

- Topics:** Brain function, cognitive performance with age, mild cognitive impairment (MCI), Alzheimer's Disease (AD), omega-3 fatty acids, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), long chain polyunsaturated fatty acids (LC-PUFAs), fish, fish oil
- Objective:** To review the current knowledge about the way omega-3 fatty acids (specifically EPA and DHA) are thought to regulate nerve cell function, degeneration and survival with particular emphasis on their inflammatory and survival/apoptotic impact in Alzheimer's Disease (AD).
- Background:** The incidence of age associated dementia is rising dramatically in Westernized countries. Studies have shown that dietary intake of DHA and EPA can reduce its risk and progression. DHA is the most prevalent fatty acid in nerve tissue within the brain and its concentration is decreased in the blood of people with dementia. Preclinical studies have confirmed that low blood levels of omega-3 LC-PUFAs including DHA are associated with impaired learning ability while infant studies have reported that adding DHA to their milk formulas can enhance mental development and function. Intervention trials in people with age associated impairment and more severe forms of dementia including AD have reported some benefits. However, the mechanisms whereby omega-3 LC-PUFAs impact normal and degenerative nerve cell function are not well understood.
- Observations:** Based on scientific evaluation of experimental results, the following mechanisms of action have been proposed for the effects of DHA in particular on AD:
- 1) **Increased Cell Membrane Fluidity** – DHA is highly concentrated in the nerve cells in the brain and retina of the eye. Both of these tissue types require high fluidity within their membranes to ensure flexibility that allows proper enzyme, carrier molecule and receptor activity. Since DHA has six double bonds, it is a high flexible molecule and is responsible for providing the membrane fluidity required in these membranes.
 - 2) **Altered Lipid Raft Composition and Function** – Lipid rafts are specialized organizational sites (sort of like little factories) within cell membranes that are responsible for separating different cell functions, acting as super highways to transport and process proteins within cells, and for enabling communication between cells (cell signaling). One type of lipid raft in particular is involved in the formation of amyloid precursor protein. This protein is produced in excess in the brains of people with AD and leads to the development of damaging protein plaques within their brain tissue. DHA may modify the lipid raft composition sufficiently to reduce formation of amyloid precursor protein.
 - 3) **Altered Formation of Inflammatory Mediators and Regulators** – Both EPA and DHA give rise to compounds that have strong anti-inflammatory effects.
 - 4) **As a Precursor of Bioactive Compounds** – It has recently been discovered that DHA can be made into compounds called docosanoids. One of these, Neuroprotectin D1, provides anti-inflammatory and neuroprotective activity within the brain.
 - 5) **As a Modulator of Cell Death (apoptosis) within the Brain** – DHA reduces the activity of an enzyme called *caspase* which is involved in progressing brain cell death in AD. In addition, DHA enhances the accumulation of phosphatidylserine (PS) within nerve cells which protects them from cell death.
 - 6) **Inhibitor of Oxidative Stress within the Brain** – Oxidative stress occurs within the brains of people with AD before beta-amyloid protein deposition and formation of nerve fiber tangles. DHA protects against this oxidative damage.
 - 7) **Altered Brain Gene Expression** – Increases in brain DHA alter the expression of a variety of genes including those controlling the cytoskeleton and membrane associations, raft formation, signal transduction, ion channel formation, energy metabolism and regulatory proteins. Many of these impact brain cell function.

8) Reduced Beta-Amyloid Peptide Formation – DHA reduces the accumulation of beta-amyloid peptide formation in the brain. The build up of this protein to eventually form plaques is the key physical brain change in patients with AD.

Conclusion: Omega-3 fatty acids, in particular DHA plays a major role in the prevention of AD.

Relevance to: Efalex Active 50+

Reference: Calviello G, Serini S, Piccioni E. Alzheimer's disease and n-3 polyunsaturated fatty acids: Beneficial effects and possible molecular pathways involved. *Current Signal Transduction Therapy* 2008;3:152-157.

PRESS RELEASE**A new scientific review identifies 8 ways that DHA reduces risk and/or progression of Alzheimer's Disease¹.**

Researchers at the Institute of General Pathology, Catholic University, Rome, Italy have proposed eight different plausible ways that docosahexaenoic acid (DHA) can reduce the risk of developing and the rate of progression of Alzheimer's disease (AD)¹. These mechanisms include enhanced function of brain cell membranes and specialized compartments, protection from oxidation, inflammation and cell death, and reduced formation of detrimental protein plaques that are present in the brains of those with AD. These observations are based on substantial scientific evidence generated from a multitude of preclinical studies demonstrating the benefits of omega-3 long chain polyunsaturated fatty acids (LC-PUFAs) for brain function.

