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Docosahexaenoic Acid (DHA), in the Prevention and Treatment of Neurodegenerative Diseases

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1. Introduction

The scientific and technological development observed since the late nineteenth century until nowadays has caused a significant increase in the life expectancy of the population, being people over 65 a significant and yearly increasing 15% of the population (Szymański et al., 2010). As result, the increase in the life expectancy has also increased the prevalence of diseases associated to ageing, especially neurodegenerative diseases such as Alzheimer's disease, Multiple sclerosis and Parkinson's disease (Habeck et al., 2010). These diseases, besides its increasing with age, are also associated to the socioeconomic status, work and physical activity, family history and genetic, and in the last two decades, the nutrition has also aroused as a relevant factor (Stampfer, 2006). In this sense, there is general consensus that a healthy diet may prevent the development of many diseases such as obesity, hypertension, diabetes mellitus, stroke, certain kinds of cancers and now neurodegenerative diseases (Massaro et al., 2010). Epidemiological evidences suggest that populations having a significant consumption of fish, a food rich in n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA), show lower incidence of neurodegenerative diseases (Tully et al, 2003). n-3 LCPUFA, especially docosahexaenoic acid (DHA, C22: 6 Δ 4, 7, 10, 13, 16, 19; n-3), play a fundamental role in the development and preservation of the nervous system, and in the recent years solid evidences of their involvement in the prevention and/or eventually in the treatment of neurodegenerative diseases have appeared (Ikemoto et al., 2001). In neuronal tissue DHA is found in high concentrations, especially in the phospholipids of neuronal and glial membranes. However, as ageing progress and during the development of neurodegenerative diseases, a significant reduction in the DHA content of the brain is produced (Tully et al., 2003), especially in the cortex, cerebellum and hypothalamus, which result in a considerable reduction in the fluidity of neuronal membranes and an alteration of the neuronal homeostasis (Sodeberg et al., 1991; Kalminj et al., 2004). Beyond the effect of DHA at the neuronal membranes, the fatty acid also exerts other protective effects which are mediated by a metabolic derivative named neuroprotectin D-1 (NPD-1) which may protect neurons against oxidative stress, inflammation, disruption of the cytoskeleton and from the activation of apoptotic signaling pathways (Bazan, 2009). NPD-1, formed from DHA, is normally present in the nervous system, especially in the brain, but it is especially relevant

in states and/or situations that may compromise the activity, integrity and neuronal viability, as it is the case of neurodegenerative diseases, brain injury by ischemia – reperfusion, leukocyte infiltration and activation of proapoptotic signaling pathways (Bazan, 2009; Belayev et al., 2009). In this context, NPD-1 has anti-inflammatory, antiapoptotic and even neuroregenerative effects, which would help to preserve in general, both the neuronal functioning and the nervous system (Reinoso et al. 2008). A significant reduction of the neuronal DHA content is produced during the developing of neurodegenerative diseases. This reduction, which is not only produced by dietary factors, (i.e. low intake), it is also produced by metabolic process such as increased DHA metabolism and/or oxidation (Tully et al., 2003). The greatest evidence about the neuroprotective effect of DHA has been observed in Alzheimer's disease. DHA may suppress the cytotoxic effects of the accumulation of the β -amyloid peptide, being the main mechanism associated to the neuroprotective action of the fatty acid (Bazan, 2009; Reinoso et al., 2008). Facing this evidence, it is reasonable to consider the beneficial effect of increasing the consumption of DHA by eating foods rich in the fatty acid, such as fatty fish or DHA containing supplements. This chapter reviews the neuroprotective effects of DHA in the context of the brain ageing and some neurodegenerative diseases. It is also suggested to promote the consumption of food and/or supplements rich in DHA, as an effective strategy for preserving the brain function during ageing and especially to prevent the incidence, or to delay the onset of neurodegenerative diseases.

