AN Advances in Nutrition An International Review Journal

ω-3 Fatty Acids in the Prevention of Cognitive Decline in Humans[1–3]

Tommy Cederholm,[4]* Norman Salem Jr,[5] and Jan Palmblad[6]

[4]Clinical Nutrition and Metabolism, Uppsala University, and Department of Geriatric Medicine, Uppsala University Hospital, Sweden; [5]Nutritional Lipids, DSM Nutritional Products, Columbia, MD; and [6]Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

ABSTRACT

The brain is a lipid-rich organ where docosahexaenoic acid (DHA) is enriched and where eicosapentaenoic acid (EPA) may have anti-inflammatory effects. The potential role for n–3 (ω-3) fatty acids such as DHA and EPA in the prevention of cognitive decline, including Alzheimer's disease (AD) has attracted major interest for the past 20 y. This review presents our understanding of recent observational, interventional, and experimental studies, with the aim of providing some answers to the following question: Can n–3 FA intake modulate cognitive function during aging? In longitudinal observation studies we mainly observe inverse relations between fish intake or serum concentrations of DHA and cognitive impairment. Intervention studies of EPA and DHA supplementation in healthy old individuals have been negative so far (i.e., after up to 2 years of treatment, no differences in cognitive decline between treated and nontreated participants have been observed). In studies that provided EPA and DHA to adults with mild cognitive impairment or age-related cognitive impairment the data seem to be positive. However, when patients with established AD were supplemented with EPA and DHA it appears no benefit was gained. For studies on healthy individuals, a major concern is that the treatment periods may have been too short. There might also be subgroup effects because of the carriage of apolipoprotein Eε4 alleles or risk factor burden. Experimental studies appear to be consistently positive (i.e., n–3 FA supplementation in rodents over a substantial portion of their lives reduces amyloid-β deposition and hippocampal neuron loss and improves cognitive functioning). We are getting closer to providing evidence-based recommendations on fish and fish oil intake to facilitate memory function during old age. In the meantime it is advised to follow the general CDC dietary recommendations of 2–3 fish meals per week or the equivalent intake of long chain n–3 fatty acids, particularly DHA. *Adv. Nutr. 4: 672–676, 2013.*

Introduction

The brain is highly enriched in lipids. Thus, it is reasonable to assume that the composition of fatty acids in the brain has relevance for brain functions, including cognition and neuropsychiatric development. The content of DHA (22:6n–3) in the human brain generally increases with age over the first 2 decades and then levels off (1). In 1991 it was reported (2) that DHA as well as arachidonic acid (ARA[7]; 20:4n–6) and its elongation product, adrenic acid (22:4n–6), were all greatly decreased in various phosphoglyceride fractions [e.g., phosphatidylcholine (PC) and phosphatidylethanolamine (PE)] in 4 areas of the brain with Alzheimer's disease (AD) and in the frontal cortex (2). Whether such changes are causal or consequential effects with regard to cognitive function cannot be determined from observational studies. However, these observations clearly indicate interesting possible relations between FAs and cognition and dementia disorders.

To understand potential effects from FA intake, we need to rely on the combined evaluation of observational, interventional, and experimental studies. Epidemiological studies, whether cross-sectional or longitudinal, may use fish intake or FA profiles in tissues (e.g., blood or adipose tissue)

[1] Presented at the symposium "Nutritional Prevention of Cognitive Decline" held 25 April 2012 at the American Society of Nutrition Scientific Sessions and Annual Meeting at Experimental Biology 2012 in San Diego, CA. The symposium was sponsored by the American Society for Nutrition, Nutrition Epidemiology RIS, and a grant from the Office of Dietary Supplements at NIH.

[2] A summary of the symposium "Nutritional Prevention of Cognitive Decline" was published in the September 2012 issue of *Advances in Nutrition*.

[3] Author disclosures: T. Cederholm and J. Palmblad, no conflicts of interest. N. Salem is employed by a company that produces and sells essential fatty acids, including the n–3 fatty acids EPA and DHA.

* To whom correspondence should be addressed. E-mail: tommy.cederholm@pubcare.uu.se.

