Genotype Specific Alterations Detected in the Neurochemical Profiles of Aged Transgenic Mouse Models of Alzheimer's Disease

M. Marjanska[1], G. L. Curran[2], T. M. Wengenack[2], P-G. Henry[1], R. L. Bliss[3], J. F. Poduslo[2], C. R. Jack, Jr. [4], K. Ugurbil[1], M. Garwood[1]

[1]Center for Magnetic Resonance Research and Department of Radiology, University of Minnesota, Minneapolis, MN, United States, [2]Neurology, Neuroscience, Biochemistry/Molecular Biology, Mayo Clinic College of Medicine, Rochester, MN, United States, [3]Cancer Center, University of Minnesota, Minneapolis, MN, United States, [4]Department of Radiology and MR Research Laboratory, Mayo Clinic College of Medicine, Rochester, MN, United States

Introduction

Proton magnetic resonance spectroscopy offers a non-invasive way to quantify many metabolites *in vivo*. Metabolite levels are sensitive to different *in vivo* pathologic processes at the molecular or cellular level; e.g. *myo*-inositol (mIns) and taurine are thought to be markers for osmotic stress or astrogliosis. Murine models of Alzheimer's disease (AD) have been created by inserting human mutations associated with abnormal processing of amyloid β protein. These mutations of amyloid precursor protein (APP) and presenilin (PS) 1 or 2 produce hereditary AD in humans. Recently spectroscopic analysis of single transgenic APP[1], and double transgenic PS2APP[2] and APP-PS1[3] mice brains showed neurochemical profiles which deviate from that seen in wild-type mice as the transgenic mice age. The purpose of this study was to compare the levels of the metabolites in question, mIns and taurine, in different mouse models of Alzheimer's disease: APP, PS1, APP-PS1 and wild-type. We hypothesized that the neurochemical profiles of these transgenic mice at old age would be genotype specific and vary as a function of age and amyloid burden.

Methods

Three 624-day-old APP, four 655-day-old PS1, seven 605-day-old APP-PS1, and four 610-day-old wild-type mice were scanned. Mice were anesthetized using 1.5% isoflurane and O_2/NO_2 and positioned in a custom-built device to immobilize the head during experiments. Body temperature was maintained at 37^0C by warm water circulation, and physiological monitoring for temperature, respiration and ECG was performed.

In vivo ^{1}H NMR spectra were obtained using a previously described LASER sequence. MR experiments were performed with a 9.4-T (31-cm horizontal bore) magnet equipped with Varian INOVA console to localize a 18 μL voxel placed in the cortex and the hippocampus. Each individual FID was stored separately and then frequency and phase corrected based on total creatine (tCr = creatine and phosphocreatine) signal at 3.03 ppm prior to summation. Small residual eddy currents effects were corrected using a reference water signal.

The obtained spectra were analyzed using LCModel which calculates the best fit of the experimental spectrum as a linear combination of model spectra (simulated spectra based on the known chemical shifts and *J*-couplings of metabolites). The spectra of eighteen metabolites and the experimentally measured spectrum of macromolecules were included in the basis set. The quantification was obtained using tCr resonance as an internal standard.

Results and Discussion

The neurochemical profiles of age-matched (~630-day-old) APP, PS1, APP-PS1 and wild-type mice were obtained. The ratios of concentration of mIns to tCr (creatine and phosphocreatine) and taurine to tCr are plotted for each scanned mouse in the figure.

Levels of mIns are higher for APP-PS1, compared to wild-type, APP and PS1 mice but do not differ between wild-type, APP and PS1 mice. The taurine levels are higher for APP than for APP-PS1, PS1 and wild-type mice. The taurine levels found in the APP-PS1 mice do not differ from those found in wild-type and PS1 mice. These results confirm a genotype specific neurochemical profile in aged transgenic AD mice.

PS1 mice do not deposit amyloid plaques while both APP and APP-PS1 mice do, although this process starts earlier (3 months) and is greatly accelerated in APP-PS1 mice. The elevation in mIns in aged APP-PS1 mice may therefore be a function of amyloid plaque burden. It remains to be seen whether APP mice with the same plaque burden found in 630-day-old APP-PS1 mice also exhibit an elevation in mIns.

The elevation in taurine in only the APP mice would indicate that the neurochemical alteration in these mice is not a function of amyloid plaque burden; because, at a similar age of roughly 600 days the plaque load is greater in APP-PS1 mice which do not exhibit elevated levels of taurine. The fact that APP mice do exhibit an increase in taurine while APP-PS1 mice do not indicates that the taurine increase can not simply be due to the presence of the APP mutation alone in the mouse genome. One purely speculative proposition is that PS1 somehow acts to modulate the effect of APP on taurine in the APP-PS1 mice.

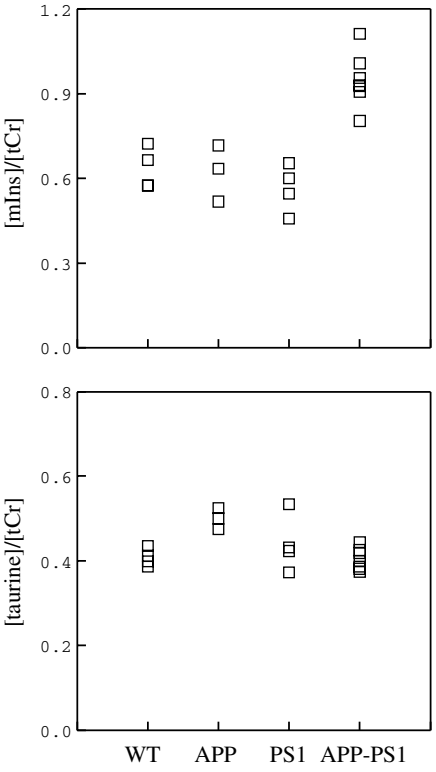

Figure. The ratios of concentration of mIns and taurine to tCr for age matched (~630-day old) B6/SJL wild-type (n = 4), APP (n = 3), PS1 (n = 4) and APP-PS1 (n = 7) mice.

References

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