2. DHA and brain physiology

DHA is a LCPUFA with six double bonds, which belong to the series or family of the n-3 polyunsaturated fatty acids (Figure 1). It is relevant that DHA is the most unsaturated fatty acid in our organism and is found specifically concentrated in the brain, retina and sperms of higher animals (Uauy et al., 2001). DHA, when provided by the diet, comes mainly from marine organisms such as fish (fatty or blue species), shellfish, and algae (Horrocks et al., 2004). The first report of a deficiency of n-3 fatty acids was documented in 1982, which described the case of a six years girl, who received parenteral nutrition without the addition of n-3 fatty acids for five months after intestinal surgery (Holman et al., 1982). After the nutritional intervention, the girl presented low plasma DHA levels, dermatitis associated with neurological symptoms including neuropathy, blurred vision and psychological disturbances, which suggested an important role of n-3 LCPUFA, especially DHA, in the nervous system functions. In fact, it is now accepted that DHA is the most important n-3 LCPUFA in the formation of neuronal plasma and synaptosomal membranes (synaptic vesicles), especially in the brain (McNamara & Carlson, 2006). DHA amounts approximately 30-40% of fatty acids of the phospholipids forming the gray matter of the cerebral cortex and retinal photoreceptors (Carlson, 2002). The most important growing of the brain in humans is produced during the third trimester of fetal development and in the first two years of life. It is during these periods that the requirements of n-3 and n-6 LCPUFA are roused considerably, especially the requirements of DHA and arachidonic acid (AA, C20: 4 Δ 5, 8, 11, 14; n-6). Animal studies have shown that the reduced availability of DHA during the perinatal period is associated with deficits in the establishing of neuronal networks, and also with multiple expressions of synaptic pathologies, including deficits in serotonin neurotransmission and alterations in the mesocorticolimbic dopamine pathway, neurocognitive deficits, and a greater anxious behavior, aggression, depression and

decreased visual acuity (McNamara & Carlson, 2006). Similar problems have been observed in preterm primates and humans, which may be reversed after n-3 LCPUFA supplementation. DHA intake remains also essential after the end of the brain development. It is required to maintain the normal brain functions, including synaptic plasticity, neurotransmission and visual function (McCann & Ames, 2005).

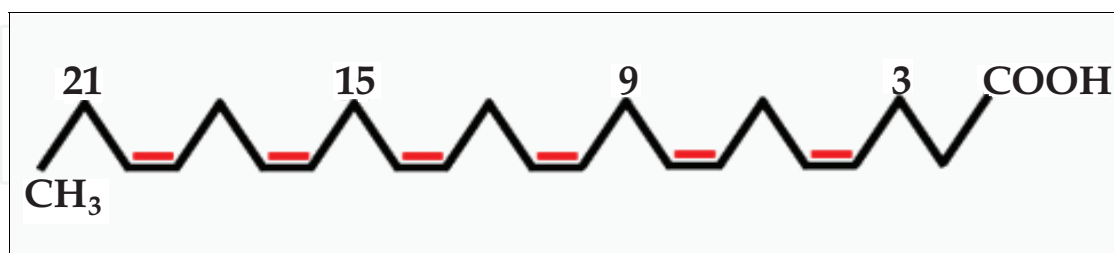


Fig. 1. Molecular structure of docosahexaenoic acid (DHA)

