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Review Article

Role and Progress of DHA Dietary Supply in Brain Development of Maternal and Golden Periods

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ABSTRACT

Docosahexaenoic acid (DHA) dietary supplementation has highly increased in recent years. Sufficient DHA supplementation during gestation and early childhood is supremely clinical important. Some substantiation has been constructed for neurocognitive and brain benefits of supplementation with long chain polyunsaturated fatty acids (LC PUFA) such as DHA by the time before, during and after gestation. Acceptable in quality and quantity of DHA availability in the fetus and infant optimizes brain and retinal maturation development by affecting neurotransmitter pathways. DHA role as anti-inflammatory agent is significantly interceded over modulating of signaling pathways by directly binding to receptors or alteration in lipid raft formation and receptor presentation. Here, we intend to review the current progress on DHA supplementation, specifically brain development of fetus during pregnancy and infant, as a pharmacologic agent with both preventative and therapeutic endeavors. These findings provide benefits of routine DHA supplementation in pre-, during and post-gestation to improve neurodevelopmental outcomes in fetus, infant and early childhood. However, optimal composition of the supplement and dosing and treatment strategies still need to be determined toward advance nutrient for routine DHA dietary supply.

Key words: DHA, LC PUFA, brain development, supplementation

1. INTRODUCTION

Docosahexaenoic acid (DHA) is a structural component of membrane cells particularly in the central nervous system (CNS) [1]. DHA accumulation in the fetal brain occurs mainly during the last trimester of gestation and it will increase up to the end of the second year of life. Since the endogenous formation of DHA is relatively low, DHA intake may contribute to optimal brain development. The associations between DHA levels and brain development during the lifespan justify the indication of DHA role in differentiation to brain function for neuronal

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cell growth. Previous studies indicate that DHA may affect brain in early development in fetus, infancy and early childhood[2-4].

DHA is the most unsaturated fatty acid, it is known as a building block of mammalian tissue[5]. DHA is normally appointed 22:6ω3 or 22:6ω3, indicates that it has 22 carbon atoms and six double bonds[6]. More than 95% of PUFA in mammalian tissues have double bonds in a specific arrangement known as 'homoallylic'[7], where double bonds and methylene units (-CH_2-) alocate along the carbon chain[8]. Number of double bonds and the ω3 (omega-3) position in PUFA completely specify the position of every double bond in the molecule. Thus, DHA shows consistency with most other mammalian unsaturated fatty acids and PUFA due to its structure feature its double bonds in the cis configuration[9,10].

Moreover, DHA is found in relatively high concentrations in all neural tissue, specifically in the brain[1] and retina[11]. Early evidence showed that brain DHA concentration is highly constant across terrestrial species irrespective of the diversity of their natural diets, ranging over less than 50% [12,13]. In contrast, the liver in these same species have DHA concentrations that vary over 30-fold[13]. These observations are consistent with DHA supply as a limiting factor in adult brain size. More specifically, DHA's role cannot be completely replaced by the closest ω6 PUFA molecular homologue, docosapentaenoic acid (DPAω6, 22:5ω6), which is of identical structure to DHA with the exception of one missing double bond [14,15].

Although DHA can be synthesized from its ω3 precursor (ALA)[16], studies have shown that DHA from the maternal diet is more efficient in source of neural tissue DHA than in an equivalent amount precursor of ALA [17, 18]. Precursor ALA only 10% could be converted into DHA[19, 20]. DHA is one of the most variable fatty acids in human milk, its concentration being directly influenced by the amount of DHA in the maternal diet and parity[21] in which the reported level of DHA in breast milk (by weight) of total fatty acids within the range of 0.06–1.4% [22]. Current formula recommendations are between 0.2–0.5% DHA (g DHA/100 g of total fatty acids)[23,24].

Increasing attention over the last 20 years upon DHA in pregnancy and lactation for its role in brain development, as it accounts for over 10% of brain fatty acids is essential for infant brain development[25-28]. Infant brain doubles in weight, and the large brain to body weight ratio for infants (0.1) compared with adults (0.02) may put the infant at higher risk of deficiency in brain nutrients and energy[29,30]. To anticipate this condition, mother diets in DHA intake is recommended in corresponding to the formation of neural synapses which are rich in DHA, neurite outgrowth, dendritic complexity and neurotransmitter metabolism are also highly reliant on DHA[17,31,32]. This review will give wide aspects on role and progress of DHA dietary supply in brain development, especially in pre-conception, maternal and early childhood which is known as golden age period.

