EFFECTS OF DOCOSAHEXAENOIC ACID ON THE PREVENTION AND DEVELOPMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment of activities of daily living, and a variety of neuropsychiatric symptoms and behavioural disturbances. Prevalence studies suggest that in 2000 the number of persons with AD in the US is 4.5 million (1). About 1% of 60-year-olds and about 25% of 80-year olds have the disease. Without significant advances in therapy, the number of symptomatic cases in the US is predicted to rise to 13.2 million by 2050. The cost of caring for patients with AD is estimated to be more than 80 billion US dollars. These figures underline the urgency of finding new and more effective therapeutic interventions than those available today.

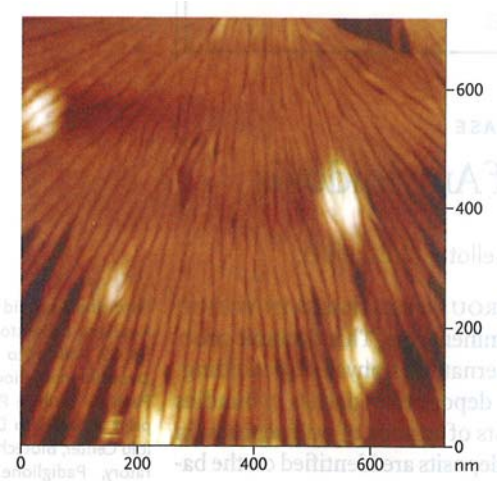
Treatment of AD includes five major components: neuroprotective strategies, cholinesterase inhibitors, non-pharmacologic interventions and psychopharmacological agents to reduce behavioural disturbances, health maintenance activities, and alliance between clinicians and family members. Treatment requires accurate diagnosis and is increasingly based on an understanding of the pathophysiology of the disease.

Symptoms of AD are related to deposition of pathologic protein called amyloid on the surface of brain neurons and within the cells, leading to nerve cell degeneration. This so called amyloid-beta (Aβ) peptide is derived from a normal transmembrane protein containing about 700 amino-acids called amyloid precursor protein (APP), located in the limbic system as well as other parts of the brain. The physiologic function of this protein has not been fully elucidated, and the reason for its potential deterioration into the Aβ peptide, with consequent toxic effects on the neurons, has been a matter of scientific interest for many years. Aβ peptides promote proinflammatory responses and are activators of neurotoxic pathways leading to brain cell dysfunction and cell death. Another type of amyloid in AD is located inside the neurons, forming so-called fibrillar tangles. The precursor protein for this type of amyloid is the tau protein. The role of fibrillar tangles in the onset and progression of AD remains unresolved.

How can a normal protein turn into a toxic compound inducing local damage in brain cells? APP is certainly not the only example of a normal protein turning into amyloid fibrils. Today we know of 24 precursor proteins in humans capable of being transformed into amyloid fibrils in the same way (2). Peptides are formed by cleavage of the protein chain by secretases. Some of the secretases produce non-amyloidogenic fragments while others generate a variety of potentially amyloidogenic species. The reason for this pathophysiologic reaction is not known but it is probably related to genetic modifications suppressing the normal and promoting formation of potentially harmful protein secretases. The importance of dietary components which could promote or prevent development of amyloid is a subject of debate as well as a providing a theoretical basis for epidemiologic and intervention studies. Amyloid as such is nothing more than accumulation of peptide chains, not in the normal loose configuration of alfa and beta chains but with a solid packing of beta-sheets, rendering the amyloid fibrils practically resistant to degradation by proteases and lysosome (Fig. 1). When accumulation has started and a critical mass of amyloid has been deposited, a point of no return seems to

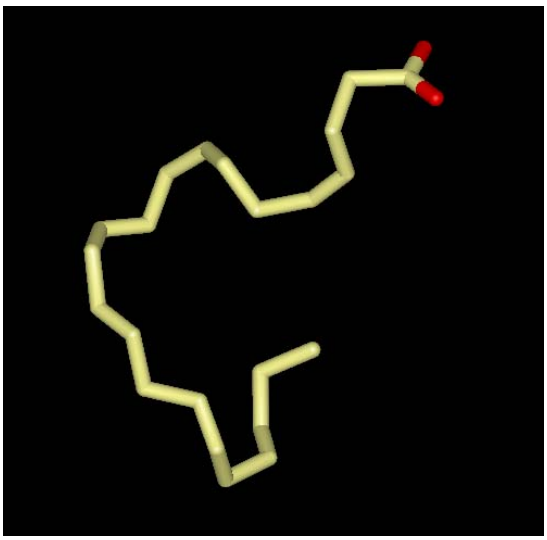
be reached after which degradation mechanisms have only minimal effect. Whether all these mechanisms are normal procedures in the aging process of the organism or a pathological feature induced by some risk factors is not known at present.