3. DHA and brain metabolism

Due to lack of enzymes necessary for neuronal de novo synthesis of DHA and AA, these fatty acids must be obtained preformed directly from the diet, or be synthesized from their precursors, α -linolenic acid (ALN, C18: 3 Δ 9, 12, 15; n-3) for DHA, and linoleic acid (LA, C18: 2 Δ 9, 12, n-6) for AA (Williard et al., 2001). This synthesis is carried out mainly in the liver and to a lesser extent in the cerebral endothelium by the astrocytes, which may export these fatty acids to the neurons (Lesa et al., 2003, Kalant & Cianflone, 2004). Although it is still under discussion how these fatty acids (ALN, LA) can cross the blood-brain barrier, it has been demonstrated that they may diffuse through the phospholipids of neuronal membranes (McCann & Ames, 2005). Other evidences suggest that some membrane proteins may facilitate the transport of ALN and/or DHA through the hematoencephalic barrier. One of these transporters has been identified as a caveolin binding protein type or CD36 (Williard et al., 2001 ; Lesa et al., 2003). However, plasma levels of LCPUFA are poorly correlated with the dietary intake of the precursors (Kalant & Cianflone, 2004). In fact, in healthy individuals, Δ 5- and Δ 6-desaturases, the key enzymes in the conversion process of LA to AA and ALN to DHA, are only induced in the absence of precursors and suppressed when the intake of the precursors (LA and ALN) is sufficient (Kalant & Cianflone, 2004). In contrast, the Δ 6-desaturase activity appears to decrease with age, as has been demonstrated in rodent models (Cho et al., 1999; Hrelia et al., 1990). The reduction of the activity of this enzyme could be significantly important during ageing, considering that the elderly shows low tissue levels of DHA, especially when the intake of ALN is chronically low (Strokin et al., 2006; Kalmijn et al., 1997). This situation could lead to profound alterations in the metabolism of the nervous system, especially in the density of the synaptosomes and/or in the release of neurotransmitters, as suggested from studies carried-out in the nematode *Caenorhabditis elegans* deficient for the enzyme Δ 6-desaturase (Lesa et al., 2003). DHA is present in the phospholipids of neuronal membrane predominantly at the sn-2 position; therefore the incorporation of DHA in membrane phospholipids depends of the cycle deacylation - reacylation which occurs at the sn-2 position (Serhan et al., 2008). In rodent brains, this cycle has significant activity (Rapoport et al., 2001) and is dependent directly on the specific activities of the enzymes acyl-CoA synthetase (ACS) and phospholipase A2 (PLA2). ACS performs the activation process by binding the fatty acid to CoA, which is an

ATP-dependent reaction. Once activated, the fatty acids can be incorporated into phospholipids. ACS isoenzymes 3, 4 and 6 are specific to LCPUFA, and in the brain the ACS 6 isoform is specific for the acylation of DHA (Marszalek et al., 2005). At present, there is not sufficient background about the type of phospholipase that participate in the release of DHA from phospholipids. However, it has been established that in astrocytes the release of DHA involve a mechanism dependent of ^{2+}Ca but independent of PLA2 (Strokin et al., 2003). The role of PLA2 in neurons has not been clearly demonstrated, but a study in the hippocampus of rats, indicated that the enzyme may be of fundamental importance in the release of DHA in neuronal tissue (Strokin et al., 2006). Figure 2 shows a proposal of how DHA may be incorporated into the phospholipids of neuronal membranes.

