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Omega-3 fatty acids in mental and neurological development

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Abstract

Omega-3 fatty acids is composed of two common substances: docosahexaenoic acid (DHA 22: 6n-31) and eiocosapentaenoic acid (EPA 20: 5n-3) that have a significant effect from conception to the late stage of human existence by effect human development and survival. Its physiologic contribution to the human heart, eyes, brain and other cranial compositions has been researched for understanding the gravity of the substance's effects in human survival. As we have known from most previous studies that omega-3 participates in fetal development, however, researches nowadays emphasize the contribution of omega-3 to mental development particularly in promoting psychological stability and functionalities, and try to portray a significant association of DHA and EPA in certain neurological disorders e.g. dyspraxia, attention deficit hyperactivity disorder (ADHD). Moreover, current researches aim to comprehend the linkage between omega-3 and Alzheimer's disease and other related neurodegenerative disorders. Future researches should provide more information to understand and discover other possible linkages for curative treatment of the existing incurable diseases.

Keywords: Omega-3 fatty acids, DHA, EPA, mental, neurological development

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กรดไขมันโอเมกา 3 กับการพัฒนาจิตและประสาท

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**ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

บทคัดย่อ

ไขมันโอเมก้า 3 ประกอบด้วยกรด docosahexaenoic (DHA 22: 06 n - 31) และกรด eiocosapentaenoic (EPA 20: 05 n - 3) ซึ่งมีผลอย่างมากต่อมนุษย์ตั้งแต่การปฏิสนธิจนถึงการดำรงอยู่ของมนุษย์ โดยมีบทบาทในการพัฒนาทางร่างกายและจิตใจอย่างต่อเนื่อง ส่งผลต่อการพัฒนาการและการมีชีวิตอยู่รอด ไขมันโอเมก้า 3 มีส่วนสำคัญต่อการทำงานของหัวใจ, ตา, สมอง และองค์ประกอบอื่น ๆ บททบทวนวรรณกรรมนี้เน้นความสำคัญของโอเมก้า3, DHA และ EPA ต่อการพัฒนา และการทำงานของจิตใจ ในอดีตพบว่าไขมันโอเมก้า 3 ช่วยในการเจริญเติบโตของทารกในครรภ์ และต่อเนื่องจนถึงหลังคลอด แต่ปัจจุบันพบว่า DHA และ EPA มีความสัมพันธ์อย่างมีนัยสำคัญต่อความผิดปกติของระบบประสาท เช่น ทำให้กระบวนการเรียนรู้ที่เกี่ยวข้องกับการทำงานของระบบกล้ามเนื้อผิดปกติ (dyspraxia) และมีผลต่อโรคสมาธิสั้นในเด็ก นอกจากนี้ไขมันโอเมก้า 3 ยังมีความเชื่อมโยงกับโรคสมองเสื่อม รวมถึงความผิดปกติอื่นๆ ที่เกี่ยวข้องกับความเสื่อมต่างๆ ภายในระบบประสาท การวิจัยเพื่อความเข้าใจเกี่ยวกับบทบาท และความเชื่อมโยงต่อภาวะต่างๆ อาจนำไปสู่การรักษาโรคที่ไม่อาจรักษาให้หายขาดได้ในปัจจุบัน

Introduction

Omega-3 is essential for maintaining a healthy heart and developing a healthy brain during brain growth spurts particularly during perinatal period that development of cognitive function, mood, sensory system e.g. vision are some of the many explored brain benefits of omega-3[1, 2]. Eiocosapentaenoic acid (EPA 20:5n-3) and docosahexaenoic acid (DHA 22:6n-3) are 20- and 22-carbon members of omega-3 that are most beneficial for growth and heart function[3]. These substances are integrated structurally and functionally through phospholipid of cell membranes. The ongoing researches of DHA and EPA to human heart paved way to increase conscious curiosity in obtaining factual and modern usage and effects of the substance to the brain. This review article focused on effects of omega-3 (DHA, EPA) to mental and neurological development.

Literature Review

From the last trimester of pregnancy to the childhood period, development of brain undergoes a massive transformation known as the spurt in brain development[4]. During this period, it is compelling to provide a sufficient amount of DHA and EPA in order to produce a good neurological network or systems that will enhance a normally functioning network of neurons. It is established that DHA plays the major role in promoting sensory-motor, cognitive and conceptual development[2,5]. Moreover, this substance is one of the crucial elements in colostrum of breast milk[6].

The demand for DHA and EPA is significantly rising after birth due to progressing developmental brain. If a child is born prematurely, the demand of these substances is much greater because of various physiologic changes that should be compensated primarily. During childhood period, the demand mostly depends on the ability of the body's synthesis, lipid metabolism and intake of dietary milk formulas. However, it would be beneficial to encourage child taking breast milk that contains a plenty amount of DHA and EPA than mile formula[7].

