neuroprotection. Prostagland. Lipid Mediat. 77, 65-76

Corey E.J., Shih C., Cashman J.R., 1983. Docosahexaenoic acid is a strong inhibitor of prostaglandin but not leukotriene biosynthesis. Proc Nat. Acad. Sci. USA 80, 3581-3584

Darios F., Davietov B., 2006. Omega-3 and omega-6 fatty acids stimulate cell membrane expansion by acting on syntaxin 3. Nature 440, 813-817

Dunstan J.A., Simmer K., Dixon G., Prescott S.L., 2006. Cognitive assessment at 2½ years following fish oil supplementation in pregnancy: a randomized controlled trial. Arch. Dis. Child Fetal Neonatal. ED. 93, F45-50

Farquharson J., Jamieson E.C., Abbasi K.A., Patrick W.J.A., Logan R.W., Cockburn F., 1995. Effect of diet on the fatty acid composition of the major phospholipids of infant cerebral cortex. Arch. Dis. Child. 72, 198-203

Farooqui A.A., Horrocks L.A., 2005. Signaling and interplay mediated by phospholipases A2, C, and D in LA-N-1 cell nuclei. Reprod. Nutr. Develop. 45, 613-631

Fernstrom J.D., 1999. Effects of dietary polyunsaturated fatty acids on neuronal function. Lipids 34, 161-169

Flak D., Greń A., Czauderna M., Gajewska A., Kochman K., 2009. Effects of nutrition on the brain development, its function and aging. In: Proceedings of 18th International Symposium: Molecular and Physiological Aspects of Regulatory Processes of the Organism. Kraków (Poland), pp. 102-103 (Abstr.)

Fukaya T., Gondaira T., Kashiyae Y., Kotani S., Ishikura Y., Fujikawa S., Kiso Y., Sakakibara M., 2007. Arachidonic acid preserves hippocampal neuron membrane fluidity in senescent rats. Neurobiol. Aging 28, 1179-1186

Gerbi A., Zérouga M., Debray M., Durand G., Chanez C., Bourre J.M., 1994. Effect of fish oil diet on fatty acid composition of phospholipids of brain membranes and on kinetic properties of Na^+, K^+-ATPase isoenzymes of weaned and adult rats. J. Neurochem. 62, 1560-1569

Gordon G., Joiner-Bey H., 2004. The Omega-3 Miracle. Freedom Press

Greiner R.S., Moriguchi T., Hutton A., Slotnick B.M., Salem Jr. N., 1999. Rats with low levels of brain docosahexaenoic acid show impaired performance in olfactory-based and spatial learning tasks. Lipids 3, S239-S243

Hagariwara N., Irisawa H., Kameyama M., 1988. Contribution of two types of calcium currents to the pacemaker potentials of rabbit sino-atrial node cells. J. Physiol. 395, 233-253

Helland I.B., Smith L., Saarem K., Saugstad O.D., Drevon C.A., 2003. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics 111, E39-E44

Hibbeln J.R., Davis J.M., Steer C., Emmett P., Rogers I., Williams C., Golding J., 2007. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 369, 577-585

Holman R.T., Mohrhauer H., 1963. A hypothesis involving competitive inhibitions in the metabolism of polyunsaturated fatty acids. Acta Chem. Scand. 17, S84-S90

Horrocks L.A., Farooqui A.A., 2004. Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. Prostagland. Leuk. Essent. Fatty 70, 361-372

Horrocks L.A., Yeo Y.K., Health benefits of docosahexaenoic acid (DHA). Pharmacol. Res. 40, 211-225

Huguenard J.R., 1996. Low-threshold calcium currents in central nervous system neurons. Annu. Rev. Physiol. 58, 329-348

Hussain S.T., Roots B.J., 1994. Effect of essential fatty acid deficiency and immunopathological stresses on blood brain barrier (B-BB) in Lewis rats: a biochemical study. Biochem. Soc. Trans. 2, 338 (Abstr.)

Ikemoto A., Nitta A., Furukawa S., Ohisi M., Nakamura A., Fuji Y., Okuyama H., 2000. Dietary n-3 fatty acid deficiency decreases nerve growth factor content in rat hippocampus. Neurosci. Lett. 12, 99-102

Innis S.M., 2008. Dietary omega 3 fatty acids and the developing brain. Brain Res. 1237, 35-43.