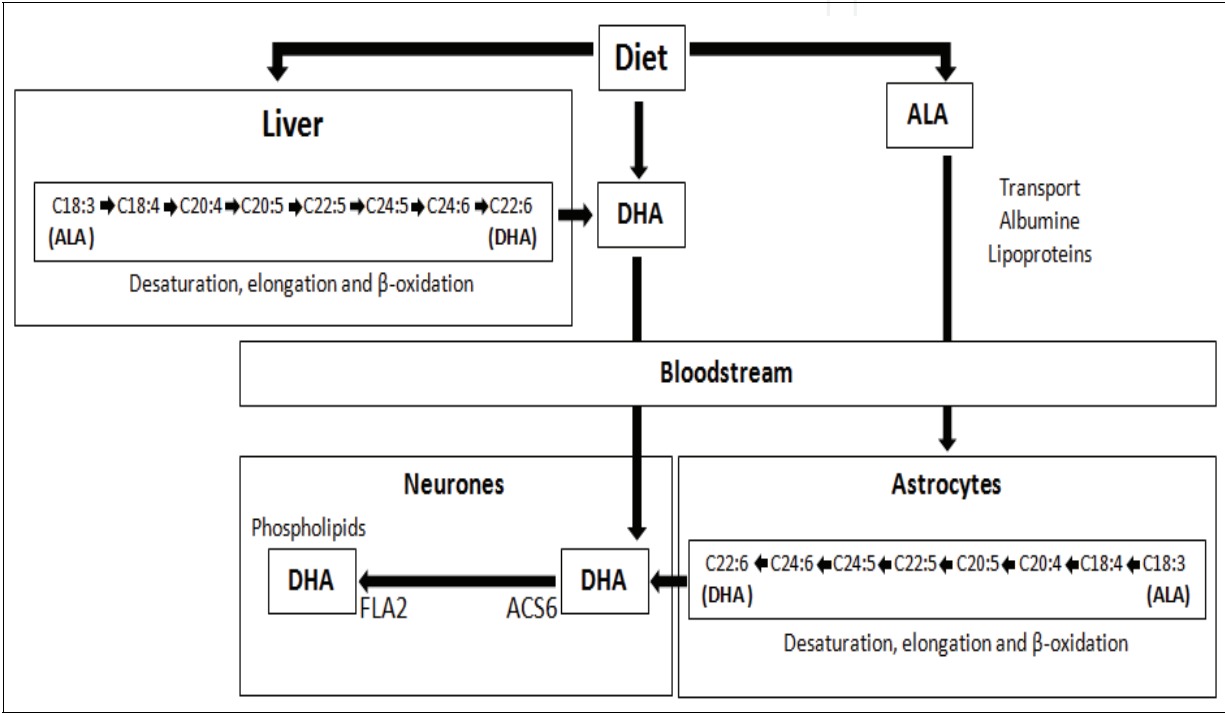


Fig. 2. Incorporation of DHA into the phospholipids of neuronal membranes

4. DHA and brain ageing

The presence of high concentrations of DHA, especially in the phospholipids of neuronal membranes, has been encouraged for more than 30 years the research about the roles of DHA in the nervous system. The evidence has demonstrated that during the embryonic stage and the first years of life, DHA plays a key role in the growth and development of the nervous and visual systems, actively participating in the processes of neurogenesis, neuronal migration, myelination and synaptogenesis (Uauy et al., 2001), thus directly impacting on cognitive development, visual, auditory, and in the memory and learning capabilities (McNamara & Carlson, 2006). As result of these observations, it is now strongly recommended to increase the consumption DHA during the pregnancy and childhood, in order to ensure the proper development of the nervous and visual systems (Uauy et al., 2001). The close relationship between DHA and the developing of the nervous system, encouraged investigators to study what happens with this fatty acid during ageing. It was observed that as the individual ages, the content of DHA in neural tissue is significantly

reduced, being even greater this decrease in the population that develops neurodegenerative diseases (Sodeberg et al., 1991). This significant reduction may be caused either, by a lower intake of the fatty acid or of its metabolic precursor and/or by an increased in the cellular utilization of DHA (Jicha & Markesbery, 2010). DHA plays a relevant role in the preservation of both the histology and physiology of the neuronal tissue as the individual ages, by preserving the nervous system functions among which memory and learning are the most remarkable (Lukiw & Bazan, 2008). Several epidemiological studies have strongly established that a higher intake of foods rich in DHA (fatty fish and/or nutritional supplements based on fish oils or microalgae) is highly correlated with a lower risk of developing neurodegenerative diseases (Kalmijn et al., 2004; Kalmijn et al., 1997), which is also associated with a clinical history indicating that patients with neurodegenerative disease have significantly lower levels of DHA in plasma and brain (Tully et al., 2003; Sodeberg et al., 1991).

