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COMMENTARY

Docosahexaenoic Acid (DHA) as a Nutritional Determinant of Cognitive Aging: A Hippocampal-Centric Commentary

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ABSTRACT: The quality of life in older adulthood is greatly influenced by cognitive aging, which in turn is affected by nutrition, especially as it relates to hippocampal function. Although the link between hippocampal function and nutrition is defined, the exact mechanics are still unknown. The commentary addresses how docosahexaenoic acid (DHA) contributes to age-related cognitive decline and may play a role in promoting neurogenesis and neuroplasticity on the molecular level. The current challenge to our understanding is to investigate how DHA influences hippocampal function and cognitive aging, which would be possible and even more detailed with the investigation of the mechanisms of signaling pathways. We also discuss what types of future studies are needed to clarify the mechanisms, optimal conditions, and individual factors influencing the hippocampal effects of DHA supplementation.

KEYWORDS: Cognitive functions; aging; hippocampus; nutrition; docosahexaenoic acid (DHA)

1 Introduction

Cognitive aging plays a crucial role in shaping the quality of life in older adulthood. Studying cognitive aging not only helps us understand the natural processes of brain aging but also opens pathways for prevention and intervention. Lifestyle factors, especially nutrition, are increasingly recognized as modifiable contributors to cognitive health [1]. The hippocampus is a critical brain area in cognitive aging, playing important roles in various mental abilities such as spatial and episodic memory and learning. Importantly, neurogenesis declines significantly in adulthood and with aging, especially in the hippocampus [2]. The link between nutrition and the hippocampus is well described, but the mechanisms and cell and molecular pathways are relatively unknown. The hippocampus is one of the first brain regions affected in Alzheimer's disease, leading to memory loss and spatial disorientation. The prevention strategies and the decreased progression of this disease are important goals of current neuroscience and public health efforts because approximately every three minutes, someone gets a diagnosis of Alzheimer's disease somewhere in the world. In this commentary, we focus specifically on docosahexaenoic acid (DHA), highlighting molecular roles in hippocampal structure and function in cognitive aging. As we already know, a one standard deviation higher omega-3 index was associated with approximately 2.1 cm^3 greater total brain volume and 50 mm^3 greater hippocampal volume [3]. While DHA has been the primary focus of this commentary due to its well-established effects on hippocampal structure and function, other nutritional factors such as flavonoids, vitamin D, a wider range of polyphenols, and overall dietary patterns (e.g., Mediterranean diet) may also influence cognitive aging.

2 DHA as a Nutritional Determinant

DHA, an omega-3 fatty acid, is essential for cognitive functions. The role of this polyunsaturated fatty acid in neurogenesis and neuroplasticity is not well published. The evidence from studies performed in cognitively impaired populations suggests that DHA may interact with other nutritional factors to influence its effect on the brain, such as the B complex (vitamins B6, B9, B12) or EPA (eicosapentaenoic acid) combined diet [4]. The synergic effects of DHA with bioactive molecules such as folic acid, caffeic acid, curcumin, pre- and probiotics should be interesting and may provide more cognitive benefit than supplementation alone [5,6]. The imbalance between omega-3 and omega-6 is another global nutritional concern, particularly in countries where fish consumption is not prevalent. Consequently, the lack of omega-3 intake contributes to the increasing risk of age-related neurological disorders. It is important that aging reduces the transport of DHA across the blood-brain barrier (BBB) via passive diffusion, which may contribute to cognitive decline [7–9]. Because BBB plays a crucial role in the development and progression of neurodegenerative diseases such as dementia and Alzheimer's disease, studying the cholinergic activity and activated cyclic AMP-response element-binding protein-mediated molecular signaling pathways and the expression of tight junction proteins and genes may identify new therapeutic targets in the hippocampus [10].