[7] Abbreviations used: Aβ, amyloid-β; AD, Alzheimer's disease; ARA, arachidonic acid; GM, gray matter; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; RCT, randomized controlled trial; WM, white matter.

as exposure variables and use cognitive decline or incidence of dementia or AD as outcome variables. Intervention studies [i.e., those that provide EPA (20:5n–3) and DHA] could be done on individuals with various stages of cognitive decline [i.e., cognitively intact, mild cognitive impairment (MCI)] or in patients with different grades of severity of AD or dementia. Moreover, the basal concentrations of EPA and DHA in the bloodstream and brain may vary according to geography, fish availability, and other dietary habits. Finally, experimental studies could be performed in either animal models or in vitro studies to define specific EPA and DHA effects.

The objective of this review is to examine some of the most relevant recent evidence in the light of previous knowledge to try to answer the question of whether we can treat or prevent cognitive decline with long-chain n–3 FAs, especially DHA.

Brain Lipid Composition

The potential role of altered FA intake on brain function can be comprehended by first understanding the lipid composition of the normal brain. Brain fat content varies with tissue type. An early report indicated that brain gray matter (GM) was composed of 36–40% of dry weight as lipid, white matter (WM) had 49–66%, and myelin had the highest lipid content at 78–81% (3). Phosphoglycerides comprise 20–30% of the brain's dry weight, with the amount increasing as follows: GM > WM > myelin (3,4). Cholesterol makes up ~6–8% of the GM's dry weight, 11–13% of WM, and 19–21% of myelin. Cerebrosides, including ceramide and cerebroside sulfate, are also major lipids in the brain with low amounts in GM but greatly increased amounts in WM and myelin (3). The major brain phosphoglycerides are PC and PE; secondarily are phosphatidylserine (PS) and sphingomyelin; and then small amounts of phosphatidic acid, phosphatidylglycerol, and lyso-phospholipids are present (3). Brain lipids are also notable for their small but important amount of gangliosides.

The brain differs from the blood stream and many peripheral organs because it contains very low amounts of triglycerides, nonesterified FAs, and cholesterol esters. The fatty acyl distribution in the brain is also distinct from that in the blood stream and peripheral organs. The brain has relatively little linoleic acid (18:2n–6) or α-linolenic acid (18:3n–3) and more C18 and less C16 saturated FAs than many peripheral tissues (4,5).

In terms of the n–3 FAs, DHA predominates, with only docosapentaenoic acid (22:5n–3) contributing as a minor component. Because only trace amounts of α-linolenic acid and EPA are present in the brain (4–6), most reports of brain FA analyses do not even list these components. DHA is concentrated in the GM, and very small amounts are found in purified myelin (4–6). Within the GM, the amino-phospholipids PE and especially PS have very high concentrations of DHA and PC has a lower concentration (4–6). The observation that DHA can be 37% of GM PS (4), coupled with the positional distribution exclusively within the sn-2 position of the brain phospholipids (7), indicates that >73% of GM PS molecules contain DHA. The amino-phospholipid DHA is found at a high concentration across several brain subcellular fractions, including nerve terminals, microsomes, synaptic vesicles (7), and synaptosomal plasma membranes (8).

Current Knowledge about the Relation between AD, DHA, and EPA

Epidemiological evidence. In the past 15 y, >20 large-scale epidemiological cohorts have been used to investigate the relation between long-chain n–3 FAs and cognition. The Rotterdam Study was 1 of the first to publish positive results on the longitudinal effects of increased fish intake (i.e., >19 g fish/d), indicating a >50% reduced risk of dementia incidence after 2 y in a group of >5000 healthy participants, > 55 y of age (9). However, when 6-y follow-up data were presented from the same cohort, ~4% of the cohort had developed dementia and this positive relation could no longer be observed (10). Over the years, a majority of the published epidemiological studies have displayed an inverse relation between fish intake and the risk of cognitive decline or AD (11). For example, the French PAQUID Study observed a 35% reduced risk of AD over 7 y in 1600 older adults (>68 y) who had at least 1 fish meal/week (12). The CHAP Study from Chicago reported reduced decline in global cognition over 6 y in 3700 participants >65 y with a similar fish intake (13). As an alternative to fish intake, plasma DHA concentrations may be studied. For example, in the Framingham Study, decreased plasma DHA concentrations were related to subsequent cognitive decline (14). In a subgroup of 899 participants who were >76 y of age and not demented, those in the highest quartile of plasma DHA had half the risk of dementia compared with those in the lowest quartiles within 9 y of follow-up even after statistical adjustment for relevant confounders (14).