5. Neuroprotectin D-1 and neuroprotection

A relevant question about the attributed neuroprotective effects of DHA in ageing and especially against neurodegenerative diseases is referred as how this fatty acid exerts these effects at the molecular level. Their role in the fluidity of the neuronal membrane appears as one of the most relevant attributes (Saiz & Klein, 2001). In fact, up to day the classification of membrane fluidity is based on the level of DHA present in the phospholipids that form the membrane matrix (Stillwell et al., 2005). However, the higher fluidity that confers DHA to neuronal membrane is not sufficient to explain the neuroprotective effects attributed to the fatty acid. As result of multiple investigations, it has been established that acylation of DHA at the sn-2 position in the membrane phospholipids and the activity of PLA-2, are additional features of DHA, by itself, to achieve an additional neuroprotective action of the fatty acid against certain cytotoxic situations, as are neurodegenerative diseases (Stillwell et al., 2005; Brown & London, 2000). It is no casual that DHA is present mainly at the sn-2 position in the phospholipids of neuronal membranes (48% in phosphatidylcholine, 52% in fosfatidilserine and 20% in phosphatidylethanolamine) (Avelano & Bazan, 1983). It was the discovery of a number of bioactive compounds derived from DHA, called protectins and resolvins, which show cytoprotective properties that open the way to a better understanding of how DHA may exert at the molecular level its neuroprotective actions (Mukherjee et al., 2004). Among these bioactive DHA-derivatives, NPD-1 (protectin D1 or D1 neuroprotectin: 10R, 17S-dihydroxy-docosa-4Z, 7Z, 11E, 13E, 15Z, 19Z-hexaenoic acid), appears the most relevant neuroprotective agent (Serhan et al., 2008). NPD-1 is generated once DHA is released from the phospholipids by the hydrolytic action of PLA-2, where the enzyme 15 lipoxygenase initiate a complex process of lipooxidation, epoxidation and hydrolysis resulting in the formation of NPD-1 (Serhan, 2005). Figure 3 shows a diagram of the formation of NPD-1. NPD-1 may exert its neuroprotective function either through a receptor (as yet unidentified), which may act in an autocrine form and/or NPD-1, once formed, may be diffused to other neurons. The mechanisms involved in the neuroprotection afforded by NPD-1 may include: (i) inhibition of the expression of proinflammatory cytokines (TNF α and IL1 β), (ii) inhibition of the generation and neurotoxicity of β -amyloid peptides and Ab42 (iii) increased gene expression of antiapoptotic molecules (Bcl-2 and Bcl-xL), (iv) reduction in the gene expression of proapoptotic molecules (Bax and Bad) and (v) increased neuronal antioxidant potential (Chu Chen & Bazan, 2005). Moreover, inflammatory

cytokines and oxidative stress may activate the synthesis of NPD-1 (Aksenov & Markesbery, 2001).