Fig. 1
Tight packing of amyloid fibrils (atomic-force microscopy)



Docosahexaenoic acid (DHA, 22:6n-3), the second most abundant of the omega-3 fatty acids in fish oil, is concentrated in brain cells as well as in the photoreceptors of the retina (fig. 2). So far it has been assumed that the DHA integrated into the phospholipid membrane of the brain cells has mainly exerted actions relating to normal cell function, such as propagation of electrical signals conducted in the neurons. Patients with AD have reduced levels of DHA (3) but it is not known whether this is due to a seafood-deficient diet or if it is a secondary reaction to an inflammatory process such as free-radical mediated lipid peroxidation. Reduced DHA serum content has even been correlated with general cognitive impairment in people not diagnosed with AD (4).

Fig. 2
Three-dimensional image of the DHA molecule



So, in addition to being a structural component of nerve cell membranes, what subtle memory-related function might DHA have in the brain? Epidemiologic studies in healthy people have clearly demonstrated that eating fish has a protective effect against development of AD. Cohort studies from Rotterdam, Holland (5), Bordeaux, France (6), and the US (7) have unanimously demonstrated a lower risk of developing dementia in people with a regular intake of seafood compared with non-fish eaters.

In the brain cell membrane DHA is integrated into the phospholipid bilayer. DHA is released. by activation of the enzyme phospholipase A2, and is used as the raw material for synthesis of other compounds in the brain. After being released, DHA is converted into docosatrienoic acid (DTA, 22:3n-3) by the enzyme 15-lipoxygenase. Recently DTA has been demonstrated to have a neuroprotective effect against brain ischemia in a mouse model (8). In vitro experiments using retinal pigment epithelial cells demonstrated potent anti-apoptotic as well as anti-inflammatory actions (9). The compound has therefore been given the name Neuroprotectin, underlining the importance of this fatty acid in the protection of brain cells.

In another in vitro experiment in human neurons and glia cells, production of Aβ peptides increased as a function of the number of weeks in culture, mimicking the aging procedure of brain cells. However, when DTA was added, a repression of Aβ-triggered activation of proinflammatory and antiapoptotic genes was observed (10). These results indicated that DTA promoted cell survival via the induction of antiapoptotic and neuroprotective gene-expression programs that suppress Aβ peptide-induced neurotoxicity. In the same study, the production of Aβ peptides was also reduced due to down-regulation of the specific gene.

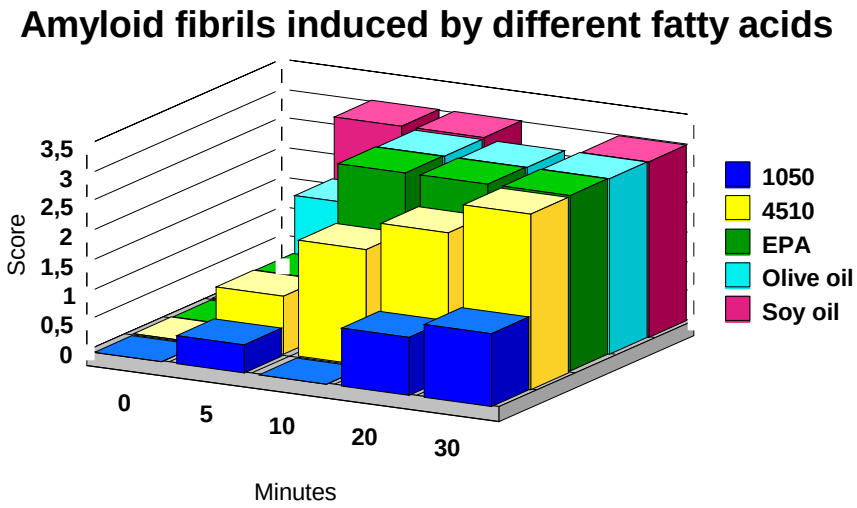
We are now starting to realise the importance of DHA in the brain, not only as a structural component of brain cells, but also as a natural compound that protects the aging brain cells from degradation by neurotoxic mechanisms. In a clinical context this would mean that the DHA normally integrated into the nerve cell wall could have a protective effect against brain cell death induced by the pathologic formation of amyloid. At this stage we do not know whether the formation of Aβ amyloid and tau amyloid is a degenerative function of aging or whether it is induced by some other pathological event in the brain. However, DHA and its metabolite DTA seem to have a preventive effect against the development of brain cell death.

