

## Dietary fatty acids and the aging brain

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FROM ABSTRACT

Aging contributes to physiological decline and vulnerability to disease.

In the brain, even with minimal neuronal loss, aging increases oxidative damage, inflammation, demyelination, impaired processing, and metabolic deficits, particularly during pathological brain aging.

High-fat diabetogenic diets, cholesterol, and the omega-6 fatty acid arachidonate and its prostaglandin metabolites have all been implicated in promoting the pathogenesis of Alzheimer's disease.

Evidence presented here shows DHA acts to oppose this, exerting a plethora of pleiotropic [more than one effect] activities to protect against the pathogenesis of Alzheimer's disease.

#### KEY POINTS FROM THESE AUTHORS:

- 1) "In the United States, the government projects Medicare deficits amounting to 52 trillion dollars will arise from an aging baby boomer population's chronic diseases of aging." **[52 trillion dollars]** "This expense literally threatens to bankrupt the government and mandates healthcare reform legislation." A plethora of expensive new medications, would likely add to costs.
- 2) "Therefore, from the economic standpoint alone, there is a need for a fresh approach to the diseases of aging, including those disabling diseases that emerge with the aging brain, with the focus placed on cost-effective prevention measures."
- 3) Because diseases of aging are "primarily the consequence of chronic imbalances or dysregulation of normal pathways with important functional roles," it is unlikely that the "standard pharmacologist's strategy of finding the most potent and specific drug" will be the best approach for their prevention and management.
- 4) "Nutritional interventions are inherently pleiotropic [more than one effect] and are key regulators of signal transduction pathways that have evolved to adjust and respond to the nutrient environment."
- 5) "Nutritional interventions are not only highly relevant to aging in general, they are also inherently more likely to have lower costs and a more favorable safety profile than novel drugs." **[Key Point]**

- 6) Aging of the brain is accompanied by oxidative damage, low levels of chronic inflammation, myelin loss and loss of neurons and synapses.
- 7) Brain ageing is coupled with inflammation, oxidative damage, and reduced metabolism, and possibly mitochondrial failure. **[Low Level Laser Therapy]**
- 8) Alzheimer's disease (AD) shows an accumulation of pathological  $\beta$ -amyloid ( $A\beta$ ) protein and tau entanglements.
- 9) The risk factors for cardiovascular disease (CVD) strongly overlap those for AD. "One of the CVD dietary interventions, intake of the omega-3 (n-3) fatty acids, is not only relatively inexpensive but also has an excellent safety profile and has already been shown to reduce CVD mortality by 19–45%."
- 10) AD incidence doubles every 5 years after age 65.
- 11) "While aging is the biggest single risk factor, AD is not an inevitable consequence of aging." **[Important]**
- 12) The development of AD is subject to multiple genetic and environmental risk factors.
- 13) The apolipoprotein E4 (ApoE4) is by far the single most potent and best-established genetic risk factor for AD. This gene is involved in cholesterol metabolism, oxidative damage, and inflammation.
- 14) "Environmental factors that may impact AD risk include essential polyunsaturated fatty acids, which are substrates for pathways dysregulated in AD pathogenesis such as lipid peroxidation and cyclooxygenase (COX) and lipoxygenase (LOX) enzymes."
- 15) Increased consumption of "fish/n-3 fatty acids, and lipid-soluble antioxidants like vitamin E that prevent lipid peroxidation has been reported to reduce AD risk."
- 16) AD is initiated by increased  $A\beta$  protein accumulation.  $A\beta$  protein interacts with metals to cause oxidative damage and neuroinflammation causing synaptic dysfunction and loss along with tau neurofibrillary tangles.
- 17) Diabetes doubles the AD risk.
- 18) "Western diets are typically high in n-6 fatty acids, notably linoleic acid, which is an AA precursor, and comparatively low in the n-3 fatty acids, alpha linolenic acid, and the long-chain marine fatty acids, DHA, and eicosapentaenoic acid (EPA)."