DHA is one of the most abundant fatty acids in the human brain and it gradually decreases as human age[8]. A good source of these fatty acids comes from its precursor alpha-linoleic acid, or DHA or even EPA. It has been established that a lack of these substances lead to problems in brain biogenesis, genetic expression and development, oxidation process protection, and alteration in the process of neurotransmission[8]. However, a true linkage on how DHA and EPA directly affect the brain is still unclear particularly how they pass through the blood brain barriers (BBB) that allows nothing but glucose in blood [9].

Blood brain barrier serves as the regulator of the brain that protects neurological attribution from organisms and other substances except for glucose. For fatty acids, DHA and EPA pass through the BBB via the non-esterified pool (NEFA)[10] as a result of the competing states of hydrophobic albumin domain at the BBB's endothelial layer.

Aim to understand the real effects of DHA to the brain, copious hypotheses have been discussed and researched e.g. fluidity change of membranes in the neuronal section[11], transformation of the substance to active metabolites[12], suppression of A-beta-42 neurotoxicity[13], suppression of prostaglandin-like F4-neuroprostanes[14], precursor in neuronal stem cell differentiation promoting neurogenesis[15], neurite outgrowth synaptic protein promoter activator[16], arachidonic acid content decrease effecter in brain phospholipids[17], and DHA-rich diacylglycerols former for membrane phosphatides synthesis through the Kennedy Cycle[18].

To understand the real function of DHA, researchers underwent a study involving phosphatidylcholine brain production rate among gerbil and rat brains with the presence of three significant precursors, DHA, uridine and choline[19]. Pregnant rats were fed with the three dietary constituents that used for phosphatidylcholine synthesis. Feeding started 10 days prior to parturition until 20 days postpartum. It was discovered that level of phosphatidylcholine in the brain and level of and phosphatides in other membranes had increased by at least 50%. Furthermore, level of synaptic proteins increased significantly in adult animals and hippocampal neuron dendritic spines significantly increased by 30% or more. However, beta-tubulin and other ubiquitous proteins did not increase.

Another similar study provided a concrete evidence of DHA and EPA's influence to adult brain development. Beltz BS et al used lobsters to study neurogenesis activities by feeding three kinds of diets with different concentrations of DHA and EPA. The study revealed that the enriched fatty acid diets resulted to a 50% increase in the noted brain cells over a period of 4 hours[20].

Dyspraxia, a development coordination disorder defined as the difficulty in learning motor skills due to inaccurate transmission from brain to the body is also linked to DHA and EPA insufficiency. Accounting to 5% of children in school-age group, dyspraxia includes specific motor function impairments[20]. This condition exists along with problems in behavior, psychosocial adaptation and learning that occasionally overlap with ADHD and dyslexia. Researches showed that children who received a supplementary DHA (provision of supplementary omega-3 and omega-6) increased in reading skills three times greater than the

normal expected result, two times greater in spelling skills and a significant positive change in individual behavior[21]. As part of the control group, children who received olive oil placebo showed no significant increase after a period of three months but they eventually showed a "catch-up" gains after switching to omega-3.

ADHD is also correlated to fatty acids: reduction of unsaturated fatty acid concentration in children with ADHD compared to a control group[22]. A low level of omega-3 FAs, without a direct relation to the clinical diagnosis, is associated with a wide range of behavioral e.g. impulsivity, conduct disorder, temper tantrums, anxiety, sleeping difficulties and learning difficulties[23]. However, there were negative results obtained from other researches after a four-month supplementation of 345 mg pure DHA. There were no significant changes on the behavior displayed including level of inattention and impulsivity by 63 children who participated in the study[24].

An established linkage could also be drawn between DHA/EPA and affective disorders. A meta-analytic review of double-blind, placebo-controlled trials showed significant antidepressant efficacy of omega-3 PUFAs. However, validity of this finding may be inconclusive because of publication bias and heterogeneity[25]. It was noted that DHA alone without EPA was insufficient in improving depression while EPA provided without DHA showed more benefits particularly in those with bipolar disorder[26, 27]. However, there was inconsistency of EPA's effect to mood disorder when the negative outcome was discovered by the similar study[28].

Current Trends and Future Research

DHA and EPA play significant effects to the metabolite production, increase in fluidity etc. The demand of DHA and EPA is determined as increasing as the developmental

Table 1. Recommended adequate intakes (AI) for omega-3 fatty acids (Food and Nutrition Board, USA, 2002)[40]

Age (years)	< 1	> 1-3	4-8	9-13	14-18	≥ 19	Pregnant	Lactating Mother
Male (g/day)	0.5	0.7	0.9	1.2	1.6	1.6	-	-
Females (g/day)	0.5	0.7	0.9	1.2	1.1	1.1	1.4	1.3

process (Table 1). To increase human ingenuity, researchers do look into the other functionalities and future DHA and EPA considerations in terms of significance and effects.