2. DHA BIOSYNTHESIS

Approximately sixty percent of the wet weight of the mammalian brain comprises lipids. Approximately 70% of the fatty acid amount is synthesize biochemically in mammalian cells, and 30% must be obtained from diet. Seafood, fish oils, and fortified foods are rich sources of ω3 polyunsatuated fatty acids (omega-3 (ω3) PUFAs: eicosapentaenoic acid (EPA), docosapentaenoic acid (DPAω3), and docosahexaenoic acid (DHA), as well as cholesterol[33]. DHA constitutes 14% of total fatty acids in the body and it is greatly concentrated in neuronal membranes and synapses[34-36]. Obviously, there are some evidence that DHA is required for neural and retinal cells that neither DPAω3 nor DPAω6 can replace it. In infancy period, DHA concentrations are much higher than DPAω3 in mother's breast milk and all tissues[37-41]. It might probably not entirely concurrent due to breast milk has a similar chemical structure of long chain PUFA as it is found in neural tissue, which is the most rapidly growing tissue during infancy period[42].

According to the general pathway of DHA biosynthesis, the major plant-based ω3 is a-linolenic acid (ALA). ALA is considered as a precursor of ω3 PUFA due to it is the only ω3 found in seed oils and plants in the modern food supply. The primary fate of dietary ALA is oxidation for energy; however, a variable fraction of ALA is converted by a series of desaturations and elongations to the long chain ω3 PUFA, finally resulting in DHA. Any of the intermediate ω3 PUFA can be converted to DHA as well[43,44], as shown in Fig. 1.

Fig 1: DHA Biosynthesis Pathways

Previous studies reported that, animal maintains costly metabolic and genetic mechanisms to biosynthesize DHA when it is not in the diet. Recent data indicate that neurons can perform synthesis of DHA[1,45,46]. However, DHA synthesis pathway appears to be very inefficient and essentially only results DPAω3 in adult people[19]. Mammalian biosynthesis of DHA is metabolically expensive[47]. Tissue DHA is ultimately acquired from the diet either as DHA itself or any of some ω3 PUFA which can be metabolically converted into DHA[48].

Literally, supplementation of ALA during pregnancy does not increase DHA in infant blood lipids[49]. Similarly, during lactation, ALA supplementation has no detectable effect on the amount of DHA present in human milk[50-52]. By adding high amount of ALA in infant formula also do not significantly increase the blood levels of DHA in formula-fed infants[53]. Thus, for both maternal and infant period, DHA diet supply is completely essential.

3. DHA ROLE IN PRECONCEPTION, MATERNITY AND AFTER BIRTH

DHA is essential structural building block of the CNS [54-57]. DHA is a greatly importance due to it is specifically concentrated in the structural membrane lipids of the brain and visual elements of the retina[54-57]. The human brain undergoes rapid growth during the first 2 years of life[58,59], which there is a 12-fold increase of DHA concentration in tissue. The amount of DHA in the brain is continually turned over, recycled, and replenished by uptake from blood plasma[60]. DHA accumulation is ~1.45 mg/day in infant brain while DHA turnover rate is ~3.75 mg/day[61]. The dietary requirement to compensate accretion and turnover is estimated around ~5.2 mg/day (1.45+3.75 mg/day)[62,63]. DHA intake is suggested from either DHA dietary supply or from the conversion of DHA from ALA (α-linolenic acid)[1].

As we know, the conversion of ALA to DHA in the body is very limited (<1%)[64-66]. To maintain homeostasis of DHA (5.2 mg/day) in the brain, over 200 mg/day of dietary DHA is needed (Fig.2), assuming that only 1.7% of performed dietary DHA reaches the brain [67-69] and the other source is provided from conversion of ALA to DHA[61]. Furthermore, earlier infant will need higher the level of DHA than maternal term, thus contributing the optimal neurodevelopment could be optimum[70-73].

Widely consensus statements recommend minimal diet is 200 mg per day of DHA for maternity and lactating women (Fig.2)[3,4]. In fact, many lactating women are only receiving around 25% of this recommended amount[13,39]. The breast milk DHA concentration was 4–6 times lower in the current baseline sample compared with those with the highest fish intake[18,43] and 1.5 times lower than the worldwide mean[18]. Supplementation was able to achieve a concentration similar (low dose) or slightly higher (high dose) than the worldwide mean, suggesting that supplementation is necessary for those with low dietary intake. Thus, DHA supplementation results in an increase in breast milk and maternal DHA at that levels would reflect adequate dietary intake and beneficially impact fatty acid ratios in infants important for brain development.