Today we have access to so-called transgenic mice which develop neuron amyloid resembling the human amyloid deposition in brain cells that leads to AD. These animals are ideal for understanding the pathophysiology of the diseases and as a tool for the development of new therapeutic regimes. Two recently published studies have confirmed data from the in vitro studies presented above. One study demonstrated a protective effect of DHA on brain cell death (11). The other study showed positive effects in the prevention of amyloid formation in the mouse brain (12). Together these studies confirm the protective and even preventive effect of DHA in AD. However, we will need to conduct prospective clinical studies that demonstrate effects on cognitive impairment in AD patients before we can fully understand the potential and importance of DHA substitution in elderly individuals for the prevention and treatment of AD.

It was not possible to use pure DHA in a clinical study, since this would have required a full preclinical and clinical evaluation of safety prior to testing in AD patients. Therefore a series of tests were performed incubating precursor proteins which spontaneously form amyloid fibrils with solutions of different fatty acid combinations. The experimental setup has been described by Wilson and Binder (13). Essentially, it involves detecting the occurrence of amyloid fibrils at defined time intervals by fluorescence spectroscopy. We tested the following omega-3 preparations: EPAX 1050TG (containing 50% DHA), EPAX

4510TG (containing 45% eicosapentaenoic acid, EPA), and pure EPA (95% EPA) and compared them with olive oil (72% oleic acid, OA) and soy oil (53% linoleic acid, LA). As in the Wilson and Binder study, fibrils appeared earliest in the LA solution. OA and EPA also seemed to provoke fibril formation (Fig. 3). However, the solution containing the highest concentration of DHA, EPAX1050, seemed to prevent in vitro amyloid fibril formation (data on file).

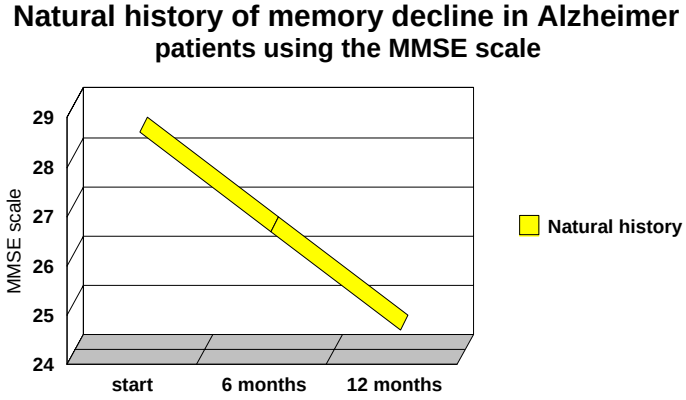
Fig. 3



Therefore EPAX1050 was considered to have potential in the prevention or even treatment of amyloid. A clinical study, The OmegAD study at the Karolinska Hospital in Stockholm, Sweden, was planned to test the hypothesis that AD patients in an early stage of the disease could benefit from treatment with this study drug. The main parameters were linked to cognition, using the Mini Mental Stage Examination (MMSE) and the Alzheimer's disease Assessment scale (ADAS cog). 204 patients with AD and no other serious illness were included. All patients were treated with cholinesterase inhibitors. The patients were randomly allocated to treatment with EPAX1050TG, providing a daily dose of about 1,7g of DHA, or with matching placebo. The placebo-controlled part of the study had a duration of 6 months after which all the patients were treated with EPAX1050TG for another 6 months. 174 patients completed the protocol and the drop-out rate did not differ between the treatment groups (14). The study drug was well tolerated and safe.