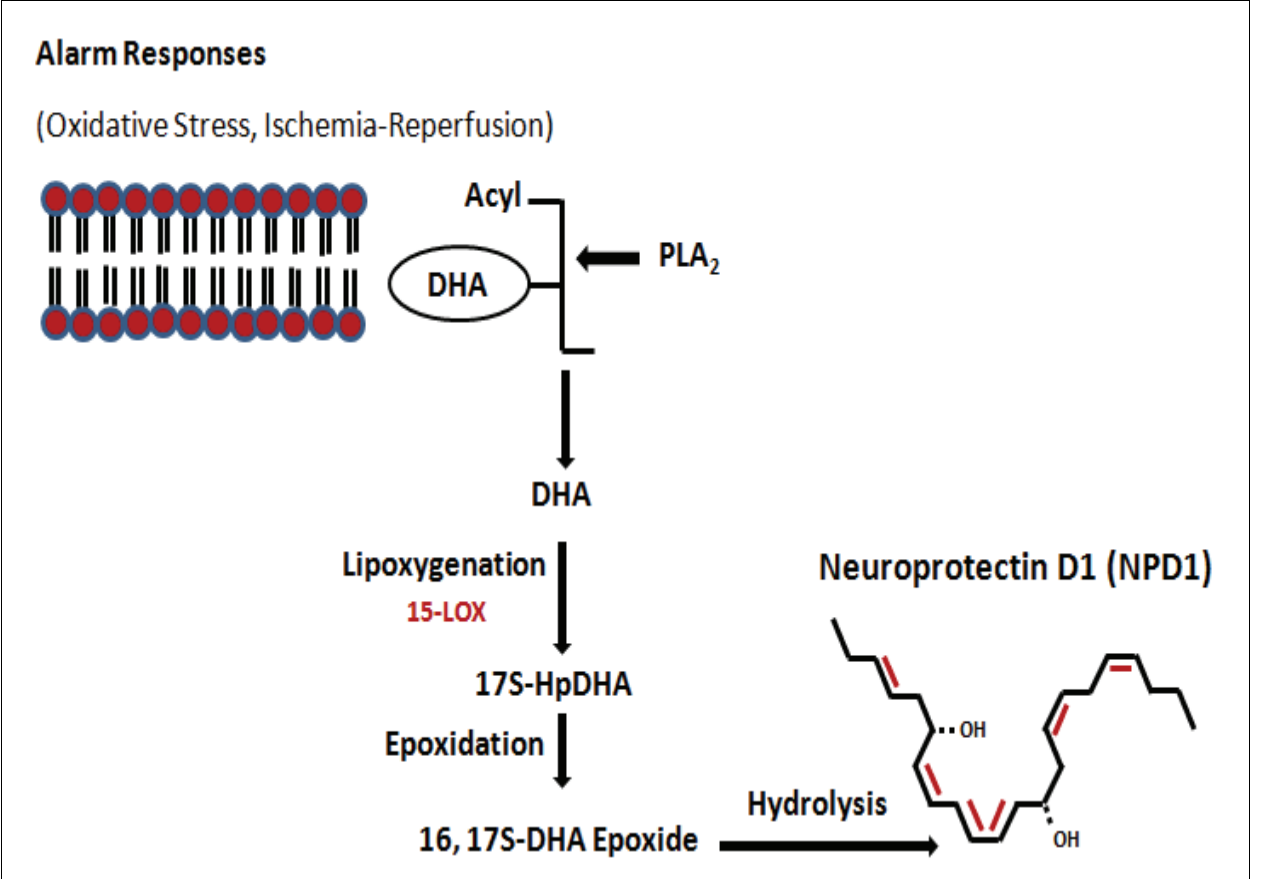


Fig. 3. Biosynthesis of Neuroprotectin D-1 (NPD-1)

6. DHA and neurodegenerative diseases

Several epidemiological, clinical and basic-experimental studies have demonstrated the beneficial effects of n-3 LCPUFA against various diseases, among which; cardiovascular disease (Hamer and Steptoe., 2006), some cancers (Gillet et al., 2011), inflammatory diseases such as rheumatoid arthritis (Kremer et al., 1990) and asthma (Yokoyama et al., 2000), neurological disorders such as schizophrenia (Laugharne et al., 1996), depression (Hibbeln & Salem, 1995), migraine (Wagner & Nootbaar-Wagner, 1997) and neurodegenerative diseases such as Alzheimer's disease (Morley & Banks, 2010), Multiple sclerosis (Mehta et al., 2009) and Parkinson's disease (Calon & Cole, 2007). The evidence of the beneficial effect of DHA has been clearly demonstrated mainly in neurodegenerative diseases.

6.1 DHA and Alzheimer’s disease

Alzheimer's disease (AD) is a progressive dementia that is early manifested by the loss of synaptic function and memory capacity of the individual. The number of patients who are diagnosed the neuropathological disorder has increased substantially in all countries, mainly in those where has been produced an increase in the life expectancy. In fact, it is

estimated that about 5% of the population that borders 65 is affected by AD. The prevalence of the disease doubles every 5 years over 65 years (Cummings, 2004), and many studies suggest that almost half the population up to 85 years show symptoms related to the disease (Nussbaum & Ellis, 2003; Forsyth & Ritzline, 1998). The presence of the β -amyloid peptide, which is associated with neurotoxic effects, is one of the characteristic expression of the molecular damage observed in patients (Hardy & Higgins, 1992; Yankner, 1996). Its origin occurs from the degradation (altered or incomplete) of the β -amyloid peptide precursor (APP) (Selkoe, 1994). A significant reduction in DHA levels, both in erythrocytes and in the brain, is observed in AD, specifically in the frontal lobe, and occipital and temporal cortex (Guan et al., 1994). It is also produced a replacement of DHA in phospholipids by saturated fatty acids (SFA) among which myristic acid (14:0), palmitic (16:0) and stearic acid (18:0) are the most frequent (Skinner et al., 1993). Thus, it is likely that changes in the ratio AGS/n-3 and n-6 LCPUFA could alter the neuronal function, especially at the membrane phospholipids, which in turn could result in neurological deficits. The altered fatty acid composition observed in the brains of AD patients could be caused by a deficiency in the LCPUFA transport from blood to the brain. It is remarkable that in patients with certain types of dementia or cognitive impairment it is observed the same reduction in the levels of n-3 LCPUFA, especially DHA (Kyle et al., 1999; Conquer et al., 2000). Interestingly, a decrease of DHA in plasma does not appear to be unique to AD, it is also common in the general cognitive impairment observed in ageing (Catalán et al., 2002). Many studies have demonstrated that a high intake of DHA is associated with a lower risk of AD, and in individuals diagnosed the disease, consumption of DHA result in a decrease in the progression of the characteristic symptoms, especially in relation to the cognitive impairment (Barberger-Gateau et al., 2002).