Fig 2: Recommended dietary DHA amount in preconception, maternity and after birth

4. DHA DIETARY SOURCES

The type of DHA sources may also affect neurocognitive function in infants and childhood. The majority of studies have considered both neurocognitive function and growth and development have used infant formulas for maternal and infant term that contain DHA obtained from DHA from fish oil [72,74], eggs[75,76] and micro algae have been considered. This is noteworthy for both maternal[77-80] and infant term[81,82]. These DHA sources genuinely important due to it has positive impact in neural growth.

Table 1: Source of Natural DHA from fishes, plants and marine organisms

Source of Fatty Acid (FA)	Total PUFA (g/100 total FA)	DHA (g/100 gtotal FA)	Energy g(kcal)	Reference
Fish				
Trout	1.831	0.52	128	[83]
Salmon	3.256	1.429	155	[83]
Catfish	0.636	0.136	89	[83]
Tuna	*N/A	0.223	N/A	[16]
Sardine	N/A	0.509	N/A	[16]
Plant				
Canola (Rapeseed)	30	0	540	[84]
Flaxseed	56.31	0	N/A	[85]
Corn oil	0.94	0	N/A	[44]
Marine organism				
Microalgae (*Crypthecodinium cohnii*)	51.8	27	N/A	[86]
Krill	N/A	7	N/A	[87]

***N/A: Not Available**

Fish consumption is considered as surrogate for omega-3 fatty acid consumption, which associates with cognitive outcomes in pregnant women [88,89]. Children from mothers with no seafood consumption were at greatest risk of adverse or suboptimal verbal IQ. Overall, consumption of more than 340 g seafood per week was beneficial for the child`s neurodevelopment.

The most available source of DHA is fish, especially marine fatty fish, thus food enriched with fish oil is excellent source. DHA is naturally found in human milk and now included in almost all commercially available infant formulas. In fetus, DHA and other LC PUFA is derived from the mother by placental transfer and after birth by the infant diet (human milk or formula). There is a specific transport mechanism for the placental transfer of DHA from the mother to the fetus[90]. The levels of DHA in human milk is increased by increasing maternal intake[52]. Human milk concentration of DHA vary widely and range from 0.17 to 0.99%, with the highest levels in Japanese milk and the lowest levels in Canadian and US samples [91]. However, only modest variations in ARA levels in human milk are observed (0.36-0.49%) across different populations[91].

Recent studies have shown that DHA status is influenced not only by diet, but also by genetic variants, single nucleotide polymorphisms (SNPs) in the fatty acid desaturates (FADS)[92-95]. The genetically explained variability of red blood cell DHA and ARA levels were very low (0.51% and 1.13%, respectively)[94]. Furthermore, the effect of FADS

genetic variants on LC PUFA metabolism, specifically ARA, appears to vary at the population level[96].

Moreover, there has been a trend in increased consumption of refined vegetable oils, such as soybean and canola, as the sources of good fat in the diet and subsequent decreased animal fat consumption. However, it has resulted in an overall increase in ω6 in the diet as well as decreased plant sources of ω3, including walnuts and flax, suggesting a greater importance for intake of DHA diet [97,98]. These dietary changes, taken together with the overall shift in available dietary fatty acids over the past several decades have resulted in a significant increase value in the ratio of ω6:3 fatty acids to 15–20:1, meanwhile ratios closer to 2–4:1 have been recommended for health[99-101].

ALA is practically the sole ω3 PUFA in plant foods, and it is found primarily in components of leafy foods such as lettuce, spinach, cabbage, and Brussels sprouts, particularly in dry climate regions[102]. Animal metabolism is therefore required to synthesize most DHA from plant foods that cannot be obtained from animal foods with preformed DHA[7]. Though DHA can be a predominant fatty acid in specialized tissue. Animal part other than the brain specifically provide only few DHA accumulation. Thus DHA diet in food consumption will provide at least 35% DHA which can be used for energy [24, 103].

5. CONCLUSION

In conclusion, the essential role of DHA in neurological development during the pre- and postnatal periods have been defined. Overall, evidence for the therapeutic advantages of LCPUFAs supplementation is strong. Of primary concern are the low levels of dietary DHA consumption in women of child bearing age from westernized countries and that sufficient quantities of DHA may not be available for optimal neurological development and/or immunological support to the developing infant. This is especially important in the preterm or small for gestational age infant. Clinical recommendations exist for pregnant and lactating women which should be focused on optimizing supplementation strategies to provide optimal outcomes for all childhood.

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