



DHA and cholesterol containing diets influence Alzheimer-like pathology, cognition and cerebral vasculature in APP_{swe}/PS1_{dE9} mice

C.R. Hooijmans^a, C.E.E.M. Van der Zee^b, P.J. Dederen^a, K.M. Brouwer^a, Y.D. Reijmer^a, T. van Groen^c, L.M. Broersen^d, D. Lütjohann^e, A. Heerschap^f, A.J. Kiliaan^{a,*}

^a Radboud University Nijmegen Medical Center, Donders Institute for Brain, Cognition and Behaviour, (department: Anatomy and Cognitive Neuroscience) Geert Grooteplein noord 21, PO BOX 9101, 6500 HB, Nijmegen, The Netherlands

^b Radboud University Nijmegen Medical Center, Donders Institute for Brain, Cognition and Behaviour, (department: Cell Biology), NCMLS, Geert Grooteplein zuid 26, 6525 GA, Nijmegen, The Netherlands

^c University of Alabama at Birmingham, Department of Cell Biology, AL 35294-0006, Birmingham, USA

^d Danone Research, PO Box 7005, 6700 CA, Wageningen, The Netherlands

^e University of Bonn, Institute of Clinical Chemistry and Pharmacology, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany

^f Radboud University Nijmegen Medical Center, Donders Institute for Brain, Cognition and Behaviour, (department: Radiology), Geert Grooteplein zuid 10, 6500 HB, Nijmegen, The Netherlands

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ABSTRACT

Cholesterol and docosahexenoic acid (DHA) may affect degenerative processes in Alzheimer's Disease (AD) by influencing A β metabolism indirectly via the vasculature. We investigated whether DHA-enriched diets or cholesterol-containing Typical Western Diets (TWD) alter behavior and cognition, cerebral hemodynamics (relative cerebral blood volume (rCBV)) and A β deposition in 8- and 15-month-old APP_{swe}/PS1_{dE9} mice. In addition we investigated whether changes in rCBV precede changes in A β deposition or vice versa. Mice were fed regular rodent chow, a TWD-, or a DHA-containing diet. Behavior, learning and memory were investigated, and rCBV was measured using contrast-enhanced MRI. The A β load was visualized immunohistochemically. We demonstrate that DHA altered rCBV in 8-month-old APP/PS1 and wild type mice [AU1]. In 15-month-old APP/PS1 mice DHA supplementation improved spatial memory, decreased A β deposition and slightly increased rCBV, indicating that a DHA-enriched diet can diminish AD-like pathology. In contrast, TWD diets decreased rCBV in 15-month-old mice. The present data indicate that long-term dietary interventions change AD-like pathology in APP/PS1 mice. Additionally, effects of the tested diets on vascular parameters were observed before effects on A β load were noted. These data underline the importance of vascular factors in the APP/PS1 mouse model of AD pathology.

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Introduction

The cause of Alzheimer's disease (AD) is still largely unknown despite many years of extensive research. Since AD is characterized by the presence of neurofibrillary tangles and amyloid- β (A β) containing aggregates in neuritic plaques and cerebral vessel walls, it has been suggested that accumulation of cerebral A β is the primary influence driving AD pathogenesis (the amyloid- β hypothesis; Selkoe, 2002). However, gene mutations in presenilin 1 (PS1), presenilin 2 (PS2), or amyloid precursor protein (APP) responsible for increased production of A β (Selkoe and Schenk, 2003), are only responsible for approximately 5% of all cases of AD worldwide. Therefore, it could be suggested that beside A β , other AD risk factors such as cardiovascular-, lifestyle- or environmental factors, play an

important role in the development of AD (Breteler, 2000; Dosunmu et al., 2007; Meyer et al., 1998).

