Neurochemistry International 89 (2015) 51–62

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Review

Essential role of docosahexaenoic acid towards development of a smarter brain

Kusumika Gharami [1], Moitreyi Das [1], Sumantra Das*

Neurobiology Department, Cell Biology & Physiology Division, Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Jadavpur, Kolkata, 700032, India

ARTICLE INFO

Article history:
Received 10 April 2015
Received in revised form
18 August 2015
Accepted 26 August 2015
Available online 28 August 2015

Keywords::
Brain development
Docosahexaenoic acid
Memory
Neurogenesis
Nutraceutic

ABSTRACT

Evolution of the high order brain function in humans can be attributed to intake of poly unsaturated fatty acids (PUFAs) of which the ω-3 fatty acid, docosahexaenoic acid (DHA) has special significance. DHA is abundantly present in the human brain and is an essential requirement in every step of brain development like neural cell proliferation, migration, differentiation, synaptogenesis etc. The multiple double bonds and unique structure allow DHA to impart special membrane characteristics for effective cell signaling. Evidences indicate that DHA accumulate in areas of the brain associated with learning and memory. Many development disorders like dyslexia, autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia etc. are causally related to decreased level of DHA. The review discusses the various reports of DHA in these areas for a better understanding of the role of DHA in overall brain development. Studies involving laboratory animals and clinical findings in cases as well as during trials have been taken into consideration. Additionally the currently available dietary source of DHA for supplementation as nutraceutics with general caution for overuse has been examined.

Contents

1. Introduction

Brain development is a continuous evolving process which begins from early fetal life and continues till reaching adulthood when myelinogenesis is mostly complete. Various genetic, physiological and environmental factors, during intrauterine life as well as after birth, ultimately, influence the development of the brain of an individual. Nutrition is, therefore, an essential requirement for

* Corresponding author. Neurobiology Division, Cell Biology & Physiology Department, CSIR-Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Kolkata, 700032, India.
E-mail addresses: sdas@iicb.res.in, sumantra00@gmail.com (S. Das).
[1] Joint first author.

http://dx.doi.org/10.1016/j.neuint.2015.08.014
0197-0186/

the morphogenesis of the brain of which the polyunsaturated fatty acids (PUFAs) play an important role.

The beneficial effects of the ω-3 PUFA, docosahexaenoic acid (DHA), in maintaining various bodily functions are well documented. Investigations on animals as well as epidemiological and clinical studies have revealed a plethora of information on the potential role of this ω-3 PUFA in various disease conditions like diabetes, cardiovascular disease, brain, kidney, liver and gastrointestinal disorders etc. (Halade et al., 2010; Hendrich, 2010; Holub, 2009; Scorletti et al., 2014; Tabbaa et al., 2013; Zhang et al., 2011). DHA also possesses demonstrable pro-apoptotic activity against a wide range of tumor cells and is being used as a supplement in cancer therapy (Merendino et al., 2013). The present review, has tried to focus on the role of ω-3 PUFAs in general and DHA in particular, on the various aspects of brain development. First, we have presented an overview of a link between ω-3 PUFAs and brain evolution. Then we have discussed the distribution and turnover of DHA in the brain. The transport of DHA from the placenta to the fetus is an important feature of intrauterine brain development, which has been addressed. We have also reviewed the literature on the role of DHA in the various stages of brain development and the developmental disorders linked with inadequate intake of DHA and ω-3 PUFAs with special mention of their role in memory and learning. Current information on the mechanism of action of DHA has been reviewed. Finally, we have briefly discussed the emerging view of the importance of DHA as nutraceuticals and its source in various forms of food.

2. DHA and brain evolution

A possible link of DHA with the large brain size in human stems from the series of evolutionary studies carried out by Trinkaus and coworkers. They observed that encephalization in the Neanderthals were smaller than in early 'anatomically modern' humans (Ruff et al., 1997). Direct isotopic evidence for Neanderthal and early modern human diets in Europe suggested the Neanderthals were top-level carnivores, having a similar diet through time in different regions of Europe and obtained all, or most, of their dietary protein from the red meat of large herbivores (Richards and Trinkaus, 2009). In contrast, in early modern humans, a number of individuals showed evidence for the consumption of aquatic (marine and freshwater) resources. This pattern includes Oase 1, the oldest directly dated modern human in Europe ($\approx$40,000 cal BP) with the highest nitrogen isotope value of all of the humans studied, likely because of freshwater fish consumption which contains mainly the ω-3 FAs Eicosapentaenoic acid (EPA) and DHA. That nutrition plays an important role in human evolution, is reflected from a number of studies. Marine and estuarine ecosystem had mainly provided the proper stimulus to hominid brain to develop into a relatively large and neurologically complex organ (Cunnane et al., 1993). Plentiful, easily harvested seafood rich in EPA and DHA, available in land–water interface, got included in the diet of early modern humans (Crawford et al., 1999; Crawford, 2002) coinciding with the rapid expansion of cerebral cortex and gray matter thus increasing intelligence, development of language and tool making ability (Broadhurst et al., 1998). Modern *Homo* spp. are believed to be originated in Africa and specially associated with lake shore (lacustrine) environments in the East African Rift Valley (Broadhurst et al., 1998).

