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Docosahexaenoic acid (DHA), a fundamental fatty acid for the brain: New dietary sources

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ABSTRACT

Docosahexaenoic acid (C22: 6n-3, DHA) is a long-chain polyunsaturated fatty acid of marine origin fundamental for the formation and function of the nervous system, particularly the brain and the retina of humans. It has been proposed a remarkable role of DHA during human evolution, mainly on the growth and development of the brain. Currently, DHA is considered a critical nutrient during pregnancy and breastfeeding due their active participation in the development of the nervous system in early life. DHA and specifically one of its derivatives known as neuroprotectin D-1 (NPD-1), has neuroprotective properties against brain aging, neurodegenerative diseases and injury caused after brain ischemia-reperfusion episodes. This paper discusses the importance of DHA in the human brain given its relevance in the development of the tissue and as neuroprotective agent. It is also included a critical view about the ways to supply this noble fatty acid to the population.

1. Introduction

Strong and wealth information have been accumulated about the essentiality of n-6 and n-3 fatty acids since the first studies of George and Mildred Burr in the late 1920s, demonstrating the importance of lipids in the growth and development of the rat [1]. In the mid-1960s, Hansen et al., regarded the essentiality of linoleic (C18: 2n-6, LA) and alpha-linolenic (C18: 3n-3, ALA) fatty acids [2]. Later, the reports from Bang and Dyerberg demonstrated the cardio protective role of n-3 long-chain polyunsaturated fatty acids (C20-22; n-3, LCPUFA) from marine origin [3]. Then, research from Bazan and Joel identified that docosahexaenoic acid (C22: 6n-3, DHA) and arachidonic acid (C20: 4n-6, AA) are accreted in significant amounts into the brain tissue [4,5]. Up to day, multiple and robust experimental, clinical and epidemiological evidence have been established about the health and nutritional importance to humans of polyunsaturated fatty acids (PUFAs), especially those of long-chain (20 or more carbon atoms) [6,7]. It is in this context that in the last three decades, one of these fatty acids, DHA, has acquired special interest for researchers due to their unique physicochemical characteristics and from the biochemical and physiological effects resulting from the presence of the fatty acid at cellular membranes [8]. DHA is of particular interest due to its highly unsaturated structure (six double bonds, being the fatty acid most unsaturated in our body) and cell location, which is mostly concentrated at the sn-2 position of phospholipids forming cell membranes, thus providing a great fluidity to these structures [9].

DHA is almost exclusively present in significant amount in diverse seafood (fish, shellfish, micro- and macroalgae and even some mammals). Precisely, it has been proposed that was the incorporation of these seafoods to the human nutrition which marked a significant turning point in human evolution [10], a process that was characterized by the increase in size and complexity of the brain tissue and by the development of mental, behavioral and motor skills with strong cognitive components [11]. Additionally to the evolutionary importance of DHA for our specie, its relevance is magnified during pregnancy and the early stage of childhood where the fatty acid plays a crucial role in brain and retinal development [12], and function, directly affecting the cognitive function [13] and the visual acuity of child [14]. Along with the benefits for brain and visual development, which transform DHA into an essential fatty acid in the perinatal period, most recently several studies have demonstrated a neuroprotective role for the fatty acid, specifically during aging and in neurodegenerative diseases and brain

Abbreviations: LA, linoleic acid; ALA, alpha-linolenic acid; PUFA, polyunsaturated fatty acids; LCPUFA, long-chain polyunsaturated fatty acids; DHA, docosahexaenoic acid; AA, arachidonic acid; NPD-1, neuroprotectin D-1; TNF – α, tumor necrosis factor-alpha; IL-1β, interleukin 1-beta; EPA, eicosapentaenoic acid; IL-6, interleukine; PCBs, polychlorinated biphenyls

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ischemia-reperfusion episodes [15,16]. It is now accepted that neuroprotectin D-1 (NPD-1), a structural derivative of DHA, shows significant neuroprotective actions, particularly in the preservation of the structure and physiology of neurons and glial cells [17]. This paper reviews the current information, from different backgrounds, supporting the importance of DHA for humans, particularly in brain development and in the neuroprotective properties of the fatty acid, as well as how to get a sustainable way to increase the consumption of DHA by the population.

2. DHA, diet and evolution

The strong evidence supporting the crucial role of DHA in the evolution of our specie, mainly on the growth and physiology of the central nervous system [18,19], was obtained by studies from fossils indicating that the turning point in human evolution was precisely produced after early humans began the consumption of seafood, mainly fish, shellfish, some mammals and algae [20,21]. It is estimated that late archaic humans (*Neanderthals*) consumed protein from terrestrial hunted animals or from the remains let by other hunters such as, wolves, hyenas and big cats. These foods contained very low fat and were also very low in n-3 LCPUFA, in contrast to the significant consumption of marine-derived foods by the considered modern humans (from the second half of the upper Paleolithic period) [22], which supplied significant fat high in n-3 LCPUFA. The inclusion of seafood in the diet was coincident with the advent of the first cultures that produced ceramics, textiles and tools and practicing personal ornamentation and decoration of their cemeteries, skills which later led to the origin of people which formed the first Asian and Mediterranean civilizations [11]. Based on this background authors such as Crawford, Cunnane and others researchers [22–25], proposed a direct link between diet and brain size, specifically on how the usual inclusion of seafood in the diet allowed the expansion of the gray matter in the brain cortex. This evolutionary process characterized as encephalization was very limited and slow for *Australopithecus* and similar hominids but reached an exponential growth in the last 200,000 years, particularly in the stage were the *Homo erectus* was evolved to *Homo sapiens* [24]. Actually the human brain, compared with other species (42 species in total) [25], has the highest amount of DHA (35–40% of total polyunsaturated fatty acids) and this fatty acid is mainly located at the phospholipids forming the neuronal membranes and the retina [25,26]. A particular aspect of the growth of the human brain associated with the intake of food from marine origin, when compared to other species, is the size of the tissue with relation to the body size [24]. In contrast, in other studied mammals, the brain size decreases logarithmically with the increase of the body size [24–26].