There are also null studies. In the VA Normative Aging Study from the Boston area, the relation between fish intake according to FFQs and various cognitive domains, including the Mini Mental State Examination (MMSE), was studied in 1025 healthy men with a median age of 68 y (15). No relation could be demonstrated among quartiles of fish or EPA and DHA intake for cognition either at baseline or at 3- or 6-y of follow-ups.

In 1 recent study from the Framingham Offspring Study, Tan et al. (16) reported a positive association between a high concentration of DHA in red blood cell membranes and visual memory, abstract skills, and executive function. Moreover, total cerebral brain volume was greater in participants who had higher concentrations of DHA in red blood cell membranes compared with those with lower concentrations.

In summary, it is clear that the epidemiological data are not fully consistent, although the majority of published reports are positive. It is thus important to understand the limitations of epidemiological observations. On one hand, there is a clear risk of publication bias, because several negative observations may never have been published in the

international literature. On the other hand, the competing risk of death is a potential peril leading to an underestimation of the protective effects of EPA and DHA. That is, it is plausible that a low fish intake increases cardiovascular risk burden and that death occurs before reaching the age at which one is likely to develop cognitive decline.

Intervention studies. Since the first large-scale randomized controlled trial (RCT) of EPA and DHA in patients with AD (i.e., the OmegAD Study), reported in 2006 (17), >10 such intervention studies of good quality have been published with cognition as the outcome. Recently, a meta-analysis of 10 RCTs selected for their quality was published (18) (**Table 1**). Three studies concerned supplementation to healthy old adults (19–21), 4 were done on individuals with MCI (22–25), and 3 in patients with AD (17,26,27). Treatment periods varied from 6 mo to 2 years. The studies used DHA predominantly, with doses of DHA and EPA ranging from 0.3 to 1.7 and 0 to 1.7 g/d, respectively. Positive effects could be concluded for n–3 FA supplementation in participants with MCI. This conclusion was especially true for the domains of immediate recall, attention, and speed. Forest plots showed Hedges' *g* values for immediate recall (0.16; 95% CI: 0.01, 0.32) and attention and speed (0.32; 95% CI: 0.03, 0.61). i.e., in favor of treatment. No effects could be observed in either patients with AD or healthy individuals.

The outcome of this meta-analysis (18) is in line with that of the OmegAD Study (17), in which 204 patients with mild to moderate AD received either 1.7 g/d DHA or placebo for 6 mo (RCT) and then all patients received 1.7 g/d DHA for 6 mo (open treatment). This treatment did not provide any benefits when the whole population was evaluated, whereas the decline rate in cognitive function was reduced by DHA and EPA supplementation in the subgroup of patients with very mild AD (i.e., MMSE 27–30). The study by Yurko-Mauro et al. (24) was also consistent with the OmegAD Study. About 500 adults >55 y of age with age-related cognitive decline (i.e., MMSE >26) were provided with 900 mg/d algal DHA for 6 mo. This treatment doubled the DHA plasma concentrations and improved cognitive testing to a level that corresponded to a gain of 3.4 y of cognitive age. Quinn et al. (27) studied 402 patients with AD, but with more severe disease (i.e., MMSE 14–26), over an 18-mo RCT in which the active treatment was 2 g algal DHA. Overall, no effects were found on either cognitive functioning or brain MRI. However, cognition declined less in the subgroup of patients (42%) who did not carry apolipoprotein Eϵ4 alleles. The most recent RCT with predominantly DHA studied 36 Malayan participants with MCI (28). After 12 mo of treatment those given 1.3 g DHA and 0.45 g EPA daily showed greatly improved short-term and working memory, verbal memory, and delayed recall capability, again indicating patients with slightly reduced memory functions as the major target group for DHA treatment.

Two large-scale studies [the Dutch MEMO Study (19) and the UK OPAL Study (21)] have evaluated the effect of EPA and DHA supplementation in older healthy individuals. The Dutch study included 302 participants (>55 y, MMSE >21) with a median age of 70 y and a mean MMSE of 28. Six months of EPA and DHA treatment up to1.8 g/d had no effect; cognitive decline over the short period of time was equal in the 2 groups (19). The OPAL Study involved 867 participants between 70 and 79 y of age with a mean MMSE of 29 (21). They were randomly assigned to receive 0.5 g DHA and 0.2 g EPA daily for 24 mo. Although the treatment period was relatively long for this type of study, no cognitive changes were observed in any of the groups, thus, no conclusions could be drawn. Similar conclusions came from the latest Cochrane review on possible prevention of cognitive decline by n–3 FA in healthy older people (29)