The official recommended daily allowance (RDA) for DHA is currently not clearly defined in most countries. Still, several recommendations and consensus exist for health maintenance and specific purposes (e.g., cognitive health). Most studies have examined the effects of high-dose DHA, and very few clinical trials or those that have been conducted are relatively old and have used low-dose DHA. There are valuable clinical studies that provide balanced evidence of the potential cognitive benefits of long-term, high-dose omega-3 fatty acids (EPA and DHA) [11]. In contrast, in the other study, there is no significant effect on slowing cognitive decline over two years in healthy older adults [12]. The differences between the dosage, the duration of the intervention, and the gender of the participants are important, especially on the molecular level, and these factors could explain the contradictions of the studies.

On the molecular level, the high-dose DHA resulted in increased synaptogenesis and reduced microglia markers, namely triggering receptor expressed on myeloid cells 2 (TREM2) and cluster of differentiation 68 (CD68) β pathology (soluble Aβ42 and insoluble Aβ42 protein expressions) in the Tg2576 Alzheimer's disease mouse model [13]. These results have been confirmed by transcriptomic analysis, where activation of genes related to synaptogenesis, neurogenesis, dendritic spine density, and axon growth was observed in the hippocampus. In addition to measuring protein expression, transcriptomic analysis can be important in any case because it provides a comprehensive picture of gene-level regulation, allowing the mapping of early, post-transcriptional changes and complex regulatory networks that are not always directly reflected at the protein level. Research is currently underway to develop human neurogenesis biomarkers and human testing tools. Brain-derived neurotrophic factor (BDNF) is a known marker of neuroplasticity and neurogenesis. Although BDNF levels are not specific to neurogenesis, they have been associated with neurogenesis and cognitive function in several studies [14]. Nevertheless, there are relatively few publications on the topic of serum pro-BDNF/BDNF and DHA supplementation. Thus far, clinical studies not specific to Alzheimer's disease have reported promising results [15,16]. In addition, proteomic profiling and the polygenic risk scores opened new possibilities in human cognitive decline research [17,18]. One important consideration when interpreting the effects of DHA supplementation, especially in relation to hippocampal structure, function, or signaling pathways, is the high inter-individual variability in DHA absorption, transport, and utilization in the brain. Bioavailability depends on the chemical form (e.g., phospholipid, triglyceride, ethyl ester), delivery method (e.g., emulsified, non-emulsified), and physiological or dietary background [19]. Genetic factors also play a major role: polymorphisms in genes involved in fatty acid metabolism (such as the FADS-gene family, phosphatidylethanolamine N-methyltransferase (PEMT), and apolipoprotein E (APOE)) may modulate how

efficiently DHA is incorporated into brain membranes [20,21]. These sources of variability mean that two subjects given the same dose of DHA may have very different hippocampal DHA levels, BDNF responses, or functional outcomes.

DHA plays a critical role in brain antioxidant protection, with a focus on indirect antioxidant mechanisms such as regulation of glutathione peroxidase 4 (GPX4) and nuclear factor erythroid 2-related factor 2 (Nrf2), and the role of selenium in protection against oxidative stress *in vitro* and *in vivo* [22]. In addition, DHA modulates GPX4 gene expression in hippocampal cells [23]. Moreover, DHA can improve neuroinflammation and attenuate oxidative stress via Nrf2, heme-oxygenase-1 (HO-1), 3-nitrotyrosine (3-NT), and mediate the Nrf2-Keap1-ARE signaling pathway, but the DHA dose and administration form used in this study may not necessarily reflect dietary or supplement-based doses used in humans, so translational relevance may be limited [10]. A 2023 study found that DHA supplementation reduced oxidative stress and mitochondrial dysfunction, as well as inhibited caspase-3 expression, suggesting a neuroprotective effect in the hippocampus [24]. Although the oxidative stress-mediated changes can decline the cognitive functions during aging, no human studies have simultaneously measured oxidative stress markers, cognitive functions, and administered DHA supplementation in elderly, healthy individuals.

Cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 (CYP) enzymes share the commonality that they metabolize fatty acids through oxidative mechanisms and are thus closely linked to oxidative stress, both as a cause and a consequence. DHA is crucial for cell signaling through lipid mediators. LOX- and CYP450-derived DHA bioactive lipid metabolites are neuroprotective molecular targets for human hippocampal neurogenesis [25]. While the role of LOX- and CYP450-derived DHA metabolites in neuroprotection and hippocampal neurogenesis is promising, the current evidence is largely based on preclinical or *in vitro* studies. Direct causal links in humans remain limited, and further research is needed to substantiate these molecular pathways in the aging brain *in vivo*. Low-density lipoprotein receptor (LDLR), ATP-binding cassette sub-family G member 1 (ABCG1), sortilin 1 (SORT1), LOX_1, ubiquitin-like protein 3 (UBL3), and synaptotagmin-13 (SYT13) are potential DHA-mediated regulating effect in the brain of mice. The beneficial effects of DHA may depend on regulating the expression of vesicular transport and neuroprotection-related proteins, as well as influencing phospholipid and fatty acid metabolic processes [26]. Although the role of COX, LOX, and CYP pathways in the neuroprotective effects of DHA derivatives is increasingly recognized, additional components of lipid metabolism—such as endocannabinoids, sphingolipids, and plasmalogens—are also important but understudied players in the regulation of cognitive function.

3 Perspectives and Conclusion

Along these lines, we discussed the immense importance of DHA in the age-related cognitive decline. The current challenge to our understanding is to investigate how DHA influences hippocampal function and cognitive aging. Nonetheless, most studies examine single nutrients or compounds rather than considering their combined or synergistic effects. The lack of evidence is the interaction studies, which would map the relationships between individual molecules and groups of molecules at the cellular and molecular level. Another shortcoming is the lack of long-term follow-up; these studies would be a gap-filling study. Secondly, a critical point is that many studies lack a comprehensive analysis of the underlying molecular and cellular pathways modulated by diet. On the other hand, it would be valuable to design experiments that investigate and combine *in vitro* and *in vivo* experimental results, focusing on the hippocampus and DHA. In addition, the combination of gender and age may provide a better understanding of gender or age-specific effects of DHA supplementation. Although the commentary primarily examined the direct, cellular, and structural effects of DHA in the hippocampus, it did not address the microbiome-mediated,

indirect mechanisms of action of dietary components. However, it can be recognized that the role of the gut microbiota is an important additional factor that should be included in future, more complex studies. Addressing these research gaps through advanced models such as organoid systems, longitudinal human studies, and multi-omics profiling will enhance our understanding of the key dietary determinants necessary to support hippocampal resilience and preserve cognitive function across the lifespan. Organoid systems, especially human brain organoids, offer the opportunity to model brain development and aging *in vitro*, including the effects of nutritional factors such as DHA. These systems contain human-specific cell types, thus better reflecting the human brain environment than animal models. Multi-omics approaches—such as transcriptomics, proteomics, lipidomics, and metabolomics—allow us to gain a comprehensive picture of how cellular processes change in response to nutritional interventions. Combining these methods may help identify key molecular pathways that are activated or impaired during cognitive aging. In future research, these tools may be particularly useful in separating and interpreting direct and indirect (e.g., microbiome-mediated) nutritional effects. In addition, given the significant inter-individual variability in DHA absorption, transport, and brain incorporation, further well-designed studies are essential to elucidate the precise molecular mechanisms through which DHA influences hippocampal function and cognitive aging.

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Abbreviations

3-NT	3-nitrotyrosine
ABCG1	ATP-binding cassette sub-family G member 1
APOE	Apolipoprotein E
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
CD68	Cluster of differentiation 68
COX	Cyclooxygenases
CYP	Cytochrome P450
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
GPX4	Glutathione peroxidase 4
HO-1	Heme-oxygenase-2
LDLR	Low-density lipoprotein receptor
LOX	Lipoxygenases
Nrf2	Nuclear factor erythroid 2-related factor 2
PEMT	Phosphatidylethanolamine N-methyltransferase
RDA	Recommended daily allowance

SORT1	Sortilin 1
SYT13	Synaptotagmin-13
TREM2	Triggering receptor expressed on myeloid cells 2
UBL3	Ubiquitin-like protein 3

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