The capacity of human brain for the biosynthesis of DHA from its precursor ALA is very low. It has been estimated that less than 1% of ALA consumed is converted into DHA [5], enzymatic process that occurs mainly in the liver [5]. This limitation introduces a metabolic inability to ensure an adequate supply of DHA to the brain, which was probably limiting at a particular time in our evolution [27]. This fact strengthens the hypothesis about the importance of the inclusion of seafood in the diet of our ancestors and its relation to the significant increase of the cortex and the total brain volume and mass, with the subsequent development of language and the first tools used by humans [26,27]. Living near the sea and/or lakes allowed hominids a wide access to a variety of seafood, less complex and easy to digest than terrestrial animal food and requiring less preparation for consumption compared to red meat, which probably ensured an adequate supply of high quality nutrients, mainly proteins, energy and n-3 LCPUFA [26].

3. DHA and brain development

As discussed above, DHA is the most abundant n-3 LCPUFA in the central and peripheral nervous system, representing the major proportion of PUFAs in brain and retina. This fatty acid is present in large amounts in phospholipids of brain gray matter [28]. DHA takes an important role in neurogenesis and synaptogenesis, particularly in fetal development and during the first two years of life [26]. Fetal DHA accretion occurs actively along pregnancy but is most active during the third trimester as has been demonstrated after the supplementation of pregnant women with fish oil (200 mg DHA/day) where it was also observed that DHA supplementation during pregnancy limited the decline in maternal DHA status during the last trimester [29]. For this reason the nutritional status of DHA for the pre-gestational mother and during pregnancy and lactation represents a critical step for the brain and visual development of her child [30,31]. Neonates with higher concentrations of DHA in umbilical plasma phospholipids have longer gestational length in comparison to neonates with low concentration [32]. A study in women with less than 20 weeks of pregnancy who received 600 mg DHA/day, demonstrated a significant reduction of preterm delivery and low-weight birth with good tolerance to supplementation and no adverse effects [33]. As many other studies, this protocol demonstrated that DHA supplementation improves the nutritional status of the fatty acid both in the mother and her child because the efficient transfer of the fatty acid through the placenta [34], by the increase of DHA levels in maternal milk [35] and in the phospholipids of umbilical cord blood during lactation [36]. This supplementation should be most relevant for mothers having low ingestion of marine foods [37]. It was demonstrated that DHA supplementation during pregnancy increases the expression of fatty acid transport proteins and consequently increases the transport of n-3 LCPUFA through the placenta and to fetal the blood [38]. Pregnant women, who consumed fish oil rich in DHA (2.2 g DHA/day), from the 20th week of pregnancy until the partum, with no adverse effects, delivered children who showed significant better visual and coordination capacity [39]. Similar results were obtained after the supplementation of mothers with 500 mg DHA/day along the pregnancy, which was associated with high blood DHA levels and better cognitive development evaluated at 5.5 year-old of child [40]. When DHA supplementation also included 5-methyltetrahydrofolate supplementation (400 µg/day) cognitive benefits were prolonged until 6.5 year-old [41].

It has been demonstrated that high plasma levels of DHA in the mother and particularly in breast milk, directly correlate with the better growth and development of the brain and visual system in children [42,43]. Regarding this observation, a multivariate analysis showed that a lower intake of DHA during pregnancy increases the risk of reduced visual acuity in children [44,45]. Accordingly, it has been proposed that the intake of DHA during pregnancy would predict a better visual development in infants [44]. These findings have corroborated that supplementing mother's diet with DHA during pregnancy and lactation, or consumption of formula enriched in DHA, helps to increase the tissue levels of DHA in the infant with a better visual and neurological development [44], favouring in term child a better retinal development and function [46]. Conversely, during pregnancy and/or lactation a diet low in n-3 LCPUFA may have direct implications for the visual and neurological development of the child [47,48]. An example of this effect is that infants fed breast milk poor in DHA (less than 0.17% of total fatty acids, usually woman milk contains 0.3–0.4% DHA) show lower DHA levels in erythrocytes, reduced visual acuity and reduced language development at 14 months post-partum compared to infants fed breast milk containing 0.36% DHA [12,31]. A study in pregnant women who received supplementation of DHA (400 mg/day) from the sixteenth week of pregnancy until the delivery, showed a significant increase in visual acuity, particularly in newborns males, establishing that DHA supplementation possibly is the best predictor for this indicator of nervous system development [49]. Several studies have established a direct relationship between higher erythrocyte DHA levels (in mother and children) and the best visual and neuronal development of children [50–52], which in the long-term has benefits in the development of cognitive and motor skills in these children [53]. Even, perinatal supplementation with DHA reduced the risk of lower scores