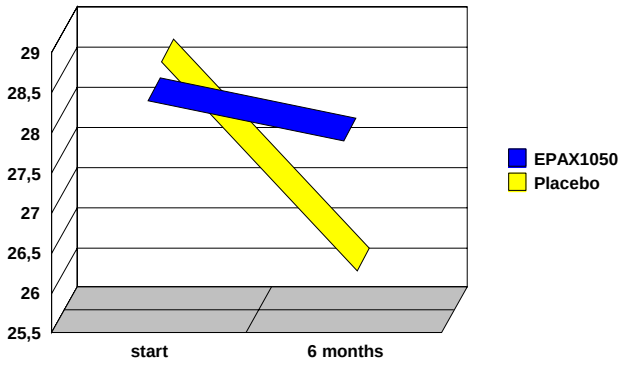
In the total group no difference was observed between the actively treated group and the placebo group. However, interesting differences were observed in the group of patients with very mild AD (defined as MMSE>27 points). Using the MMSE these patients will normally loose 4 points in a year (Fig. 4).

Fig. 4



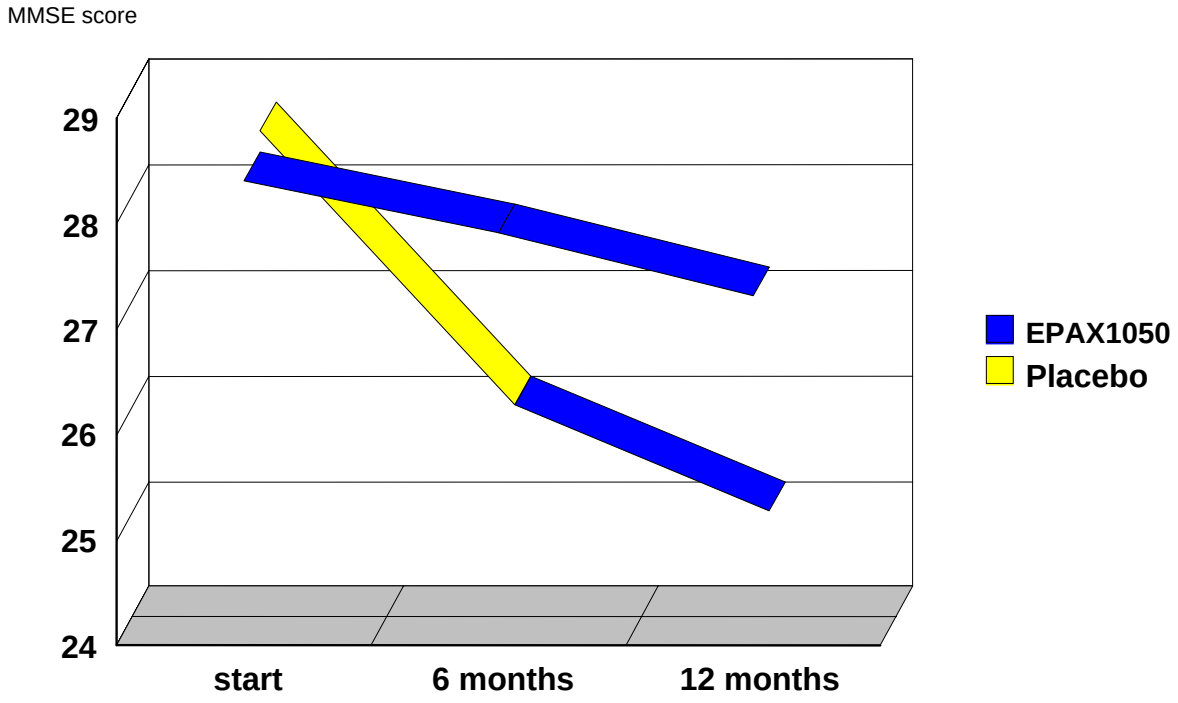
However, memory decline was halted in the group given active treatment, while the placebo group closely followed the natural history of the diseases (Fig. 5). The difference was statistically significant (p=0,024).

