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Alzheimer´s disease

Neurotoxic Beta Amyloid Peptides in Alzheimer's Disease [1]

lzheimer's disease(**AD**), also referred to simply as **Alzheimer's**, is a chronic neurodegenerative disease that usually starts slowly and worsens over time [2]. Alzheimer's disease is characterized by the presence of neurotoxic beta-amyloid (Aß) deposits in the brain, the so called “amyloid plaques”. The plaques assemble from A? peptides, which are produced by the proteolytic cleavage of the transmembrane protein amyloid precursor (APP) by secretases. The cleavage of APP by the b-secretase leads to the production of an insoluble amyloid beta peptide, which is released to the extracellular space. APP is cleaved into A? peptide isoforms (A?1–40 and A?1–42). The ratio of these two isoforms is influenced by the pattern of cleavage from APP by ?, ?, and ? secretases. The A?1–42 peptide aggregates more readily than A?1–40 [3].

The pathogenesis of Alzheimer´s Disease

There are two core pathological hallmarks of Alzheimer’s disease: The amyloid plaques and neurofibrillary tangles (NfTs). Amyloid plaques are composed of b-amyloid peptides (Ab), while NFTs contain hyperphosphorylated tau proteins [4]. Upon plaque formation, cells undergo cell death and intracellular amyloid structures become released into the extracellular space. These data imply a mechanism where the pathogenic activity of A? is attributed, at least in part, to intracellular aggregates [5].

Neurofbrillary tanglesNFTs in Alzheimer’s disease: [6]

As a key contributor to memory storage, the synapse is one of the earliest affected neuronal components in Alzheimer´s disease (AD). Under physiological conditions, the synaptic connections between neurons undergo activity-dependent functional and morphological re-organization. Thus, proteins that are implicated in preserving the organization and dynamics of synaptic connections have attracted much focus for their involvement in the malfunctioning AD synapse. Neurofibrillary tangles (NFTs) are another fundamental neuropathological hallmark of AD in addition to the amyloid plaques. NFT-bearing neurons have been characterized by loss of cytoskelettal microtubules and tubulin-associated proteins.

Synaptic activity and Alzheimer`s diseases: [7]

In the last decade, important studies demonstrated that the state of activation of synapses affects the homeostasis of beta-amyloid (A?) and tau, both of which aggregate and accumulate during AD, and are

involved in neuronal dysfunction. The loss of synapses is the best pathologic correlate of cognitive impairment in AD patients [8]. AD represents, at least initially, an attack on synapses finally leading to morphological and functional alterations to the synaptic efficiency in hippocampal neurons. Even in very mildly impaired patients, soluble A? levels in the cortex show a significant correlation with degree of synaptic loss [9]. A?-protein Induces changes in synaptic efficacy *in vivo* [10]. ^Since AD is characterized by the presence of increased numbers of neurofibrillary tangles (NFT) and amyloid containing senile plaques (SP) in the neocortex and hippocampus [11]. synaptic contacts in both the neocortex and hippocampus become less and disappear [12].

What can lipids do?

The species ***Lappula*** belongs to the Bornniaceae. *L. squarrosa* is widely distributed in European Russia except for the Arctic. It grows on waste lands, disposal sites, and shoulders of roads and in fields and gardens. Few reports of the lipid composition of seeds from *E. vulgare* and *L. squarrosa* have appeared. Studies in this area are limited to a determination of the FA compositions of seeds from these species [13, 14].

Although the Impact of Docosahexaenoic Acid (DHA) on Alzheimer's Disease is still not clarified, DHA has been suggested to exert cognitive-enhancing effects and epidemiological studies have suggested that regular consumption of fish or omega-3 fatty acid enriched diets can attenuate the cognitive decline in AD and/or lower the risk of developing AD. Relative to healthy human brain samples, postmortem AD brain samples have been shown to exhibit lower docosahexaenoic acid (DHA) levels, an essential polyunsaturated fatty acid required for normal neuronal function. [15],

Lipids from seeds of the plant *Lappula squarrosa* of the family *Boraginaceae* were determined. Four polyunsaturated acids (PUFA), linoleic (LA), g-linolenic (GLA), a-linolenic (ALA), and stearidonic (SA), were identified among the fatty acids. The highest amount of SA (16.8%) was found in . *L.squarrosa* seeds. It becomes understandable that plant oils containing these PUFA in sufficient quantities in their FAs have special biological value and bioavailability. The genera *Echium*, *Lappula*, and *Lithospermum* are the richest sources of 18:4 acid among plants of the family Boraginaceae [16].

Stearidonic acid (SA, 18:4*n*-3) is a polyunsaturated fatty acid (PUFA) that constitutes the first metabolite of a-linolenic acid (ALA, 18:3*n*-3) in the metabolic pathway leading to C20–22 PUFA, such as eicosapentaenoic acid (EPA, 20:5*n*-3), and docosahexaenoic acid (DHA, 22:6*n*-3) [17]. In figure 1 the Synthesis of DHA starting frrom stearidonic acid is shown [18].