3. DHA composition in brain

The brain is the fattiest organ in the body as nearly 60% of dry weight of brain is contributed by lipid. Interestingly, 35–40% of this lipid in brain is PUFAs, mainly the long-chain PUFAs Eicosapentanoic acid (EPA), DHA and Arachidonic acid (AA) (Steenweg-de Graaff, 2015; Singh, 2005). DHA constitutes about 15% of the fatty acids in the human frontal cortex (Carver et al., 2001) suggesting an inevitable role of this ω-3 fatty acid in brain. Additional evidences of increase in brain weight during the initial postnatal months have been attributed to the high levels of PUFA in cerebellum, occipital and frontal lobes of brain (Clandinin et al., 1980a) and suggest that early developmental period are more sensitive to DHA. Accumulation of DHA in central nervous system occurs during the developmental period depending on the availability of DHA from circulating plasma.

Although some synthesis of DHA occurs locally in the brain, it mainly depends on diet and biosynthesis in liver, the primary site for DHA biosynthesis. The precursor of DHA biosynthesis is α-linolenic acid (ALA) which cannot be produced in mammals and has to be derived from the diet. *In vitro* culture studies suggest that unlike neurons, astrocytes are capable of synthesizing DHA (Bernoud et al., 1998; Moore et al., 1991; Moore, 1994) which is again influenced by negative feedback loop for the availability of DHA, although some basic level of synthesis is continuous in all circumstances (Williard et al., 2001). Like astrocytes, cerebromicrovascular endothelial cells also elongate and desaturate the short chain fatty acids but final desaturation step is absent in them and they tend to cooperate with the astrocytes to synthesize DHA (Moore, 2001; Moore et al., 1990). However, neurons are the main site for DHA accumulation which is readily derived from the release from astrocytic membranes under both basal and stimulated conditions (Garcia and Kim, 1997; Kim et al., 1999). On the other hand, it is quite difficult to deplete DHA from the neuronal membrane in adult mammals (Kim et al., 1999) even by Ca^{++} independent phospholipase A2 (iPLA2) activity which cause release of DHA from astrocytes (Strokin et al., 2003). Studies have suggests that calcium-dependent cytosolic PLA2 (cPLA2) triggers the release of ARA from the synaptic membrane (Axelrod, 1990) whereas calcium-independent PLA2 (iPLA2) is mainly involved in the release of DHA from the neuronal cells and primary cultures of astrocytes (Strokin et al., 2003; Green et al., 2008). *In vitro* studies also confirm that the activity, protein, and mRNA of group VIA $iPLA_2$ isoform are downregulated in brains of ω-3 PUFA-deprived rats whereas other group like cPLA2 and sPLA2 are upregulated (Rao et al., 2007).

Like other FAs, non-esterified form of DHA is mainly transported to the brain (Purdon et al., 1997). It was initially thought that this free form of DHA, bound to albumin in the blood, very likely crosses the blood–brain barrier (BBB) (Spector, 1986). However recent evidences suggest that DHA crosses BBB via passive diffusion (Ouellet et al., 2009; Hamilton and Brunaldi, 2007). Recently, a new DHA transporter, Mfsd2 has been identified which also transports other FA in the form of lysophosphatidylcholine (LPC). Mfsd2a is expressed exclusively in endothelium of the blood–brain barrier (BBB) of micro-vessels (Nguyen et al., 2014) and individuals having Mfsd2a mutations in conserved residues exhibited a lethal microcephaly syndrome linked to inadequate uptake of LPC lipids (Guemez-Gamboa et al., 2015). Studies on Mfsd2a(−/−) mice demonstrate that genetic deletion of Mfsd2a lead to leaky BBB from embryonic stages which continued to adulthood although the normal patterning of vascular networks was maintained (Ben-Zvi et al., 2014).

Most investigations on the supply and turnover of DHA in the brain have been mainly carried out in adult animals. Using positron emission tomography and intravenous [1-(11)C]DHA, it has been shown that the DHA uptake rate is between 2.4 and 3.8 mg/day in the adult human brain which was equivalent to the net rate of DHA consumption by the brain (Umhau et al., 2009). Inside the brain, DHA is first esterified and incorporated in membrane phospholipid particularly phosphatidylethanolamine (PE) and phosphatidylserine