Correlation Between Neurochemical Changes and Development of Alzheimer's Plaques with Age Monitored by In Vivo High Resolution Magnetic Resonance Microimaging and Spectroscopy

N. Braakman[1], J. Matysik[1], H. J. De Groot[1], R. Schliebs[2], and A. Alia[1]

[1]Leiden Institute of Chemistry, Gorlaeus Laboratoria, Leiden University, Leiden, Netherlands, [2]Department of Neurochemistry, Paul Flechsig Institute for Brain Research, University of Leipzig, Leipzig, Germany

Introduction

Alzheimer's disease (AD) is an age-dependent neurodegenerative disorder that causes a progressive decline in cognitive function [1]. The neuropathologic features of AD include the occurrence of senile (Aβ) plaques, neurofibrillary tangles, decreased synaptic density, and loss of neurons. The development of Aβ plaque in a living transgenic mouse model of AD has been recently followed using magnetic resonance microimaging (μMRI) [2]. Recent studies in transgenic mice have shown that the neurochemical profile changes with the progression of the disease which can be used to identify potential biomarkers of AD [3]. However, relationship between the development of senile plaques and changes in the metabolic profile with age in the brain of same animals has not yet been explored. In this study we optimized high resolution magnetic resonance spectroscopy (MRS) and μMRI sequences to explore the correlation between *in vivo* plaque development and neurochemical changes with age in the same living transgenic mouse model of Alzheimer's disease. Our results show clear relationship between increase in plaque load and changes in neurochemical composition of the brain with age and suggest that these neurochemical changes can be used as a diagnostic tool for evaluating the progression of AD and the future evaluation of the efficacy of putative treatment strategies.

Methods

The transgenic mice used in this study (APP_{Tg2576}) contain as transgene the Swedish double mutation of the human amyloid precursor protein, as developed and described previously by Hsiao et al [4]. MR images were acquired using a 9.4-T vertical wide-bore imaging systems equipped with a Bruker Avance console and 1000 mT/m gradients. A series of coronal T_2-weighted images were acquired using the rapid acquisition with relaxation enhancement (RARE) sequence. The settings used were TE = 10.567 (22.45 ms effective), TR =6000 ms, RARE factor (echo train length) = 4 and averages = 4. An in-plane resolution was achieved of 78x78 μm with slice thickness of 500 μm in an acquisition time of ~25 minutes. Spectroscopic data was acquired using the point resolved spectroscopy (PRESS) with TE = 15 ms, TR = 3500 ms and 320 averages. A 2x2x2 mm (8 μl) voxel was positioned so that it included both the cortex and hippocampus.

Results and Discussion

Figure 1 show high resolution μMR images and MR spectra obtained from same APP_{Tg2576} mouse at the age between 12 and 18 month. Due to high magnetic field in conjunction with a strong gradient system, efficient shimming and the water suppression scheme and the use of short echo time, the MR spectra show higher resolution and clear separation of resonances of various metabolites than those published earlier in the APP_{Tg2576} mice at 4.7T (1). Furthermore, the analysis of the neurochemical profile with age in the same APP_{Tg2576} mice showed significant changes in the level of various metabolites which was correlated with an increase in plaque load (Fig. 1). A clear increase in the level of taurine with a small increase in myoinositol was observed with age. Furthermore, a decrease in the level of N-acetylaspartate (NAA), glutamate (Glu)/Glutamine (Gln), γ-aminobutyric acid (GABA), glutathione was registered with age.

Conclusion

Our results show a correlation between the severity of Aβ deposition and altered neurochemical profile in APP_{Tg2576} mice with age. Such an insight into the neurochemical profile provides useful information about pathological processes at molecular level and can be used as a diagnostic tool for evaluating the progression of AD and the evaluation of the efficacy of putative treatment in longitudinal studies using mouse models of AD.

References:

(1) Dedeoglu and Choi et al. Brain Research 1012: 60-65 (2004); (2) Braakman and Matysik et al. J Magn Reson Imaging 24:530-536 (2006); (3) Marjanska and Curran et al. PNAS 102:11906-11910 (2005); (4) Hsiao and Chapman et al. Science 274:99-103 (1996).

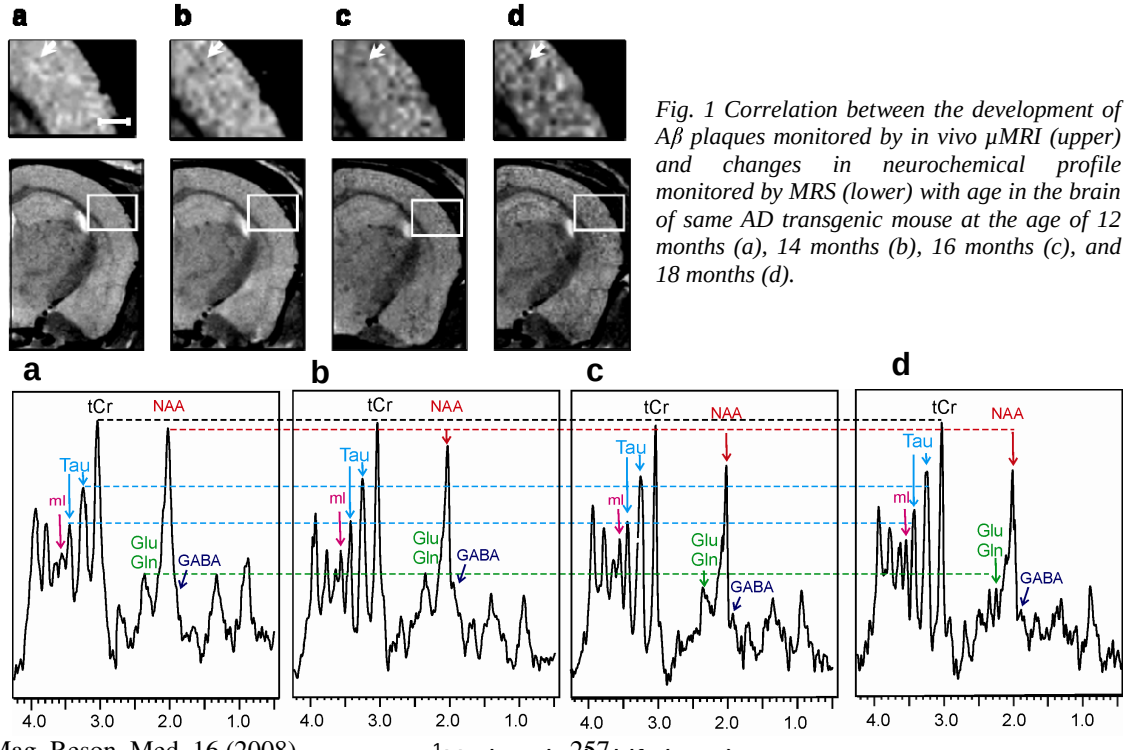

Fig. 1 Correlation between the development of Aβ plaques monitored by in vivo μMRI (upper) and changes in neurochemical profile monitored by MRS (lower) with age in the brain of same AD transgenic mouse at the age of 12 months (a), 14 months (b), 16 months (c), and 18 months (d).