In recent years, many studies have focused on potential benefits of regular consumption of fish containing omega-3 LC-PUFAs to maintain or enhance brain function with respect to dementia including AD. In November 2006, the Framingham Heart Study which followed 899 initially healthy volunteers with a median age of 76 years² showed that people who ate two or more servings of fish per week were 39 percent less likely to develop dementia, but those who ate less than that did not derive any benefit. Although oily fish contains many different fatty acids, it was only the DHA that was responsible for preventing dementia in this study. More recently a study³ included 23 people with mild or moderate AD and 23 with cognitive impairment (MCI) showed that Omega-3 LC-PUFA supplementation may improve general clinical function in patients with mild or moderate AD and mild MCI but the cognitive effects were more apparent in patients with MCI than those with AD.

A second recent study⁴ included 302 cognitively healthy adults aged 65 years or older that took either 400 mg Omega-3 (226 mg EPA+ 176 mg DHA), 1800 mg Omega-3 (1093 mg EPA+847 mg DHA) or olive oil placebo for 26 weeks. In general, cognitive test scores in all three groups improved, but changes were not significantly different among the groups and were probably mostly due to learning effects. However, men in the low dose group improved compared to placebo and people who carried the APOE-4 allele showed improvement following treatment with both doses of EPA+DHA. APOE is a gene that codes for a special protein and people with a particular form of APOE, called APOE-4 are prone to develop atherosclerosis, reduced cognitive ability and AD.

Earlier population studies have shown that DHA levels are lower than normal in people with various forms of age related cognitive decline including dementia^{5,6}. Other studies have shown that low DHA status is associated with the development of AD⁷ while high dietary fish intake⁸ and specifically DHA intake⁹ is associated with a lower incidence of cognitive decline and AD respectively. These studies clearly show low omega-3 LC-PUFA status is a risk factor for developing AD and demonstrate the importance of maintaining an adequate intake of these vital nutrients in adulthood to prevent mental deterioration. Small open, clinical studies providing DHA supplements have reported significant improvements in people with vascular dementia¹⁰ and have shown they can delay the rate of cognitive decline in patients with very mild Alzheimer Disease¹¹. Results of these studies combined with the current review on mechanism of action provide strong scientific evidence that adequate DHA intake may prevent AD.

References:

1. Calviello G, Serini S, Piccioni E. Alzheimer's disease and n-3 polyunsaturated fatty acids: Beneficial effects and possible molecular pathways involved. *Current Signal Transduction Therapy* 2008;3:152-157.
2. Schaefer EJ, Bongard V, Beiser AS, Lamont-Fava S, Robins S et al. The Framingham Heart Study. Plasma Phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer Disease. *Arch Neurol*. 2006;63:1545-1550.
3. Chiu C, Su K, Cheng T, Liu H, Chang C, Dewey M, Stewart R, Huang S. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: A preliminary randomized double-blind, placebo-controlled study. *Progress in Neuro-psychopharmacology & Biological Psychiatry* 2008;32:1538-1544.
4. Van de Rest O, Geleijnse JM, Dullemeijer C, OldeRikkert MGM, Beekman ATF, DeGroot CPGM. Effect of fish oil on cognitive performance in older subjects. *Neurology* 2008;71:430-438.
5. Tully AM, Roche HM, Doyle R, Fallon C, Bruce I et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. *British Journal of Nutrition* 2003;89:483-489.
6. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. *Lipids*. 2000;35(12):1305-12.
7. Kyle DJ et al. Low serum docosahexaenoic acid is a significant risk factor for Alzheimer's dementia. *Lipids* 1999; 34:S245.
8. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology* 2004 62(2):275-80.
9. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, et al. Consumption of fish and n-3 fatty acids and risk of incident of Alzheimer disease. *Arch Neurol* 2003;60(7):940-6.
10. Terano T, Fujishiro S, Ban T et al. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids* 1994;34 (supp):S345-S346.
11. Freund-Levi Y, Eriksdotter M, Cederholm T, Basun H, Faxén-Irving G, Garlind A, Vedin I, Vessby B, Wahlund L, Palmblad J. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer Disease: OmegaAD Study. *Arch Neurol* 2006;63:1402-1408.