6.2 DHA and multiple sclerosis

In the case of multiple sclerosis (MS), the benefits associated with n-3 LCPUFA, especially DHA, have been shown in both the mental and physical disabilities. Evaluation of patients that has been supplemented with DHA indicates a significant improvement in the symptoms characteristic of the disease (Nussbaum & Ellis, 2003; Shinto et al., 2009). Some of these beneficial effects have been observed even in patients who consume a diet low in fat, but supplemented with n-3 LCPUFA of marine origin (fish oil). However, the evidence regarding a benefic in the progression of MS is not yet fully conclusive (Weinstock-Guttman et al., 2005). Considering the information currently available, it is not yet possible to establish a direct association between the consumption of n-3 LCPUFA and a lower incidence of MS, more studies are required on the issue (Weinstock-Guttman et al., 2005; Marcheselli et al., 2003). A study showed a relationship between reduced risk of this disease and the consumption of fish, but only among women (Nordvik et al., 2000). Currently, most hypotheses about MS suggest that n-3 LCPUFA would provide the molecules needed to rebuild the myelin sheath, which is severely affected in patients with this pathology. Dietary supplementation with n-3 LCPUFA helps to reduce the severity of MS in patients recently diagnosed the pathology and may delay the onset of symptoms. This is especially effective when supplementation is from marine oils along with vitamins and dietary professional counseling (Kelley, 2001). Perhaps the severity of the MS disease can be also reduced by modulating the immune response. Several studies have shown that a reduction in the dietary fat intake and changes in the relationship n-6/n-3 produce changes in the immune

response (Kew et al., 2003). The use of nutritional supplements rich in n-3 LCPUFA is associated with a reduced activity and plasma levels of circulating immune cells (lymphocytes, polymorph nuclear neutrophils and monocytes), including the reduction in the production of inflammatory mediators (Weinstock-Guttman et al., 2005; Nordvik et al., 2000). Moreover, a reduction in the intake of n-3 LCPUFA improves a number of indexes associated with the immune response, including lymphocyte proliferation, increased macrophage activity and cytokine production (Serhan et al., 2000). These records allow the suggestion of a protective role of n-3 LCPUFA in MS, which would lead to establish the potential of the use of n-3 LCPUFA as anti-inflammatory and neuroprotective in MS, although it remains a topic for further research.

6.3 DHA and Parkinson's disease

In contrast to AD, the relationship of fat intake and the risk of developing Parkinson's disease (PD) is very limited. Two studies have only established an association between high consumption of saturated fatty acids, low intake of n-3 LCPUFA and the increased risk to develop PD (Chen et al., 2003; de Lau et al., 2005). To date researchers have not been able to establish a direct association between low intake of n-3 LCPUFA and increased risk of developing PD. However, as in patients with AD, in the brains of people with PD it is also observed a significant decrease in the levels of n-3 LCPUFA, especially DHA (Johnson et al., 1999). Research in primates allow to observe a significant reduction in the extent of levodopa-induced dyskinesia (a damage model for the PD) in animals supplemented with DHA, which suggests that these effects would be mediated by the activation of retinoid X receptors (RXR) (Samadi et al., 2006). In addition, data from these investigations show a drastic drop in neural DHA levels (Julien et al., 2006; Breckenridge et al., 1973). Also, the dietary supplementation with DHA of animals reduced the neuronal damage produced by a characteristic PD-inducer agent, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Bousquet et al., 2008). Currently, the available information is not sufficient to establish a neuroprotective effect of DHA in the development of PD, being necessary to carry out more studies on the subject.