There are indications that modification of lifestyle factors, such as nutrition, alter the risk of developing AD later in life (Dosunmu et al., 2007; Gillette Guyonnet et al., 2007). For example, high serum cholesterol, which can be caused by dietary intake, is an important risk factor in AD (Kivipelto et al., 2002, 2001). The role of cholesterol in AD is also strengthened by epidemiological studies that associate cholesterol lowering statins with diminished prevalence of AD (Jick et al., 2000) and with less deterioration of cognitive functions (Sparks et al., 2005). Identification of the cholesterol transporter apolipoprotein E4 as a major genetic risk factor for hypercholesterolemia, vascular dementia and sporadic AD (Corder et al., 1994; Poirier et al., 1993; Strittmatter et al., 1993), has reinforced the relationship between cholesterol and AD. Further support comes from cell culture and experimental animal studies. For example, reduction of cellular cholesterol levels in rat hippocampal neurons reduce the formation of A β (Simons et al.,

* Corresponding author. Fax: +31 243613789.

E-mail address: A.Kiliaan@anat.umcn.nl (A.J. Kiliaan).

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1998), whereas high dietary cholesterol intake in double transgenic AD mice increases A β accumulation (Hooijmans et al., 2007b; Refolo et al., 2000). In addition, a study in guinea pigs showed that lowering whole body cholesterol with statins decreases A β formation (Fassbender et al., 2001).

Another lipid diet factor influencing the risk of AD is the omega-3 long chain poly-unsaturated fatty acid (n-3 lc-PUFA) docosahexenoic acid (DHA). The Framingham Heart study showed that people with high plasma DHA levels have a decreased risk of developing AD (Schaefer et al., 2006). Also other epidemiological studies have indicated that sufficient DHA intake reduces the risk of developing AD (Barberger-Gateau et al., 2002; Kalmijn et al., 1997b; Morris et al., 2003). Several studies have shown that dietary intake of n-3 PUFA may reduce cognitive decline (Kotani et al., 2006; van Gelder et al., 2007), and a recent trial by Freund-Levi et al. (2006) showed positive effects of DHA supplementation on cognition in patients with very mild AD. Recent experimental studies in APP transgenic mice reported decreased brain A β levels after dietary DHA supplementation (Lim et al., 2005; Oksman et al., 2006). It has been proposed that DHA supplementation increases the amount of the neuronal sorting protein LR11 which regulates APP processing together with a subsequent decrease in A β production (Ma et al., 2007). In addition, Calon et al. (2004) showed that DHA supplementation to DHA depleted tg2576 AD mice improved memory acquisition. Taken together, the above-mentioned data show that high cholesterol levels or low plasma DHA levels are risk factors for AD. Moreover, cholesterol and DHA are also involved in cardiovascular diseases such as hypertension and atherosclerosis (Skoog and Gustafson, 2006). It could therefore be suggested that cholesterol and DHA may also exert their effects on the development of AD by influencing the peripheral and cerebral vasculature. A recent study performed in our lab, showed that a cholesterol enriched Typical Western Diet (TWD) and a DHA diet, indeed, influenced cerebral hemodynamics such as the cerebral blood volume (CBV) in 18-month-old double transgenic APP/PS1 mice (Hooijmans et al., 2007b). This is in line with studies showing that CBV is affected in AD (Harris et al., 1998). In addition a study from Niwa et al. (2002) showed that in Tg2576 Alzheimer mice cerebral blood flow (CBF) was reduced throughout the brain prior to A β deposition, suggesting that cerebrovascular abnormalities are early events in the pathogenesis of Alzheimer's disease.

Our study also showed that the cholesterol enriched TWD diet increased plaque burden in the hippocampus, whereas the DHA-enriched diet decreased the amount of A β deposits in cerebral blood vessel walls in the 18-month-old double transgenic APP/PS1 mice (Hooijmans et al., 2007b).

In the current study we investigate whether changes in the relative cerebral blood volume (rCBV), determined using susceptibility enhanced MRI, would precede changes in A β deposition in these APP/PS1 mice or vice versa. We also tested the effects of DHA and TWD diets on cognition, rCBV, the amount of A β depositions and the sterol and fatty acid profiles of the brain, from 8- and 15-month-old APP/PS1 mice. We used similar diets as in our former study (Hooijmans et al., 2007b). Explorative behavior was determined with an open field test, and spatial learning and memory with both the Morris water maze (MWM), and the 12 circular hole board in 8- and 15-month-old wild type and double transgenic APP_{swe}/PS1_{dE9} mice.