- 19) "N-6 and n-3 fatty acids compete for incorporation into the labile second position of brain phospholipids, so that high n-6, low n-3 intake ultimately leads to a preponderance of AA in brain phospholipids. Since AA is the substrate for COX and LOX enzymes, this creates a net proinflammatory environment that interacts directly with AD pathogenesis."
- 20) "Mediterranean diets appear to reduce AD and other dementia risk and have lower levels of added sugar, saturated fat, trans-fat (n-6) fatty acids, and linoleic acid, a lower glycemic index, and a lower ratio of (n-6):(n-3) fatty acids."
- 21) A key ingredient of the Mediterranean diet is higher n-3 intake in relation to n-6 fatty acids.
- 22) "N-3 fatty acids exert pleiotropic [more than one effect] effects on the cardiovascular and central nervous systems that may be protective against age-related cognitive decline caused by either vascular or Alzheimer's dementia or a mix of both."
- 23) "Low n-3 fatty acid intake is one of many overlapping risk factors for both CVD and AD that include type II diabetes, hypercholesterolemia, hypertension, hyperhomocysteinemia, dietary saturated fats, cholesterol, low intake of antioxidants, high alcohol consumption, low physical activity or sedentary lifestyle, the presence of atrial fibrillation, and atherosclerotic disease."
- 24) "Studies have often shown a 40–50% reduced risk of dementia associated with high n-3 intake."
- 25) DHA is less effective in those who are ApoE4 carriers.
- 26) Those in the upper quartile of plasma DHA (and no other lipid) have reduced dementia and AD. "The protected group had daily DHA intake estimated to average approximately 180 mg/day, which is more than double the average US daily intake."
- 27) The neuroprotective or anti-AD effects of DHA include:
- A)) Anti-inflammatory. DHA reduces AA and metabolites via COX and LOX.
  - B)) Increased synthesis of brain-derived neurotrophic factor, a major neuroprotective factor. This and other effects of DHA can be enhanced by exercise.
  - C)) Antioxidant. Stimulation of increased antioxidant enzymes (catalase, glutathione peroxidase) have been shown.
  - D)) Promotion of neurogenesis and neurite outgrowth. Dietary DHA promotes neurogenesis, neurite outgrowth, and improved cognition.

- E)) DHA improves synaptic membrane fluidity.
- F)) DHA reduces A $\beta$  production by several proposed mechanisms.
- G)) DHA limits formation of tau pathology/neurofibrillary tangles.
- 28) "DHA is remarkably pleiotropic [more than one effect], with many mechanisms for reducing A $\beta$  production, tau kinases and tau pathology, neurodegenerative pathways, and neuron and synapse loss."
- 29) "DHA is very susceptible to lipid peroxidation,... providing a very strong rationale for combining DHA with protective antioxidants like alpha lipoic acid or vitamin E." **[Very Important]**
- 30) "The combination of DHA with the polyphenolic antioxidant curcumin has also been advocated because the latter has additional anti-aging, anti-amyloid, and AD protective activities." **[Important]**
- 31) "Increasing intake of n-3 fatty acids, including marine long-chain n-3 and DHA in particular, appears to offer some protection against unhealthy brain aging that leads to dementia."
- 32) The principal neuroprotective component of fish oil is DHA.
- 33) A nutritional cocktail including DHA, antioxidants, B vitamins, and other synergistic components may prove to exert stronger protective effects for the prevention of AD.
- 34) By incorporating DHA into membrane phospholipids, DHA may also have multiple "fluidizing" effects on membrane structure and protein-protein coupling.
- 35) "DHA incorporation will also competitively reduce membrane levels of AA, whose release from membrane phospholipids by phospholipase A2 generates free intracellular AA, which is a substrate for COX and LOX enzymes that produce various prostaglandin, and leukotriene products known to promote the elevated inflammation and excitotoxicity involved in AD pathogenesis."
- 36) "DHA itself is transformed by LOX to a potent neuroprotective mediator, neuroprotectin D1, along with related mediators that have anti-inflammatory, neuroprotective, and other anti-AD activities."
- 37) "In summary, DHA has multiple pleiotropic [more than one effect] activities predicted to slow AD pathogenesis at many levels."