Proton and phosphorus MRS of a 5xFAD mouse model of Alzheimer's disease

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Introduction: Transgenic mouse models of Alzheimer's disease (AD) are useful for studying disease mechanism and for therapy testing. Mice expressing mutant amyloid precursor protein (APP) (1), those coexpressing mutant forms of human APP and presenilin 2 or 1 (PS2, PS1) proteins (2,3) and a triple transgenic model overexpressing APP, PS1 and tau protein genes (4) have been studied by in vivo proton MR spectroscopy. Interestingly, an increase of myo-inositol was observed only in the APP-PS1 model (3). The 5xFAD mouse model used in our study overexpresses APP genes with the Swedish (K670N, M671L), Florida (I716V), and London (V717I) familial Alzheimer's disease (FAD) mutations and PSEN1 gene harboring two FAD mutations, M146L and L286V. This AD model is aggressive and the mice start to develop amyloid plaques at the age of 2 months (5). In this study, development of the neurochemical profile of the 5xFAD mice with age was investigated by proton MRS. Furthermore, phosphorus spectroscopy was used for measuring relative concentrations of phosphorus-containing metabolites in brain, and the pseudo-first order forward rate constants k_{for} of the creatine kinase reaction (PCr ↔ ATP) were obtained by localized phosphorus saturation transfer experiment.

Experimental: Seven AD and seven wildtype mice anesthetized with 1-2 % isoflurane were measured at the age of about 36 weeks (^{31}P and ^{1}H), 40 and 44 weeks (^{1}H only). Experiments were done on a 14.1 T spectrometer (Varian/Magnex Scientific). Proton spectra were measured using a SPECIAL spectroscopy sequence (TR/TE = 4000/2.8 ms) (6). A home-built 14 mm diameter quadrature coil was used as a transceiver. VOIs of about 4 mm^3 were centered in dorsal hippocampus as well as near its temporal pole. 320 acquisitions were collected for each VOI. Using water signal as a reference, absolute metabolite concentrations were calculated using LCModel (7). ^{31}P spectra and saturation transfer data were measured by a dual coil consisting of a proton quadrature coil and a linearly polarized 10 mm diameter phosphorus coil using a protocol described in Ref. (8). The peak intensities were obtained by fitting to a Lorentzian function using AMARES (9) from the jMrui software (http://www.mrui.uab.es/mrui). The forward creatine kinase rate constants k_{for} were obtained from a nonlinear regression of relative PCr signal intensities M(t_{ir})/M(0) versus γ-ATP saturation time t_{ir}. A *t*-test was used to compare metabolite concentrations in the AD and wildtype mice.

Results: Comparison of the neurochemical profiles in dorsal hippocampus of the AD and wildtype mice is shown in Fig. 1. At the age of 36 weeks, no statistically significant differences were found except a decrease of NAA in the AD mice ($p < 0.003$). However, at the age of 40 and 44 weeks, changes typical for the human form of the disease, i.e., a decrease of NAA ($p < 0.004$) and an increase of myo-inositol ($p < 0.007$) were observed

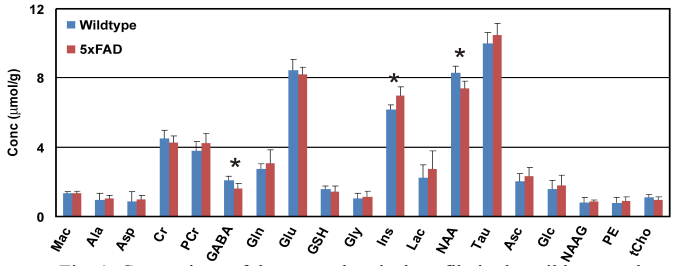

Fig. 1. Comparison of the neurochemical profile in the wildtype and AD mice at the age of 44 weeks

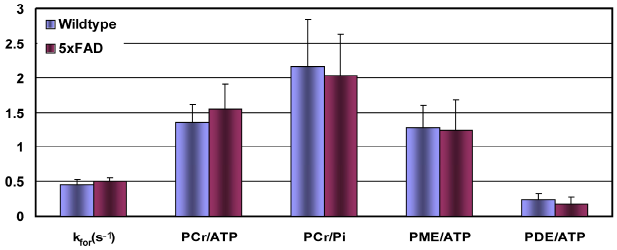

Fig. 3. Creatine kinase rate constants and relative concentrations of ^{31}P-containing metabolites in brain of 36-week old mice

(Fig. 2). In addition, the GABA concentration was also significantly decreased ($p < 0.015$) in the AD mice. The differences observed in the temporal part of hippocampus were similar, with *p*-values higher due to lower SNR. Using ^{31}P spectroscopy (Fig. 4), an indistinct increasing trend for k_{for} ($p = 0.2$) and PCr/ATP ($p = 0.14$), a decreasing trend for PDE/ATP ($p = 0.13$) but no change ($p > 0.4$) in PCr/Pi and PME/ATP were observed in the AD mouse brain compared with controls (Fig. 3).

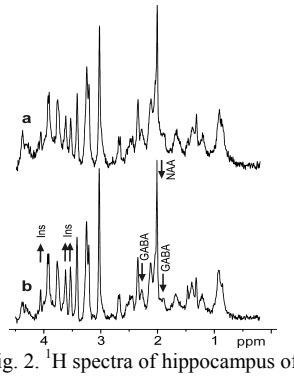

Fig. 2. ^{1}H spectra of hippocampus of a wildtype (**a**) and an AD (**b**) mice

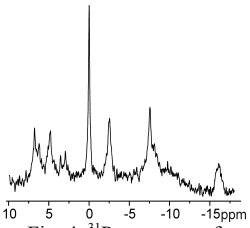

Fig. 4. ^{31}P spectrum of brain of an AD mouse

Discussion: The 5xFAD mice develop the neurochemical changes typical for human patients much earlier than the APP-PS1 mice (68th week, Ref. (3)). In contrast to a study on spontaneously hypertonic rats expressing human truncated tau protein (9), we did not observed a decrease in k_{for}. It indicates that energy consumption in the brain tissue might be depressed in this 5xFAD mouse model, while mitochondrial activity seems to be sufficient. The decrease of k_{for} observed in the previous study (9) could be related to blood circulation impairment and concomitant oxidative stress. Further studies are needed to explain the difference in energy production and consumption between both models of Alzheimer's disease.

Acknowledgments
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