Altered Neuronal and Astroglial Metabolism in APP-PS1 Mouse Model of Alzheimer's Disease

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INTRODUCTION: Alzheimer's disease (AD) is associated with memory impairment and progressive loss of cognitive functions due to synaptic dysfunction and neuronal loss[1]. We hypothesized that glutamatergic and GABAergic TCA cycle and neurotransmitter cycling will be impaired in AD. As substrate cycle, Glutamate-Glutamine and GABA-Glutamine are result of co-ordinated activity of neurons and astroglia, AD will also affect astroglial activity. APP-PS1 mice, a model of AD, exhibit enormous plaque loading and memory impairment at the age of 12 months- pathology similar to human AD. In this study, we have investigated glutamatergic, GABAergic and astroglial metabolism and corresponding neurotransmitter cycling in cerebral cortex and striatum of APP-PS1 mice brain at 12 months age by ^{1}H-[^{13}C]-NMR spectroscopy together with infusion of ^{13}C labeled substrates.

MATERIALS AND METHODS: All animal experiments were performed under approved protocols by the Institute Animal Ethics Committee. Measurements have been carried out in 12 months old APP-PS1 and age matched control mice. *In vivo* ^{1}H NMR spectroscopy was carried out in cortical and striatal regions using 600 MHz NMR microimager (Bruker Avance). For metabolic study, overnight fasted mice were anesthetized with urethane (1.5 g/kg) and tail vein was cannulated for the infusion of ^{13}C labeled substrates. Mice were infused with either [1,6-$^{13}C_2$]glucose for 10 min or [2-^{13}C]acetate for ~15 min as a bolus-variable rate infusion[2]. Brain was frozen *in situ* in liquid nitrogen at the end of the infusion. Metabolites were extracted from frozen brain tissue[3]. Concentrations and percent ^{13}C enrichment of metabolites were determined from the ^{1}H-[^{13}C]-NMR spectrum of the cortical extract obtained at 600 MHz spectrometer[4]. The percentage ^{13}C enrichment of plasma glucose-C1 and acetate-C2 was measured using resonance at 5.2 ppm and 1.93 ppm, respectively in ^{1}H NMR spectrum.

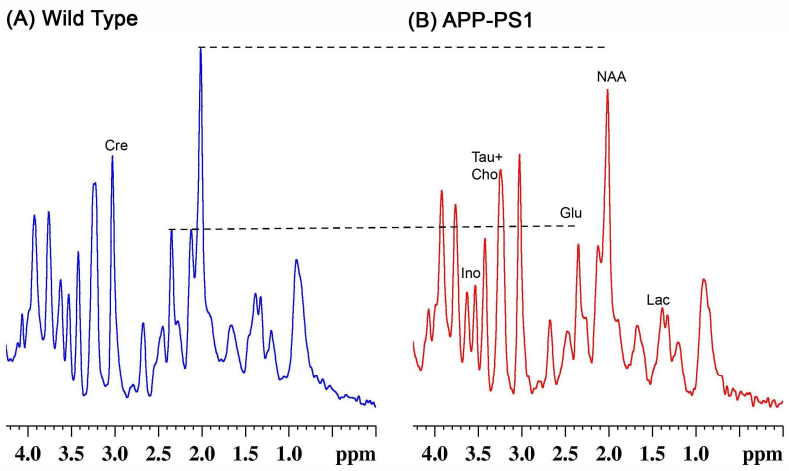

Fig.1 In vivo ^{1}H MRS from cerebral cortex of (A) Control and (B) APP-PS1 mice

RESULTS AND DISCUSSIONS: *In vivo* ^{1}H NMR spectra depicts reduced signal intensity for NAA and Glu in APP-PS1 mouse brain [Fig.1]. This together with increased level of inositol and choline indicates gliosis and impaired neuronal viability in 12 months old APP-PS1 mice. ^{13}C Labeling of cortical Glu_{C4} and $GABA_{C2}$ from [1,6-$^{13}C_2$]glucose in APP-PS1 mice was found to be lower than age matched control indicating impaired glutamatergic and GABAergic metabolism in 12 months old AD mice [Fig. 2A]. However, increased ($F[1,9]=12.7$, $p<0.01$) labeling of Gln_{C4} (APP-PS1: 0.36±0.04 μmol/g, Control: 0.28±0.03 μmol/g) from [2-^{13}C]acetate indicates higher Glial metabolism in APP-PS1 mice [Fig. 2B]. These findings are in very much consistence with findings of neuro-degeneration and gliosis in AD patients[5,6].

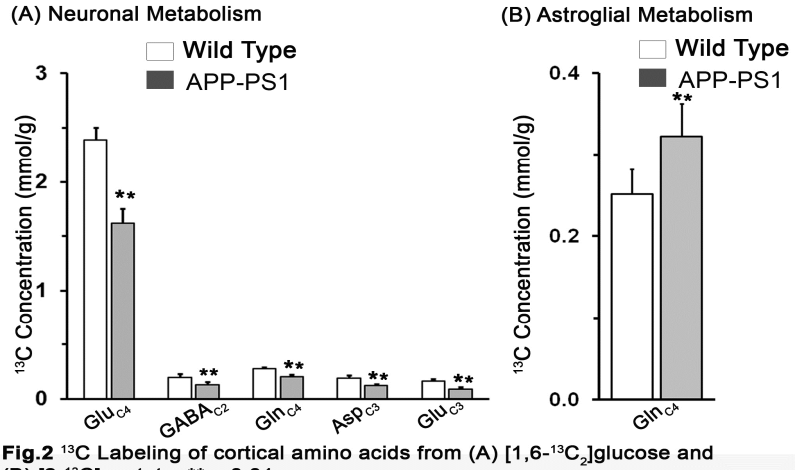

Fig.2 ^{13}C Labeling of cortical amino acids from (A) [1,6-$^{13}C_2$]glucose and (B) [2-^{13}C]acetate, **p<0.01

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