

Differential Effects of Omega-3 Fatty Acid, Docosahexaenoic Acid (DHA), In Animals and Humans

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Abstract

Lipids are essential biomolecules that make up most structural components of the cell. Omega-3 polyunsaturated fatty acids, in particular the Docosahexaenoic Acid (DHA), are probably the most important structural component. Being an integral membrane component, DHA can mediate many beneficial functions and studies in animal models have indeed witnessed these beneficial effects. However, their effects in humans have been controversial and dependent on a number of factors. Although many clinical trials have been conducted to ascertain these effects the results obtained are still inconclusive.

Keywords: Biomolecules; Brain phospholipids; Cardiometabolic

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Introduction

The omega-3 and omega-6 fatty acids are Essential Fatty Acids (EFAs) as their biosynthesis requires precursors: linoleic acid (LA; 18:2n-6), linolenic acid (ALA; 18: 3n-3); which can only be obtained through diet. Higher mammals cannot synthesize these precursors as they lack the enzymes ($\Delta 9$ -, $\Delta 12$ - and $\Delta 15$ -desaturases) which are responsible for the synthesis of linoleic acid and linolenic acid, hence justifying their procurement through diet [1]. Docosahexaenoic acid (DHA, C22: 6) is the most abundant omega-3 polyunsaturated fatty acid in the brain [2]. DHA along with Arachidonic Acid (AA, C20: 4) constitute the major polyunsaturated fatty acids in the brain. The half-life of DHA in blood of healthy human subjects is 20 ± 5.2 hours [3] and 22.4 ± 2.9 hours in brain phospholipid which is much longer than that of AA (3.79 ± 0.12 hours) implicating a preferential incorporation of DHA into brain phospholipids [4]. DHA is present as a component in all membranes and hence has a potential role in virtually all systems of the human body. This mini-review outlines some of the beneficial effects of DHA in animal models and humans and the differences in its effects with age.

Functions of DHA as Witnessed in Preclinical Studies

DHA has an important role in neurodevelopment, visual acuity [5], anti-inflammatory response [6], maintaining metabolic integrity [7] as well as in anti-apoptotic functions [8]. Chronic DHA

administration facilitated long term memory in young as well as adult rats [9]. Similarly, incorporating DHA in the diet of amyloid- β infused rats prevented the impairment of spatial cognition and learning ability by increasing anti-oxidative defenses [10]. DHA also has a preventive role in metabolic disorders as evidenced by improved chemotaxis, phagocytosis and Natural killer activity in response to mitogens in adult female obese ICR/CD1 mice when fed with a high fat diet rich in DHA [11]. Decreased development of induced congestive heart failure was witnessed in male rats when they were administered with the ethyl-ester of DHA suggesting a cardio-protective activity of DHA [12].

Several *in vitro* studies indicate that the most significant contribution of DHA was in embryonic cells. Fetal brain cells showed higher neurite development and synapse formation when supplemented with DHA [13]. This questions if the benefit of DHA supplementation is age dependent and is higher in infants and children than in adults and elders. Consistent with this expectation, pregnant female rats fed with a diet rich in DHA show a steep accumulation of DHA in the fetus just prior to synaptogenesis, an important event of neurogenesis [14,15].

While evidence presented above is only a fraction of what is available, it is a fair representation of the claim that DHA has beneficial effects in rodent models. However, this beneficial effect in humans is highly debated.

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DHA Effects on Humans: Age Dependence

Just as in rodents, DHA is believed to play a role in several physiological functions in humans such as body weight, basal metabolic rate, fatty acid oxidation, cardiometabolic and inflammatory status, mental and visual development. Several clinical studies were performed to evaluate the effect of DHA on above measures in various populations with mixed outcomes.

Role of DHA in children

DHA and AA are among the components essential for fetal development. Prematurely born infants do not have sufficient time to synthesize/procure enough DHA for the proper retinal or brain development, which may often lead to minor cognitive defects. Consistent with this, the blood DHA content of preterm infants was found to be less than that of term infants [16]. It has been hypothesized that supplementing the formula given to preterm infants with DHA could restore the DHA levels required for proper brain development as the fatty acid levels in the breast milk of mothers who delivered preterm infants revealed no difference in DHA concentrations when compared with the breast milk of mothers who underwent normal delivery [17]. Seventeen clinical trials involving the assessment of 2260 preterm infants concluded that no clear long-term benefits were demonstrated in preterm infants receiving DHA supplemented formula [18], although some mental and cognitive benefit was observed in 18-month old infants following DHA supplementation [19]. Preterm infants born to women on a DHA rich diet had no effect on normal development but provided some benefit for children from poor quality home environment [20]. Benefits of DHA supplementation in school-age children with regards to growth, visual function and cognitive development are inconclusive as clinical trials conducted yielded mixed results [21-24].

Role of DHA in adults

While some benefit of DHA supplementation was seen in infants, evidence is weak in supporting the benefits of DHA in adults.

Several trials were conducted to evaluate the effect of DHA supplementation on resting metabolic rate, fatty acid oxidation, blood pressure and lipid profile. While metabolic rate remained unaffected by DHA supplementation, there was an increase in fatty acid oxidation and a simultaneous decrease in carbohydrate oxidation [25]. Some trials report DHA supplementation attenuated the increase in mean arterial blood pressure [26], decreased triglyceride levels [27] as well as oral glucose tolerance [28] in adults. However, there was no recognizable improvement in cognitive decline [29]. It can thus be concluded that DHA supplementation may benefit adults with respect to metabolic and cardiovascular functioning and little to no benefit with respect to neuronal functioning.

Role of DHA in geriatrics

In contrast to its effects on young adults, DHA supplementation increased the resting metabolic rate in older females by 14% [30]. In healthy older males, DHA supplementation was found to modulate age-related cardiovascular responses (mean and diastolic arterial blood pressure) in response to exercises utilizing autonomic nerve activity [26]. DHA supplementation lowered the triglyceride levels in both older women [30] and men [27]. In elderly patients with established Alzheimer's disease, DHA intervention is controversial [29,31,32]. It can thus be suggested that dietary DHA intervention can be an important strategy to improve age related metabolic changes, just as in adults but its utility in dementia and AD is inconclusive.

Conclusion

The above evidence represents only a fraction of data available on the effects of DHA in animal models and human subjects. The lack of a neurological benefit of DHA in humans justifies the challenges in translating pre-clinical observations to clinical therapy. It is possible that the clinical trial design is not robust enough in considering follow-up times, gender, genetic composition etc. Conducting more clinical trials and including differences based on genes, gender and physiological health can aid in gaining better insight into whether DHA supplementation is actually beneficial.

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