Regional metabolic alteration of Alzheimer¡¯s disease in the mouse brain expressed as mutant human APP-PS1 using 1H HR-MAS

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INTRODUCTION

Early diagnosis of Alzheimer's disease (AD) is thought to be critical for successful treatment of AD. Therefore, determination of the regional metabolic changes in AD mice that express mutant human APP-PS1 at an age younger than 10 months, might provide clues to early diagnosis of AD [1]. Thus, the purpose of this study was to investigate the regional neurochemical profile of the APP-PS1 mouse brain during early stage of AD and compare the findings with the wild-type mouse brain using the high resolution magic angle spinning (HR-MAS) method.

MATERIALS AND METHODS

Ten mice that were double transgenic APP-PS1 models, B6SJL/Tg and ten littermate controls (wild-type) that were age-matched non-transgenic mice were studied. Object recognition test (ORT) was performed as behavioral test at the age of 18 and 35 weeks. At the age of 40 weeks, the brain tissues of six regions (frontal, occipital, temporal, parietal cortices, hippocampus and thalamus) were obtained and ex vivo-HR MAS and absolute quantification [2] were performed using 500MHz NMR spectrometer.

RESULTS

Although behavioral difference between Tg and WT mice was not significant at 18 weeks aged, Tg mice memory indexes were significantly lower compared with WT at 35 weeks aged (Fig. 1.). Fig. 2. shows ex vivo HR-MAS spectra of hippocampus and temporal cortex in both Tg and WT mice. As well as the 14 metabolite concentrations were absolutely quantified by these spectra (Fig. 3.). In Tg mice, the elevation of mIns and sIns was observed in six regions and the decrease of [NAA+Acet] in only temporal cortex. The [NAA+Acet]/Cr of Tg mice in temporal cortex as well as hippocampus decreased and mIns/Cr and sIns/Cr of Tg also increased in six regions compared with WT.

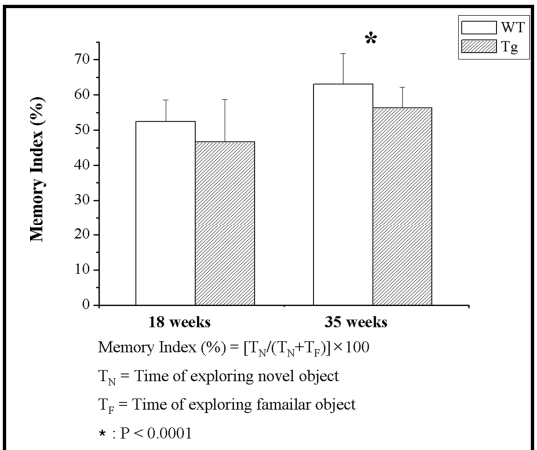

Fig. 1. At 35 weeks of age, the memory indices of the transgenic mice were significantly reduced compared to the wild-type mice (P<0.0001); although these differences were not significant at 18 weeks of age. (Bars indicate mean ± standard deviation of mean)

DISCUSSIONS AND CONCLUSION

The combination of behavioral test and HR-MAS of this study supports that the memorial/behavioral degeneration progresses after the glial cell transportation [3]. As well as we revealed that the metabolic changes of AD at early-stage which are the reduced NAA and the elevation of mIns and sIns were different according to brain regions. These support that the degradation and development of plaques by AD were started from the hippocampus and entorhinal cortex [4]. Thus, our findings demonstrated the metabolism of APP-PS1 mouse associated with early stage of AD. Furthermore, the regional neurochemical profile of APP-PS1 can be helpful to investigate physiologic and pathologic mechanism of AD.

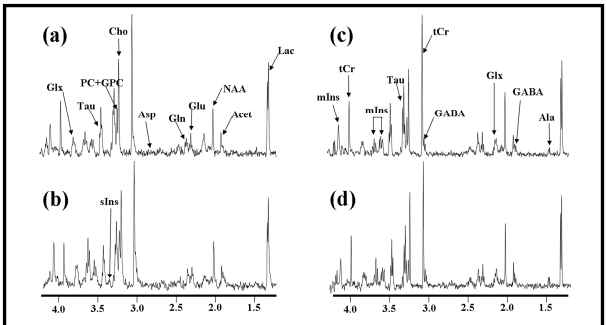

Fig. 2. Fifteen metabolite peaks were observed in the spectra of the mouse brain samples by ^{1}H HR-MAS: (a) and (b) are the MR spectra of the hippocampus of the WT and Tg mice (c) and (d) is the temporal cortex of the WT and Tg mice.

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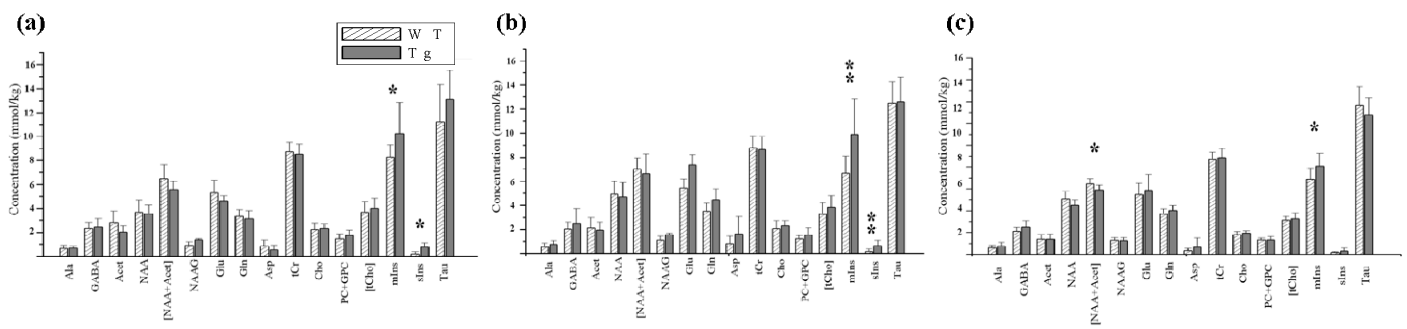

Fig. 3. The metabolite concentrations of WT and Tg mice: (a) hippocampus, (b) parietal cortex, (c) temporal cortex and. Bars indicate mean ± standard deviation of mean, *: P<0.05, **: P<0.01.