Effects of a nutrient-combination diet on cerebral blood flow, metabolites levels and brain diffusion in ApoE4 and ApoE knockout mice

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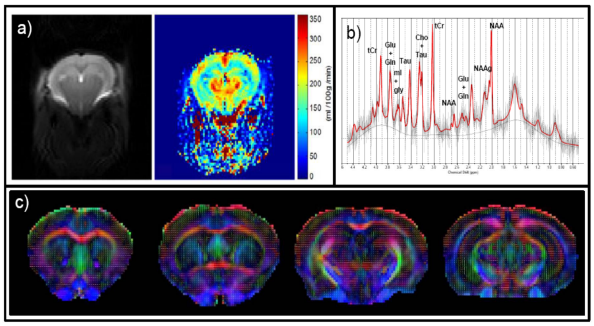
Target audience Researchers interested in the role of dietary intake and of apoE genotype in AD research. Researchers involved in the development of ASL, MRS and DTI at ultra-high field in mice.

Purpose Lipid metabolism and genetic background together strongly influence the development of both cardiovascular and neurodegenerative diseases, like Alzheimer's disease (AD). To investigate their dependence, many studies have focused on the cholesterol transporter apolipoprotein ε4 (apoE-ε4), which is at the same time a major genetic risk factor for hypercholesterolemia, vascular dementia and sporadic AD. The non-pharmacological management of lipid metabolism by means of specific diets containing fish oil has been recently proposed to prevent and treat the effects of the apoE-ε4 genotype in AD[1]. A more specific combination of omega-3 fatty acids (n-3 LCPUFAS) with precursors and cofactors in membrane synthesis (Fortasyn) was developed for the dietary management of AD. This is supported by evidences that sufficient consumption of n-3 LCPUFAS is associated with reduced risk of cognitive decline, lower number of white matter lesions and protects from cerebral microcirculatory abnormalities, as seen in AD patients[2-3]. We previously reported the possible beneficial effects of Fortasyn in restoring cerebral blood flow and metabolites levels in a mouse model for genetic AD[4]. In this study, we tested the hypothesis that a specific nutrient-combination diet containing Fortasyn is able to positively influence cerebral hemodynamics, metabolite levels and white- and gray matter diffusion in the apoE-ε4 genotype and other AD vascular risk factors carriers.



Methods We used 12-month-old wild type (WT) male mice (C57BL6/J, n=16) and two strains resembling vascular risk factors in sporadic AD by carrying human APOE-ε4 (n=17) and APOE-knockout mice (apoE-/-, n=18). From 2 months of age, mice were fed with a standard diet or a Fortasyn diet containing DHA, EPA, phospholipids, uridine monophosphate, choline, folic acid, vitamins B6, B12, C, E, selenium and l-cystine. MR measurements were performed on a 11.7T BioSpec Avance III small animal MR system (Bruker BioSpin, Ettlingen, Germany) equipped with actively shielded gradient set of 600 mT/m. We used a circular polarized resonator for transmission and an actively-decoupled receiver mouse brain coil. We measure microvascular cerebral blood flow (CBF), using a flow-sensitive alternating inversion recovery (FAIR) technique[5] (Fig.1-a), under two gas condition (O_2 and O_2+N_2O) to stimulate vasoconstriction and vasodilation, respectively. Metabolite levels were determined in the hippocampus with single voxel ^{1}H MRS (PRESS, TE=10.9ms, TR=2500ms, averages=800) and quantified with LCModel (Fig.1-b). Diffusion tensor MRI (DT-MRI) data were acquired with 30 diffusion direction and reconstructed with a robust tensor estimation[6](Fig.1-c). Genotype/diet effects in gray- and white matter water diffusion were detected with ROI-based and voxel-based approach, following spatial normalization of fractional anisotropy (FA), mean diffusivity (MD), diffusivity along (λ_1) and across the main axonal tracts (RD).

Results The CBF data revealed a reduced brain perfusion in apoE-/- mice compared to WT, especially in cortex and hippocampal regions, for both gas conditions (p=0.018 and p=0.017, respectively). ApoE-ε4 and apoE-/- mice on the nutrient-combination diet exhibited increased CBF during vasodilation stimulation (apoE-ε4: thalamus p=0.041, apoE-/-: all regions p<0.020).
The MRS data of apoE-ε4 mice on control diet showed increased taurine (Tau, p=0.004), N-acetylaspartate (NAA, p=0.011) and glutamate (Glu, p=0.029) and decreased glutamine (Gln, p=0.026) compared to WT. Only a Tau increase was found instead in the ApoE-ε4 mice on nutrient-combination diet (p=0.004). The apoE-/- showed an overall decrease in Gln levels compared to WT (p=0.008). The nutrient-combination diet increased the Tau levels in apoE-/- (p=0.001).
Diffusion parameters were quantified in several ROIs, to assess white and gray matter axonal and neuronal degeneration, respectively. In apoE-ε4 mice, we found a significant decreased FA in fornix (p=0.004) and anterior commissure (ACA, p=0.003) in the animals fed with control diet compared with WT, while the nutrient-combination diet significantly increased the FA of these same regions (p=0.024 and 0.039 respectively). In apoE-/- mice we found reduced λ_1 diffusivity in the fornix (p=0.012) and ACA (p=0.027), which were unaffected by diet.

Discussion and conclusion In the present study we successfully quantified CBF, metabolite levels and diffusion-related parameters in the apoE-ε4 and apoE-/- mouse brain at 11.7T. Our results clearly showed that at 12 months of age, apoE-/- mice have decreased brain perfusion as compared to wild type animals. Interestingly, an increased brain perfusion in apoE-ε4 and apoE-/- mice by the nutrient-combination diet was found during vasodilation stimulation, suggesting an enhanced capillary vasoactivity. Changes detected by ^{1}H MRS indicate an effect of the diet in restoring several metabolite concentrations to normal levels, particularly in apoE-ε4 mice. The changes in diffusion parameters seem to reflect a white-matter neuroprotective effect of diet in apoE-ε4 mice. Taken together, these results suggest that the specific nutrient-combination diet containing Fortasyn has the potential to positively influence brain capillary vasoactivity, metabolism and neurodegeneration in carriers of AD's vascular risk factors, and thus may contribute to slow AD pathology development.

References [1] Kariv-Inbal Z *et al.* 2012. [2] Gardener *et al.* 2012. [3] Scheltens P *et al.* 2010. [4] Zerbi *et al.* ISMRM 2012. [5] Kwong KK *et al.* 1995. [6] Zwiers MP. *2010;* This research received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 211696.