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Review

The pleiotropic effects of omega-3 docosahexaenoic acid on the hallmarks of Alzheimer's disease

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Abstract

Among omega-3 polyunsaturated fatty acids (PUFA), docosahexaenoic acid (DHA, 22:6n-3) is important for adequate brain development and cognition. DHA is highly concentrated in the brain and plays an essential role in brain functioning. DHA, one of the major constituents in fish fats, readily cross the blood–brain barrier (BBB) from blood to the brain. Its critical role was further supported by its reduced levels in the brain of Alzheimer's disease (AD) patients. This agrees with a potential role of DHA in memory, learning, and cognitive processes. Since there is yet no cure for dementia such as AD, there is growing interest in the role of DHA supplemented diet in the prevention of AD pathogenesis. Accordingly, animal, epidemiological, preclinical and clinical studies indicated that DHA has neuroprotective effects in a number of neurodegenerative conditions including AD. The beneficial effects of this key omega-3 fatty acid supplementation may depend on the stage of disease progression, other dietary mediators, and Apolipoprotein E (ApoE) genotype. Herein, our review investigates, from animal and cell culture studies, the molecular mechanisms involved in the neuroprotective potential of DHA with emphasis on AD.

Abbreviations: AA, arachidonic acid; Aβ, β-amyloid; AβO, Aβ oligomers; Acg, anterior cingulate gyrus; Amyg, amygdala; APP, amyloid protein precursor; BACE, beta-site APP cleaving enzyme; βAPP, amyloid precursor protein beta; BDNF: brain-derived neurotrophic factor; CaMKII, calcium/calmodulin-dependent protein kinase II; Cer, cerbellum; ChAT, choline acetyltransferase; Chol, cholesterol; Cx, cortex; CxFr, cortex frontal; COX-2, cyclooxygenase-2; $cPLA_2$, cytosolic phospholipase A_2; Dg, dentate gyrus; DA, dopamine; DHA, docosahexaenoic acid; DHA-EE, DHA ethyl ester; DPA, docosapentaenoic acid; EC, enthorinal cortex; EPA,eicosapentaenoic acid; ERK, extracellular signal-related kinase; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GSK-3beta, glycogen synthase kinase-3beta; GFRa1, GDNF family receptor alpha-1; Hip, hippocampus; HipV, ventral hippocampus; IRS-1, insulin receptor substrate 1;JNK, c-Jun N-terminal kinase; 5-LOX, 5-lipoxygenase; LPO, lipid peroxide; LT, leukotriene; n.d., not determined; NFκB, nuclear factor kappa B; NFT, neurofibrillary tangle; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NPD, neuroprotectin; 2-OHDHA; 2-hydroxy docosahexaenoic acid; PE, phosphatidyl-ethanolamine; PFC: prefrontal cortex; PI3-K, phosphatidylinositol 3-kinase; PPAR, peroxisomal proliferator-activated receptor; PS, phosphatidylserine; PS1, presenilin 1; RARs, Retinoic acid receptors; rCBV, relative cerebral blood volume; ROS, reactive oxygen species; RXR, retinoid X receptor; RvD1, resolvin D1; SAMP8, senescence-accelerated mouse prone 8; sAPPα, soluble amyloid precursor protein alpha; Str, striatum; +, positive effect.

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