Researches have been conducted in the area of dementia and other memory-loss disorders which produce incomplete findings. Dementia is the leading disability cause among the elderly. There are several factors noted among those patients who are experiencing this such as age, a history in the family and the noticeable existence of the apolipoprotein allele[29]. It is postulated that levels of DHA and EPA in the brain and other tissues pose significant importance in preventing the risk of dementia by increasing in fluidity of the membranes led to a stable level to prevent membrane's compression[30].

Up to date, only few data regarding role of omega-3 FA in prevention and treatment of cognitive decline had been researched. The potential role of omega-3 FA was firstly hypothesized in 1990[31]. The first pilot study of 12-week treatment of ethyl-eicosapentaenoate (ethyl-EPA) in Alzheimer's disease was conducted in 2004[32]. The authors found that there was a few difference between treatment and baseline in the declination of efficacy measures, except for a small improvement in carer's visual analogue rating. The conclusion was that it was unlikely to have treatment effects of ethyl-EPA on cognition during the 12-week treatment period but a longer treatment period study was suggested. Freund-Levi et al conducted a randomized double-blind trial study of omega-3 fatty acids treatment for 6 months in 174 patients with mild to moderate Alzheimer disease and found that omega-3 fatty acid did not delay the rate of cognitive decline. However, patients with very mild cognitive dysfunction showed significant reduction in cognitive decline rate compared to placebo group[33]. The study confirmed safety and well tolerated of using omega-3 fatty acids. Moreover, omega3 supplementation for patients with mild to moderate AD had no effect on neuropsychiatric symptoms and no influence to inflammatory or biomarkers in CSF and plasma but may have positive effects on depressive symptoms[34, 35]. A study of beneficial effects of ARA and DHA in amnesic patients caused by mild cognitive dysfunction, organic brain lesions and Alzheimer's disease (AD) reported a significant improvement of the immediate memory and attention score in mild cognitive dysfunction subgroup, and improvement of immediate and delayed memories in subgroup of organic brain lesions but no significant improvement in AD group[36]. The finding that omega-3 fatty acids could improve the cognitive function in patients with mild cognitive impairment but no effect in those with AD was repeatedly observed by

Chiu's study[37] and the recent studies indicated that omega-3 fatty acid supplementation failed to demonstrate its efficacy in the treatment of AD but it may depend on the stage of disease, other dietary mediators, and apolipoprotein E status[38, 39].

Significant Gaps

DHA and EPA have been stirring up certainties and significant researches in the present time. There are significant queries that are yet to be clarified. For example, the researchers conducted by some scientists are inconsistent depending on the various strategies identified in the process. To further exemplify, the research conducted in Japan about the relationship between dietary supplementation of omega-6 and omega-3 showed a noticeable gap with regards to the methodology used by the researchers[32]. Apparently, the manner of providing supplementary nutrients to the patients with dementia and other problems are confusing and undetermined to an extent that there are some modifications in the treatment process as the study progressed. Other researchers also used few patients or subjects in conducting their research which will defeat the purpose of drawing conclusion and generalization using the result of the study. Evidently, these individuals also pose significant steps in conducting such researches since the use of human subjects needs to meet criteria and has a rule to be followed and permits to be gathered.

Recent research and directive future

There are a number of clinical researches being conducted worldwide that more explore the potential benefits to cognition by using DHA and EPA. Researchers would specifically look into the different effects of polyunsaturated fatty acids towards human cognition as uterine development continues. Furthermore, series of independent inquiries are being done with regards to the effect of DHA and EPA in the normal toddler development, bipolar disorder in young children, autism, heart diseases, cognitive dysfunction after operation, septic encephalopathy, post traumantic stress disorder (PTSD), seizures and aging in abused and weak elders. Additional trials are also on the way in the field of establishing DHA and EPA levels on post-partum blues, various types of schizophrenia and obsessive compulsive disorder. Dementia is also an unfinished exploratory assignment for researchers since little of it is known and further investigation in the correlation is better be performed[32]. Nonetheless, in the near future, new discoveries will be published for the public to be of increased awareness which will then result to valuing DHA and EPA intake by various individuals.

Conclusion

Docosahexanoic acid and eocosapentanoic acid are two of the popular fatty acids being researched on. The significant effects of these two are understood from the late uterine pregnancy up to the late elderly stage. Associations and linkages were drawn between schizophrenia, depressive disorder and various aggressive behaviors such as those with attention deficit/hyperactivity disorder. Studies about brain effects of DHA and EPA to rats and lobsters also posed a significant relation for the ongoing determination of dietary effects and behavioral changes in the chosen subject matter. Although these substances are still on the way to reach the brim of true exploration and founded education, little by little, the value and connection between DHA and EPA to the human physical and neurological development is slowly but surely being established. These subjects are still being a continuous challenge for researches up to this date.

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