Innis S.M., Friesen R.W., 2008. Essential n-3 fatty acids in pregnant women and early visual acuity maturation in term infants. Amer J. Clin. Nutr. 87, 548-557

Jeong S.W., Ikeda R., 2000. Endogenous regulator of G-protein signaling proteins modify N-type calcium channel modulation in rat sympathetic neurons. J. Neurosci. 20, 4489-4496

Julius D., Basbaum A.I., 2001. Molecular mechanisms of nociception. Nature 413, 203-210

Kim D., Park D., Choi S., Lee S., Sun M., Kim C., Shin H.S., 2003. Thalamic control of visceral nociception mediated by T-type Ca^{2+} channels. Science 302, 117-119

Kim D., Song I., Keum S., Lee T., Jeong M.J., Kim S.S., McEnery M.W., Shin H.S., 2001. Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking α1G T-type Ca2+ channels. Neuron 31, 35-45

Kim H.Y., Akbar M., Lau A., Edsall L., 2000. Inhibition of neuronal apoptosis docosahexaenoic acid (22:6n-3). Role of phosphatidylserine in antiapoptotic effect. J. Biol. Chem. 275, 35215-35223

Kim H.Y., Edsall L., 1999. The role of docosahexaenoic acid (22 6n-3) in neural signaling. Lipids 34, 3249-3250

Kitajka K., Puskas L.G., Zvara A., Hackler L., Barcelo-Coblij L.G., Yeo Y.K., Farkas T., 2002. The role of n-3 polyunsaturated fatty acids in brain: Modulation of rat brain gene expression by dietary n-3 fatty acids. Proc. Nat. Acad. Sci. USA 99, 2619-2624

Lavialle M., Champeil-Potokar G., Alessandri J.M., Balasse L., Guesnet P., Papillon C., Pevet P., Vancassel S., Vivien-Roels B., Denis I., 2008. An (n-3) polyunsaturated fatty acid-deficient diet disturbs daily locomotor activity, melatonin rhythm, and striatal dopamine in Syrian hamsters. J. Nutr. 138, 1719-1724

Leaf A., Xiao Y.F., Kang J.X., Billman G.E., 2003. Prevention of sudden cardiac death byn-3 polyunsaturated fatty acids. Pharmacol. Ther. 98, 355-377

Lukiw W.J., Bazan N.G., 2006. Survival signaling in Alzheimer's disease. Biochem. Soc. Trans. 34, 1277-1282

Lukiw W.J., Bazan N.G., 2008. Docosahexaenoic acid and the aging brain[1-3]. J. Nutr. 138, 2510-2514

Lukiw W.J., Cui J.G., Marcheselli V.L., Boedker M., Botkjaer A., Gotlinger K., Serhan C.N., Bazan N.G., 2005. A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. J. Clin. Invest. 115, 2774-2783

Mangoni M.E., Traboulsie A., Leoni A.L., Couette B., Marger L., Le Quang K., Kupfer E., Cohen-Solal A., Vilar J., Shin H.S., Escande D., Charpentier F., Nargeot J., Lory S., 2006. Bradykardia and slowing of the atrioventricular conduction in mice lacking Cav3.1/a1G T-type calcium channels. Circ. Res. 98, 1422-1430

Marszalek J.R., Lodish H.F., 2005. Docosahexaenoic acid, fatty acid-interacting proteins, and neuronal function: breastmilk and fish are good for you. Annu. Rev. Cell Dev. Biol. 21, 633-657

Mitchell D.C., Niu S.-L., Litman B.J., 2003. DHA-rich phospholipids optimize G-protein-coupled signaling. J. Pediat. 143, 880-886

Mohrhauer H., Holman R.T., 1963. Alteration of the fatty acid composition of brain lipids by varying levels of dietary essential fatty acids. J. Neurochem. 10, 523-530

Murphy M.G., 1990. Dietary fatty acids and membrane protein function. J. Nutr. Biochem. 1, 68-70

Neuringer M., Connor W.E., 1989. Omega-3 fatty acids in the retina. In: C. Galli, A.P. Simopoulos (Editors). Biological Effects and Nutritional Essentiality. Plenum Press, New York

Nikonenko I., Bancila M., Bloc A., Muller D., Bijlenga P., 2005. Inhibition of T-type calcium channels protects neurons from delayed ischemia-induced damage. Mol. Pharmacol. 68, 84-89

Nouvelot A., Dellbart C., Bourre J.M., 1986. Hepatic metabolism of dietary alpha-linolenic acid in suckling rats, and its possible importance in polyunsaturated fatty acid uptake by the brain. Ann. Nutr. Metab. 30, 316-323

Nuss H.B., Houser S.R., 1993. T-type Ca2+ current is expressed in hypertrophied adult feline left ventricular myocytes. Circ. Res. 73, 777-782

Osenkowski P., Ye W., Wang R., Wolfe M.S., Selkoe D.J., 2008. Direct and potent regulation of gamma-secretase by its lipid microenvironment. J. Biol. Chem. 22529-22540

Perez-Reyes E., 2003. Molecular physiology of low-voltage-activated T-type calcium channels. Physiol. Rev. 83, 117-161

Piomelli D., 1994. Eicosanoids in synaptic transmission. Crit. Rev. Neurobiol. 8, 65-76