Several interesting questions emerged from the collective experience gathered from these intervention studies. First is that perhaps the duration of the studies has not been long

TABLE 1 Randomized controlled trials of n–3 fatty acid supplementation and cognitive outcome in adults who are healthy and old, with MCI/memory complaints, and with AD[1]

Study	Sample size	Duration	Outcome
	n	*wk*	
Healthy and old			
Van de Rest et al. (19)	302	26	Similar cognitive decrease irrespective of treatment
Johnson et al. (20)	49	16	Improved verbal fluency
Dangour et al. (21)	877	108	No cognitive decline in any treatment group
MCI/memory complaints			
Kotani et al. (22)	21	13	Improved immediate memory
Vakhapova et al. (23)	157	15	Improved verbal recall
Yurko-Mauro et al. (24)	485	24	Improved immediate and delayed verbal recognition
Sinn et al. (25)	50	27	Improved verbal fluency
AD			
Freund-Levi et al. (17)	204	52	No cognitive effects overall; a subgroup with mild AD displayed slower decline in MMSE
Chiu et al. (26)	35	24	No cognitive effect in AD patients; improved ADAS-Cog in MCI patients
Quinn et al. (27)	402	81	No effects on change rate in ADAS-Cog

[1] Reported in Mazereeuw et al. (18). AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination.

AN Advances in Nutrition An International Review Journal

enough. Second, the DHA dose varied extensively and so far the basal DHA status has not been taken into account. Third it is doubtful whether beneficial effects of DHA supplementation can be observed in individuals who already have sufficient DHA intake and tissue content.

Recent Advances from Experimental Studies

Animal research may indicate that EPA and DHA exposure in human intervention studies is too short (i.e., 0.5–1.8% of the participant's life span). For example, exposure periods for FA supplementation in rodent studies are often markedly longer. Recently, an interesting meta-analysis of animal studies was published (30). The authors used the following inclusion criteria: *1*) the treatment period was >10% of total life span (up to 50%) and *2*) results were reported on amyloid-β (Aβ) deposition in the brain, effects on cognitive function (e.g., using the Morris water maze test), and effects on hippocampal neuron loss. Fifteen studies were identified; 10 used transgenic AD animal models, and 5 used Aβ infusion to induce cognitive deterioration. Of great interest were the clear and consistent findings of reduced Aβ deposition, improved cognition, and reduced hippocampal neuron loss upon EPA and DHA supplementation given from 10% to 50% of the animals' expected lifetime.

Possible Mechanisms for Potential Positive Effects of EPA and DHA Treatment

Numerous in vitro, cell culture, and animal studies have provided several potential mechanisms for the effects on cognition induced by EPA and DHA supplementation. In the nervous system, DHA is mainly found in the phospholipids in cell membranes where it modulates the physical environment (31) and increases the free volume (32) within the membrane bilayer. A key mechanism is the modulation of G protein–coupled receptors, the best example of which is rhodopsin (33) because of its close association with these membrane receptors (32).

It has recently been demonstrated that DHA accumulates close to the lipid membrane rafts, thus influencing transmembrane transport and cell interaction with the exterior world (34). DHA can also modulate apoptosis (35), neuronal differentiation (36), and ion channels (37). Through cytosolic and nuclear interaction with various PPARs, both EPA and DHA have effects on gene expression and thus on translation and expression of various proteins. One such example is their influence on *SorLA* gene and protein expression, a protein that is involved in Aβ production (38). More well-known are the anti-inflammatory effects associated with substituting EPA and DHA for the n–6 FAs linoleic acid or ARA. Thus, the profiles of ARA-based prostaglandins and leukotrienes are shifted toward those based on EPA with their reduced inflammatory activity. A more recent discovery is that EPA and DHA derivatives such as resolvins, maresins, and neuroprotectins are involved in the resolution processes related to inflammation. These newly described lipid mediators actively shut off inflammatory reactions (39). Relevant for AD is the potential inhibition of Aβ generation that has been linked to neuroprotectin 1, which is a metabolite of DHA. However, little is yet understood about the involvement of these mediators in neurodegenerative disorders such as AD and MCI and their modification by EPA and DHA supplementation.

