2D L-COSY MR spectroscopy detects very early changes in the brain of Alzheimer mouse

S. van Duijn[1], F. Kara[2], N. Braakman[2,3], S. G. van Duinen[1], R. Natté[1], M. A. van Buchem[4], and A. Alia[2]
[1]Department of Pathology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden Institute of Chemistry, Leiden University, Leiden, Netherlands, [3]Catharina hospital, Eindhoven, Netherlands, [4]Department of Radiology, Leiden University Medical Center, Leiden, Netherlands

Introduction

Accumulation of beta amyloid plaques (Aβ) in human brains is one of the hallmark of Alzheimer's Disease (AD). Based on clinical and radiological criteria, a diagnosis of AD can be made with some degree of certainty but so far, the only way to prove AD is by autopsy. Thus there is an urgent need for in vivo biomarkers to diagnose AD. Because AD therapy is likely to be most successful when intervention occur before neurons are irreversibly damaged or lost, non-invasive detection of early biomarkers of AD at early stage would facilitate intervention and enhance treatment success. Proton magnetic resonance spectroscopy (MRS) provides a non-invasive way to investigate *in vivo* neurochemical abnormalities of many brain disorders. However, its role in finding early and specific metabolic changes as biomarkers for AD has not yet been established. In the present study we employed, for the first time, localized 2D MRS in young wild-type and transgenic APP/PS1 mouse model of AD to probe specific early metabolic changes during AD. Our results provide an important indication of early neurochemical changes which takes place long before Aβ plaque deposition in transgenic APP/PS1 mice.

Material and methods

Ten APP/PS1 mice and 10 non-transgenic littermates, aged ~3 month, were used in this study. All MR measurements were performed using a 9.4-T vertical wide-bore imaging systems equipped with a Bruker Avance console and 1000-mT/m gradients. Images for voxel positioning were acquired using the RARE sequence. The MRS voxel was located in the hippocampus/cortex region (3.5x3.5x1.8 mm^3; 22 µl – Fig. 1c). Field homogeneity was optimized using the Fastmap sequence, which typically yielded a water linewidth of ~16-20 Hz in live mouse brain. For 2D MRS, a localized 2D shift correlated spectroscopic sequence (L-COSY) was used [1,2]. 2D spectra were recorded using TR=1500 ms, TE=15 ms, 2048 complex points along F2, and 192 points along F1, with a spectral width of 11 ppm, and 16 averages per excitation step. Total scan time for a typical 2D measurement was ~75 minutes.

Results

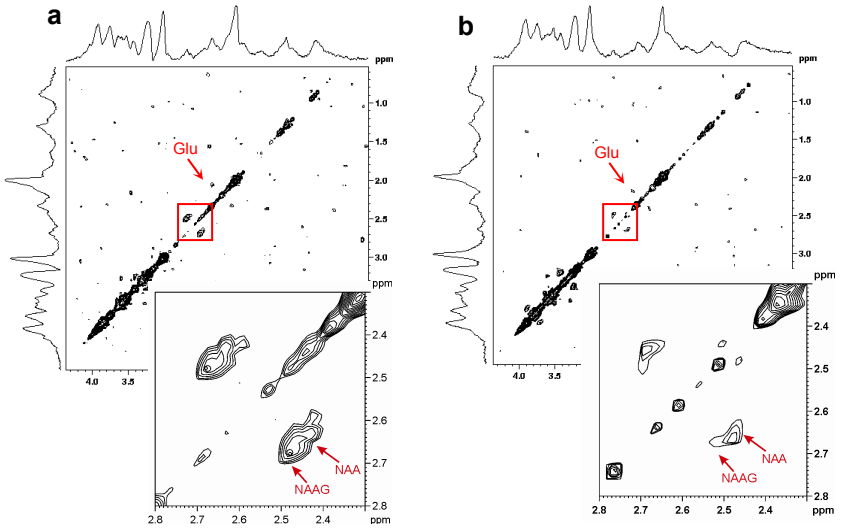
The comparison of the neurochemical profile between wild-type and APP/PS1 mice showed important differences in the level of various metabolites (Fig. 1a&b). In addition to other changes, a significant decrease in the level of N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG) and glutamate (Glu) was clearly registered in AD mice as compared to wild-type mice. Amyloid plaque deposition has not been observed in these APP/PS mice at the age of 3 month [3]. These results provide an important indication that these early metabolic changes in AD mouse brain occur long before the Aβ plaque deposition, since there were no plaques seen in these mice at the age of 3 months.

Conclusion

The 2D L-COSY MRS method allows the clear and unambiguous identification of multiple brain metabolites from a single measurement *in vivo* and provides a clear means to probe early neurochemical changes to differentiate AD mouse brain from control brain.

References: [1] Braakman N, Oerther T, de Groot HJM, Alia A. Magn Reson Med 2008; 60:449-456; [2] Thomas MA, Yue K, Binesh N, et al. Magn Reson Med 2001;46:58-67; [3] Holcomb L, Gordon MN, McGowan E et al. Nat Med 1998; 4:97-100.

Acknowledgement: This work was partly supported by grants from Center for Translational Molecular Medicine (CTMM); Internationale Stichting Alzheimer Onderzoek (ISAO) and Centre for Medical Systems Biology (CMSB).



d

Metabolite	% decrease in cross-peak area	
	Wild-type	APP/PS1
Glu	100	58±4.9
NAA	100	72±10
NAAG	100	64±9.5

Fig. 1: *In vivo 2D MR spectrum from the hippocampus/cortex region of the 3 month old wild-type (a) and APP/PS transgenic mouse brain (b). (c) Coronal MR image of the mouse brain showing the position of the 22 µl voxel; (d) Mean percentage decrease in cross-peak area of Glu, NAA and NAAG in 2D spectrum of APP/PS1 mice as compared to WT mice. Data represent standard deviation of the mean (n=5).*