Fig. 5



When the switch was made from placebo to EPAX1050TG, the pattern of memory decline also changed in what had initially been the placebo group, displaying an MMSE curve parallel to that of the group given active treatment during the whole study period (Fig. 6).

Fig. 6



An analysis of each sub-item of the MMSE scale, showed significant treatment effects over time, in particular in "delayed word recall" (p=0,036) and "attention" (p=0,047) abilities. The same pattern was also found using the ADAS-cog method.

The study indicates that the DHA-rich omega-3 concentrate EPAX1050TG given for 6 months to patients with AD leads to a slower decline of cognition in the patients with the mildest impairment compared with the placebo treated controls. This was also observed

in the second part of the study, when all patients were on active treatment. Here the rate of decline in the previously placebo-treated patients showed a deceleration corresponding to that observed in the patients who received the DHA preparation during the whole trial. The study suggests that a DHA rich omega-3 concentrate can be used for preventive as well as therapeutic purposes in early AD, and also in persons at risk of developing AD.

Very recently a poster presentation at the International Neurology Congress in Madrid also demonstrated positive effects in AD patients using the omega-3 pharmaceutical Omacor (15). Using a new imaging technique it was possible to demonstrate positive effects in the brain of the group treated with Omacor, in addition to improvement in cognition.

The positive impact of healthy eating, with a regular intake of seafood, has been convincingly confirmed in the prevention and treatment of cardiovascular, eye, and mental diseases as well as in dementia. In fact, the Alzheimer's Foundation of America recommends that consumers eat a diet with an abundant supply of omega-3 fatty acids for brain health (16).We are now at a stage where one compound, namely DHA, stands out as a natural remedy with seemingly well-defined actions in the prevention of the brain cell degradation arising when normal proteins turn evil and form amyloid deposits, leading in turn to nerve cell death. A regular intake of DHA from seafood has been demonstrated to have a preventive effect against development of AD in healthy individuals. The positive results from the OmegAD study clearly indicate that a high DHA concentrate has effects on cognition in patients in an early stage of AD. Even patients at high risk of developing AD might benefit from a regular intake of DHA. It is too early to describe the results so far as a break-through in the endeavour to find a therapy which could interact in the patophysiologic events of AD. Interestingly, however, DHA seems to offer a naturally derived remedy with a mode-of-action which seems very relevant in combination with good tolerability.

REFERENCES

1) Herbert LE, et al. Alzheimer's disease in the US population: prevalence estimates using the 2000 consensus. Arch Neurol 2003;60:119-1122
2) Westermark P, et al. Amyloid. Amyloid fibril protein nomenclature – 2002. J Protein Folding Disord 2002;9:197-200
3) Soderberg M, et al. Fatty acid composition of brain phospholipids in aging and Alzheimer's disease. LIPIDS 1991;26:421-425
4) Conquer JA, et al. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids 2000;35:1305-1312
5) Kalmijn S, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42:776-82
6) Barberger-Gateau P, et al. Fish, meat, and risk of dementia: cohort study. BMJ 2002;325:932-3.
7) Morris MC, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60:940-6.
8) Marceselli VL, et al. Novel docosanoids inhibit brain ischaemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. J Biol Chem 2003;278:43807-43817
9) Mukherjee PK, et al. Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. Proc Natl Acad Sci USA 2004;101:8491-8496
10) Lukiw WJ, et al. A role for docosahexaenoic acid derived neuroprotection D1 in neural cell survival and Alzheimer diseases. J Clin Invest 2005;September 8:1-10
11) Calon F, et al. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. Neuron 2004;43:633-645
12) Lim GP, et al. A diet rich with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci 2005;25:3032-3040
13) Wilson DM and Binder LI. Free fatty acids stimulate the polymerization of Tau and Amyloid β peptides. Am J of Pathol 1997;150:2181-2195
14) Freund Levi, Y, et al. Omega-3 fatty acid treatment of 174 patients with mild to moderate Alzheimer's disease (OmegAD): a randomised double-blind trial. Archives of Neurology 2006; 63: 1402-1408.
15) Pretorius HT, et al. Omega-3 fat use to stimulate brain perfusion for early diagnosis of dementia and possible therapy. Internat Conference Neurol Madrid July 2006
16) Brewster E. Brain and memory. Nutritional outlook June 2005:37-38