Current Status, Clinical Implications, and Conclusions

In 2010, NIH released "State-of-the Science Conference Statement: Preventing Alzheimer Disease and Cognitive Decline," (40) which stated the following about nutritional factors: "The most consistent evidence is available for longer-chain ω-3 fatty acids (often measured as fish consumption), with several longitudinal studies showing an association with reduced risk of cognitive decline." However the final conclusion was that evidence is insufficient to provide recommendations on dietary supplements to prevent cognitive decline, whereas it was acknowledged that promising research is under way. Since then, several studies and meta-analyses have been published, some reviewed here. The question that emerges is, do we now have enough data to make more clear recommendations?

We may conclude that longitudinal observation studies on fish intake and DHA plasma concentrations in older healthy adults are mainly positive when it comes to cognitive health. Intervention studies on EPA and DHA supplementation in healthy older individuals are so far null. When EPA and DHA is given to individuals with MCI or age-related cognitive impairment the data now appear to be positive. However, when patients with established AD are supplemented with EPA and DHA it appears that no clear benefit is achieved. A major concern is that the studies in general have been too short. There might also be subgroup effects because of the carriage of apolipoprotein Eϵ4 alleles or risk factor burden in general not yet clearly identified. Finally, experimental studies appear to be consistently positive (i.e., EPA and DHA supplementation in rodents during a substantial period of their lives reduces Aβ deposition and hippocampal neuron loss and improves cognitive functioning).

When future consensus initiatives are undertaken, this new information will be taken into account. Recent advances bring us closer to providing the general public with new evidence-based recommendations on fish and fish oil intake to facilitate memory function during aging.

Acknowledgments

All authors read and approved the final manuscript.

Literature Cited

1. Carver JD, Benford VJ, Han B, Cantor AB. The relationship between age and the fatty acid composition of cerebral cortex and erythrocytes in human subjects. Brain Res Bull. 2001;56:79–85.
2. Söderberg M, Edlund C, Kristensson K, Dallner G. Fatty acid composition of brain phospholipids in aging and in Alzheimer's disease. Lipids. 1991;26:421–5.
3. O'Brien JS, Sampson EL. Lipid composition of the normal human brain: gray matter, white matter and myelin. J Lipid Res. 1965;6:537–44.
4. Svennerholm L. Distribution and fatty acid composition of phosphoglycerides in normal human brain. J Lipid Res. 1968;9:570–9.