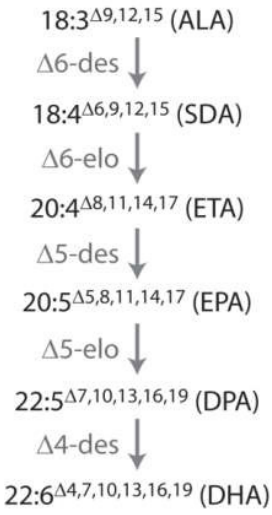

Figure 1 DHA synthesis pathway. The omega-3 long chain polyunsaturated fatty acid synthesis pathway described in this study. 'Des' refers to desaturase and 'elo' refers to elongase. The fatty acids are ALA, a-linolenic acid; SDA, stearidonic acid; ETA, eicosatetraenoic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid

The dietary essential **p**oly **u**nsaturated **f**atty **a**cid (PUFA) DHA is a critical contributor to cell structure and function in the nervous system. As described above, deficits in DHA abundance are associated with cognitive decline in neurodegenerative diseasse like Alzheimer`s. The neuroprotective function of DHA implies important determinant and regulatory interactions with the molecular-genetic mechanisms affecting the APP and the A? peptide neurobiology. Deficids in DHA or its peroxidation appear to contribute to neuronal dysfunction in Alzheimer`s disease [19].

DHA cannot be synthesized de novo in mammals, and therefore, must be obtained in the diet or **synthesized within the body from ALA**. The pathway of the biosynthesis is described above in Fig. 1. There is evidence that DHA synthesis from ALA can be sufficient to maintain brain function [20].

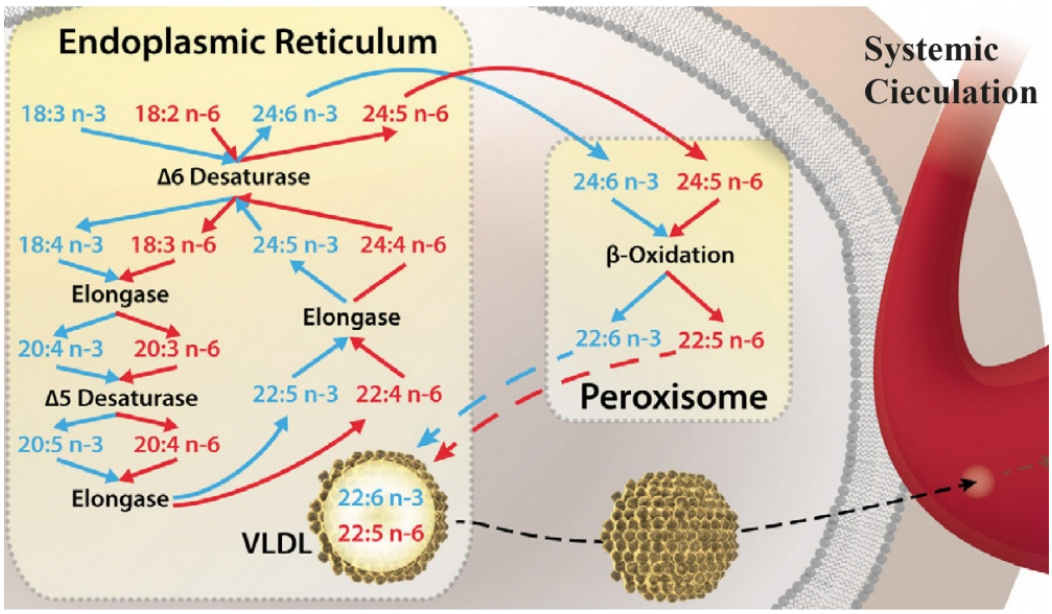

Figure 2: DHA is synthesized from ALA in the liver. by a series of desaturations, elongations and a b-oxidation. Enzymes involved in the synthesis of DHA from ALA. The desaturations and elongations occur in the endoplasmic reticulum and the b-oxidation occurs in the peroxisome. The final products (DHA and 22:5n-6) are then transferred back to the endoplasmic reticulum where they along with other PUFA can be esterified to lipoproteins (eg. VLDL) and are secreted into the blood [20].

From epidemiologic and animal studies it has been suggested that dietary fish or fish oil rich in w -3 fatty acids, for example DHA and eicosapentaenoic acid, may prevent Alzheimer disease (AD). To determine effects of dietary w -3 fatty acid supplementation on cognitive functions in patients with mild to moderate AD, Two hundred four patients (age range [mean±SD], 74±9 years were included in a randomized, double-blind, placebo-controlled clinical trial. Administration of w-3 fatty acid did not delay the rate of cognitive decline according to the MMSE or the cognitive portion of the Alzheimer Disease Assessment Scale. However, positive effects were observed in a small group of patients with very mild AD (MMSE 27 points) [21].

Summary

Lipid oil extracted from the seeds of plant *Lappula squarrosa* contains Stearidonic acid. SA is a D6-unsaturated C18 omega-3 fatty acid, which is the first metabolite of a-linolenic acid leading to C20–22 PUFA, such as eicosapentaenoic acid and docosahexaenoic acid (**DHA**) [17], of which positive effects were observed in patients with very mild AD [21]. DHA can be obtained directly from the diet or synthesized in the body from ALA in the liver.

Library

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