7. Dietary sources and intake of DHA

The metabolic precursor of n-3 LCPUFA, ALA, is found almost exclusively in land-based plant foods, such as nuts (walnuts 6%), chia seeds (*Salvia hispanica*) and flax seeds (*Linum usitatissimum*) and in some edible oils, such as soy (7 %), canola (11%), evening primrose (27%), chia (58%) and clary sage (60%). While, the already-formed DHA is found exclusively in marine foods, either of animal or vegetal origin, especially in fatty fish such as tuna, mackerel, menhaden, salmon, and some algae and microalgae. Unfortunately, the western consumption of ALA and DHA is very low, which has forced the development of nutritional supplements rich in DHA either from fish oils or microalgae, and also to add this fatty acid to foods such as vegetable oils, milk and derivatives. In this regard, in addition to the capsules containing fish oil or DHA concentrates which are very popular and available DHA can be also added to various foods such as dairy, dairy products, juices, beverages, bakery products, etc. The fatty acid may be provided in the form of triglycerides, phospholipids, and in pure form as ethyl esters (Valenzuela et al., 2006). Today, a wide variety of foods containing DHA are available from the retail and nutraceutical market.

8. Conclusion and perspectives

Neurodegenerative diseases may significantly alter the functioning of the nervous system, reducing both the number and function of neurons, which seriously affects the quality of life for those suffering these diseases. New strategies aiming to the prevention and/or the treatment of these diseases are of high priority. In this context DHA and its derivative NPD-1, emerged as a new perspective for the prevention and/or therapeutic management of these diseases, especially considering the social and economic devastation that neurological diseases may produce to the individual and the family. Future clinical research and nutritional interventions should be planned directly to establish the necessary doses of DHA needed to achieve significant beneficial effects, as well as to encourage the development and consumption of foods and/or supplements rich in this fatty acid. In this regard, the development of functional foods and/or nutraceuticals containing DHA at different concentrations is an alternative that the pharmaceutical and the food industries should consider very seriously (Valenzuela et al., 2009). To day the increase of the consumption of fish or seafood appear as not entirely feasible, due to the massive depredation of the resource, which has decreased its availability and consequently has increased the price of the products from the sea. Perhaps, in the future the increasing activity of the aquaculture may offer a viable alternative to improve the general consumption of n-3 LCPUFA to the western population and helping to prevent the early onset of neurodegenerative diseases.

9. Acknowledgment

The authors are grateful from FONDECYT and INNOVA-Chile the support of their research.

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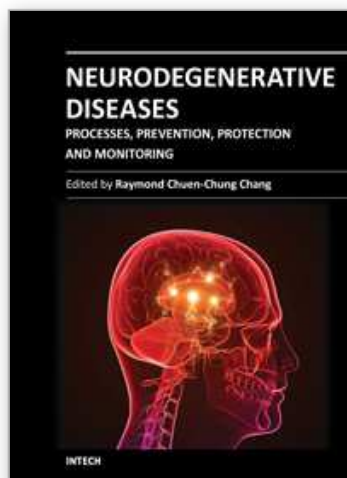
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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

Edited by Dr Raymond Chuen-Chung Chang

ISBN 978-953-307-485-6

Hard cover, 558 pages

Publisher InTech

Published online 09, December, 2011

Published in print edition December, 2011

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

How to reference

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Rodrigo Valenzuela B. and Alfonso Valenzuela B. (2011). Docosahexaenoic Acid (DHA), in the Prevention and Treatment of Neurodegenerative Diseases, Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring, Dr Raymond Chuen-Chung Chang (Ed.), ISBN: 978-953-307-485-6, InTech, Available from: <http://www.intechopen.com/books/neurodegenerative-diseases-processes-prevention-protection-and-monitoring/docosahexaenoic-acid-dha-in-the-prevention-and-treatment-of-neurodegenerative-diseases>

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