Materials and methods

Animals and diets

The APP_{swe}/PS1_{dE9} founders were obtained from Johns Hopkins University, Baltimore, MD, USA (D. Borchelt and J. Jankowsky, Dept. of Pathology) and a colony was established at the Radboud University Nijmegen Medical Center, The Netherlands. In short, mice were created by co-injection of chimeric mouse/human APP_{swe} (mouse

APP695 harboring a human A β domain and mutations K595N and M596L linked to Swedish familial AD pedigrees) and human PS1-dE9 (deletion of exon 9) vectors controlled by independent mouse prion protein promoter elements. The two transfected genes co-integrate and co-segregate as a single locus (Jankowsky et al., 2001). This line was originally maintained on a hybrid background by backcrossing to C3HeJ $\times$ C57BL6/J F1 mice (so-called pseudo F2 stage). For the present work, the breeder mice were backcrossed to C57BL6/J for 7 generations to obtain mice for the current study.

Male APP/PS1 transgenic mice and their wild type littermates were assigned to different diet groups, which varied only with respect to the composition of the 5% fat in the diets. A complete overview of the sources and contents of fatty acids in the experimental diets is available in Supplemental Table S1. Apart from that, the remaining components in all diet groups are the same as used in standard rodent chow, with whey powder, barley, wheat and a vitamin/mineral mix containing vitamin E in a concentration of 30 mg/kg in each diet group, which is about 0.12 mg vitamin E per day counting with a 4 g food intake per day. Feeding the diets started at the age of 2 months and was maintained until 8- and 15 months of age.

Transgenic mice and their wild type littermates were fed either a Typical Western Diet (TWD), containing 1% cholesterol, a high percentage of saturated fatty acids (SFA), a low percentage of long chain poly-unsaturated fatty acids (lc-PUFAs) and a high n-6/n-3 lc-PUFA ratio, or a DHA diet containing 0.4% DHA, with a low percentage SFA, a high percentage lc-PUFA and a low n-6/n-3 lc-PUFA ratio, or a standard control diet (STD), with intermediate values for SFA and lc-PUFA content and the n-6/n-3 lc-PUFA ratio.

In total 165 mice were used and supplementary data (Table S2) shows the number of mice used in each experiment. The majority of the mice were used for behavioral analyses, and subsequently for relative cerebral blood volume measurements. Mice from MRI experiments during which technical errors occurred were excluded from further analyses of the rCBV (Supplemental Table S2). The largest part of the mice used for rCBV measurements were subsequently sacrificed (transcardially perfused) and their brains processed for immunohistochemistry. The remaining mice were sacrificed to determine brain sterol and fatty acid levels. Throughout the experiments the animals were housed individually in a controlled environment, with room temperature at 21 °C, and an artificial 12:12 h light: dark cycle. Food and water were available *ad libitum*. The experiments were performed according to Dutch federal regulations for animal protection and were approved by the Veterinary Authority of the Radboud University Nijmegen Medical Center.

Body and brain weight

The body weights of the mice were determined 1 week before the start of the behavioral tests. The entire brain without the spinal cord was dissected and weighed directly after completing all experiments, respectively at 8- and 15 months of age. Brain weights are expressed as a percentage of the total body weight.

Behavioral analysis

Behavioral testing was performed in 8- and 15-month-old mice in the following order: first open field, then Morris water maze (MWM), followed by reversal MWM and finally the 12 circular hole board.

Open field

To analyze explorative behaviour an open field test as described by Streijger et al. (2005) has been used. The mice were videotaped for 30 min and the durations (s) of walking, wall leaning, rearing, sitting and grooming were scored and later analyzed in three blocks of 10 min. In addition, moving latency, the time before starting to move

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