In vivo localized two dimensional MR spectroscopy to compare the neurochemical profile in wild-type and transgenic mouse model of Alzheimer's disease

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Introduction

Currently a definitive diagnosis of Alzheimer's disease (AD) is only possible postmortem, by detecting the two hallmarks of the disease: amyloid plaques and neurofibrillary tangles in the brain tissue. There is thus a great need for *in vivo* biomarkers to diagnose AD with high specificity and sensitivity. Proton magnetic resonance spectroscopy (^{1}H MRS) provides a non-invasive way to investigate *in vivo* neurochemical abnormalities of many brain disorders. While transgenic mouse models of AD might be instrumental in discovering new *in vivo* biomarkers, the use of localized *in vivo* 1D MRS in mice is often hampered by low sensitivity of local measurements due to both the small size of the brain resulting in limited signal-to-noise ratio and low concentrations of several brain metabolites. In addition a considerable overlap of peaks of metabolites with coupled spin systems restricts the number of molecules which can be uniquely assigned in 1D MRS[1]. To overcome the problem of spectral resolution and peak overlap, a two-dimensional (2D) MRS technique has been recently employed at 9.4T to obtain highly resolved localized 2D MR spectra from the living mouse brain[2]. In the present study we employed localized 2D MRS to map the neurochemical composition of a transgenic mouse model of AD and compared it with control mice. Our results show clear differences in the neurometabolic profile of wild-type and transgenic mice.

Methods

The transgenic mice used in this study (APP_{Tg2576}) contain as transgene the Swedish double mutation of the human amyloid precursor protein (APP_{695}), as developed and described previously[3]. Age-matched non-transgenic littermates served as controls. 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 (4x4x1.7 mm^3; 27 µl – Fig. 1a). 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 20 averages per excitation step. Total scan time for a typical 2D measurement was ~96 minutes.

Results and Discussion

Figure 1 show high resolution 2D MR spectra obtained from the cortex/hippocampus region of wild-type and APP_{Tg2576} mouse. The combination of the optimized 2D sequence, high field strength, strong gradient system, efficient water suppression and the use of short echo time allowed clear detection of cross-peaks of several brain metabolites allowing their direct unambiguous chemical shift assignments *in vivo*. The comparison of the neurochemical profile between wild-type and APP_{Tg2576} mice showed important differences in the level of various metabolites (Fig. 1b&c). A clear increase in the level of taurine, glycerophosphocholine (GPC), phosphocholine (PC), and a significant decrease in the level of N-acetylaspartate (NAA), glutamate (Glu), glutamine (Gln), γ-aminobutyric acid (GABA), glutathione (GSH) was registered in AD mice as compared to wild-type mice. Understanding the significance of these changes in relation to AD pathology may provide an important clue in identifying crucial biomarkers of AD.

Conclusion

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

References: [1]Thomas MA, Yue K, Binesh N, et al. Magn Reson Med 2001;46:58-67; [2]Braakman N, Oerther T, de Groot HJM, Alia A. Magn Reson Med 2008; 60:449-456; [3]Hsiao K, Chapman P, Nilsen S, et al. *Science* 1996; 274:99-103.

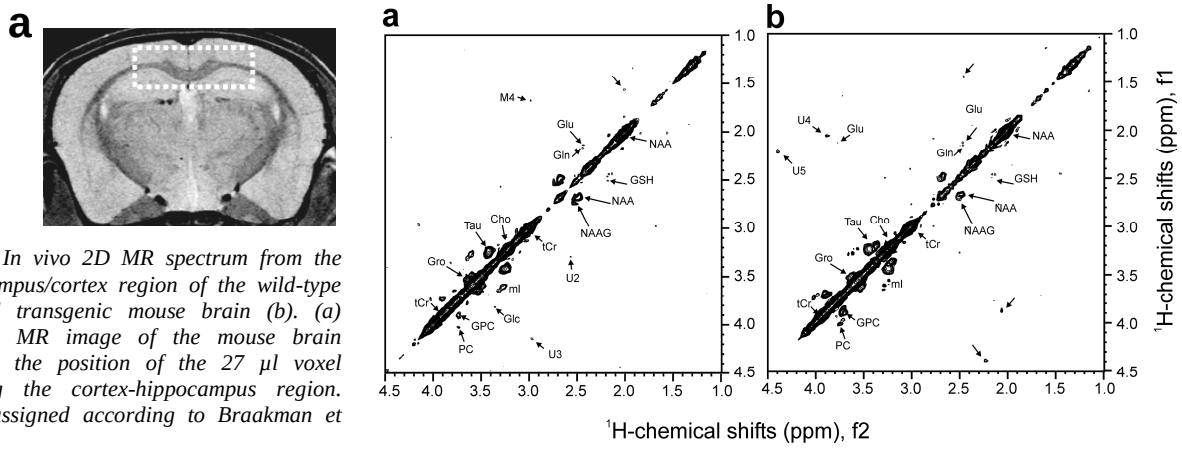

Fig. 1: In vivo 2D MR spectrum from the hippocampus/cortex region of the wild-type (b) and transgenic mouse brain (b). (a) Coronal MR image of the mouse brain showing the position of the 27 µl voxel covering the cortex-hippocampus region. Peaks assigned according to Braakman et al[2].