Salem Jr. N., Litman B., Kim H.Y., Gawrish K., 2001. Mechanisms of action of docosahexaenoic acid in the nervous system. Lipids 36, 945-959

Salem Jr. N., Niebylsky C.D., 1992. Essential fatty acids and eicosanoids. In: A. Sinclar, R. Gibson (Editors). Champaign, Il. Amer. Oil Chem., pp. 84-87

Salem Jr. N., Niebylski C.D., 1995. The nervous system has an absolute molecular species requirement for proper function. Mol. Membrane Biol. 12, 131-134

Salminen M.M., Mutanen M., Jauhiainen M., Aro A., 1998. Dietary *trans*-fatty acids increase conjugated linoleic acid levels in human serum. Nutr. Biochem. 9, 93-98

Sastry P.S., 1985. Lipids of nervous tissue: composition and metabolism. Prog. Lipid Res. 24, 69-176

Scott B.L., Bazan N.G., 1989. Membrane docosahexaenoate is supplied to the developing brain and retina by the liver. Proc. Nat. Acad. Sci. USA 86, 2903-2907

Sergeeva M., Strokin M., Reiser G., 2005. Regulation of intracellular calcium levels by polyunsaturated fatty acids, arachidonic acid and docosahexaenoic acid, in astrocytes: possible involvement of phospholipase A2. Reprod. Nutr. Develop. 45, 633-646

Siesjo B.K., Agardh C.D., Bengtsoon F., Smith M.L., 1989. Arachidonic acid metabolism in seizures. Ann. NY Acad. Sci. 559, 323-339

Stillwell W., Wassall S.R., 2003. Docosahexaenoic acid: membrane properties of a unique fatty acid. Chem. Phys. Lipids 126, 1-27

Strokin M., Sergeeva M., Reiser G., 2007. Prostaglandin synthesis in rat brain astrocytes is under the control of the n-3 docosahexaenoic acid, released by group VIB calcium-independent phospholipase A2. J. Neurochem. 102: 1771-1782

Stubbs C.D., Smith A.D., 1985. The modification of mammalian membrane polyunsaturated fatty acid composition in relation to membrane fluidity and function. Biochim. Biophys. Acta 779, 89-137

Tapiero H., Ba G.N., Couvreur P., Tew K.D., 2002. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. Biomed. Pharmacotheraphy 56, 215-222

Tassoni D., Kaur G., Weisinger R.S., Sinclair A.J., 2008. The role of eicosanoids in the brain. Asia Pac. J. Clin. Nutr. 17, Suppl. 1, 220-228

Todorovic S.M., Jevtovic-Todorovic V., Meyenburg A., Mennerick S., Perez-Reyes E., Olney J.W., Zorumski C.F., 2001. Redox modulation of T-type calcium channels in rat peripheral nociceptors. Neuron 31, 75-85

Tsakiridou E., Bertollini L., de Curtis M., Avanzini G., Pape H.C., 1995. Selective increase in T-type calcium conductance of reticular thalamic neurons in rat model of absence epilepsy. J. Neurosci. 15, 3110-3117

van der Stelt M., Trevisani M., Vellani V., De Petrocellis L., Schiano Moriello A., Campi B., McNaughton P., Geppetti P., Di Marzo V., 2005. Anandamide acts as an intracellular messenger amplifying Ca^{2+} influx via TRV1 channels. EMBO J. 24, 3026-3037

van der Vusse G.J., Reneman R.S., van Bilsen M., 1997. Accumulation of arachidonic acid in ischemic/reperfused cardiac tissue: possible causes and consequences. Prostagland. Leuk. Essent. Fatty 57, 85-93

Vreugdenhil M., Bruchl C., Voskuyl R.A., Kang J.X., Leaf A.C., Wadman W.J., 1996. Polyunsaturated fatty acids modulate sodium and calcium currents in CA1 neurons. Proc. Nat. Acad. Sci. USA 93, 12559-12653

Wainwright P.E., 2002. Dietary essential fatty acids and brain function: a developmental perspective on mechanisms. Proc. Nutr. Soc. 61, 61-69

Whelan J., 2008. (n-6) and (n-3) polyunsaturated fatty acids and the aging brain: food for thought. J. Nutr. 138, 2521-2522

Willis L.M., Shukitt-Hale B., Joseph J.A., 2009. Dietary polyunsaturated fatty acids improve cholinergic transmission in the aged brain. Genes Nutr. 4, 309-314 (on-line; DOI10.1007/s12263-009-0141-6)

Yehuda S., Rabinovitz S., Carasso R.L., Mostofsky D.I., 2002. The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. Neurobiol. Aging 23, 843-853

Xie L., Innis S.M., 2008. Genetic variants of the FADS1 FADS2 gene cluster are associated with altered (n-6) and (n-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. J. Nutr. 138, 2222-2228