5. O'Brien JS, Sampson EL. Fatty acid and fatty aldehyde composition of the major brain lipids in normal human gray matter, white matter, and myelin. J Lipid Res. 1965;6:545–51.
6. Salem N, Jr., Kim H-Y, Yergey JA. Docosahexaenoic acid: membrane function and metabolism. In: Simopoulos AP, Kifer RR, Martin RE, editors. Health effects of polyunsaturated fatty acids in seafoods. Orlando, FL: Academic Press; 1986. p. 263–317.
7. Kishimoto Y, Agranoff BW, Radin NS, Burton RM. Comparison of the fatty acids of lipids of subcellular brain fractions. J Neurochem. 1969; 16:397–404.
8. Breckenridge WC, Gombos G, Morgan IG. The lipid composition of adult rat brain synaptosomal plasma membranes. Biochim Biophys Acta. 1972;266:695–707.
9. Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997;42:776–82.
10. Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, Breteler MM. Diet and risk of dementia. Does fat matter? The Rotterdam Study. Neurology. 2002;59:1915–21.
11. Cederholm T, Palmblad J. Are omega-3 fatty acids options for prevention and treatment of cognitive decline and dementia? Curr Opin Clin Nutr Metab Care. 2010;13:150–5.
12. Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF, Renaud S. Fish, meat, and risk of dementia: cohort study. BMJ. 2002; 325:932–3.
13. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Fish consumption and cognitive decline with age in a large community study. Arch Neurol. 2005;62:1849–53.
14. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol. 2006;63:1545–50.
15. van de Rest O, Spiro, III A, Krall-Kaye E, Geleijnse JM, de Groot LCPG, Tucker KL. Intakes of (n-3) fatty acids and fatty fish are not associated with cognitive performance and 6-year cognitive change in men participating in the Veterans Affairs Normative Aging Study. J Nutr. 2009;139: 2329–36.
16. Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, Debette A, Pikula A, DeCarli C, Wolf PA, Vasan RS. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. Neurology. 2012;78:658–64.
17. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, Basun H, Faxén Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J. Omega-3 fatty acid treatment of 174 patients with mild to moderate Alzheimer's disease (OmegAD): a randomized double-blind trial. Arch Neurol. 2006;63:1402–8.
18. Mazereeuw G, Lanctôt K, Chau SA, Swardfager W, Hermann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging. 2012;33:1482. Epub 2012 Feb 3.
19. van de Rest O, Geleijnse JM, Kok FJ, van Staveren A, Hoefnagels WH, Beekman AT, de Groot LCPGM. Effect of fish oil on cognitive performance in older subjects. A randomized, controlled trial. Neurology. 2008;71:430–8.
20. Johnson EJ, McDonald K, Caldarella SM, Chung HY, Troen AM, Snodderly DM. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. Nutr Neurosci. 2008;11:75–83.
21. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, Holder GE, Knight R, Letley L, Richards M, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr. 2010;91:1725–32.
22. Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, Sakakibara M, Yoshimoto T, Guo J, Yamashima T. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res. 2006;56:159–64.
23. Vakhapova V, Cohen T, Richter Y, Herzog Y, Korczyn AD. Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in non-demented elderly with memory complaints: a double-blind placebo-controlled trial. Dement Geriatr Cogn Disord. 2010;29:467–74.
24. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, Salem N, Jr., Stedman M, MIDAS Investigators. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement. 2010;6:456–64.
25. Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, Howe PR. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. Br J Nutr. 2012;107:1682–93.
26. Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, Stewart R, Huang SY. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1538–44.
27. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack C, Jr., Weiner M, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA. 2010;304:1903–11.
28. Lee LK, Shahar S, Chin A-V, Yusoff NAM. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12 month randomised, double blind, placebo-controlled trial. Psychopharmacology (Berl). 2013;225:605–12.
29. Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst Rev. 2012 Jun 13;6:CD005379.
30. Hooijmans CR, Pasker-de Jong P, de Vries R, Ritskes-Hoitinga M. The effects of long-term omega-3 fatty acid supplementation on cognition and Alzheimer's pathology in animal models of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2012;28:191–209.
31. Eldho NV, Feller SE, Tristram-Nagle S, Polozov IV, Gawrisch K. Polyunsaturated Docosahexaenoic vs docosapentaenoic acid – differences in lipid matrix properties from the loss of double bond. J Am Chem Soc. 2003;125:6409–21.
32. Mitchell DC, Straume M, Litman BJ. Role of sn-1-saturated, sn-2-polyunsaturated phospholipids in control of membrane receptor conformation equilibrium: Effects of cholesterol and acyl chain unsaturation on the metarhodopsin I → metarhodopsin II equilibrium. Biochemistry. 1992;31:662–70.
33. Niu S-L, Mitchell DC, Lim S-Y, Wen Z-H, Kim H-Y, Salem N, Jr., Litman BJ. Reduced G protein-coupled signaling efficiency in retinal rod outer segments in response to n-3 fatty acid deficiency. J Biol Chem. 2004;279:31098–104.
34. Shaikh SR. Biophysical and biochemical mechanisms by which dietary N-3 polyunsaturated fatty acids from fish oil disrupt membrane lipid rafts. J Nutr Biochem. 2012;23:101–5.
35. Akbar M, Calderon F, Kim H-Y. Docosahexaenoic acid: a positive modulator of AKT signalling in neuronal survival. Proc Natl Acad Sci PA. 2005;102:10858–63.
36. Calderon F, Kim H-Y. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. J Neurochem. 2004;90:979–88.
37. Kang JX, Leaf A. The cardiac antiarrhythmic effects of polyunsaturated fatty acid. Lipids. 1996;31:S41–4.
38. Vedin I, Cederholm T, Freund-Levi Y, Basun H, Garlind A, Faxén Irving G, Eriksdotter-Jönhagen M, Wahlund LO, Dahlman I, Palmblad J. Effects of DHA- rich n-3 fatty acid supplementation on gene expression changes in blood mononuclear leukocytes: the OmegAD study. PLoS ONE. 2012;7:e35425.
39. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008;8:349–61.
40. Daviglus ML, Bell CC, Berrettini W, Bowen PE, Conolly ES, Jr., Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, et al. National Institutes of Health State-of-the-Science Conference statement: preventing Alzheimer disease and cognitive decline. Ann Intern Med. 2010; 153:176–81.

AN Advances in Nutrition An International Review Journal