Neuronal and Astroglial Metabolism in APP-PS1 Mouse Model of Alzheimer's Disease with Progress of Age

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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]. Currently there is no quantitative diagnosis of AD *in vivo*. Finding of biomarkers specific to disease is the focus of the current AD research. APP-PS1 mice exhibit increase in amyloid plaque with age and more closely match the neurochemical profile and pathology of AD. The objective of the current study is to evaluate glutamatergic, GABAergic and astroglial metabolism and corresponding neurotransmitter cycling in different cerebral regions of APP-PS1 mouse model at very early (1 month), preclinical (6 month) and late age (12 month) by ^{1}H-[^{13}C]-NMR spectroscopy together with infusion of ^{13}C labeled substrates.

MATERIALS AND METHODS: All animal experiments were performed under the approved protocols by Institutional Animal Ethics Committee. Measurements have been carried out in APP-PS1 and age matched wild type (WT) mice. *In vivo* ^{1}H NMR spectroscopy was carried out using 600 MHz (Bruker Avance) NMR microimager. 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 or [2-^{13}C]acetate as a bolus-variable rate infusion[2]. Mice head was frozen *in situ* using liq. 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 tissue extracts[4]. The ratio, V_{cyc}/V_{tca}, obtained from steady state infusion of [2-^{13}C]acetate was used as constraint during fitting of metabolic model to the measured ^{13}C turnover of amino acids from [1,6-$^{13}C_2$]glucose for the determination of absolute metabolic fluxes[5].

RESULTS AND DISCUSSIONS: Neurochemical profile remains unperturbed in early and preclinical age whereas level of NAA (p=0.006) and glutamate (p=0.003) was lower, and inositol (p=0.01) was higher in APP-PS1 indicating reduced neuronal viability and increased proliferation of astroglia at the late age in APP-PS1 mice. Metabolic analysis indicates deficit in glucose oxidation and neurotransmitter cycling associated with glutamatergic and GABAergic neurons in APP-PS1 mice (Fig. 1A & B). ^{13}C Labeling of cortical amino acids from [1,6-$^{13}C_2$]glucose was unaltered at very early age but reduced significantly (p=8.9e-^{09}) at the age of 6 month suggesting impaired neuronal functions at preclinical age[6] (Fig. 1C). The increased labeling of Gln_{C4} from [2-^{13}C]acetate in APP-PS1 mice (APP-PS1 0.71±0.08; WT 0.55±0.06 µmol/g, p=0.01) in cerebral cortex compared to age matched WT indicates enhanced astroglial metabolism in APP-PS1 mice (Fig. 1C). These data indicate that impairment in neuronal function precedes the appearance of clinical symptoms while the astroglial function is enhanced at the late age of AD. ^{13}C MRS has potential for the early diagnosis of AD.

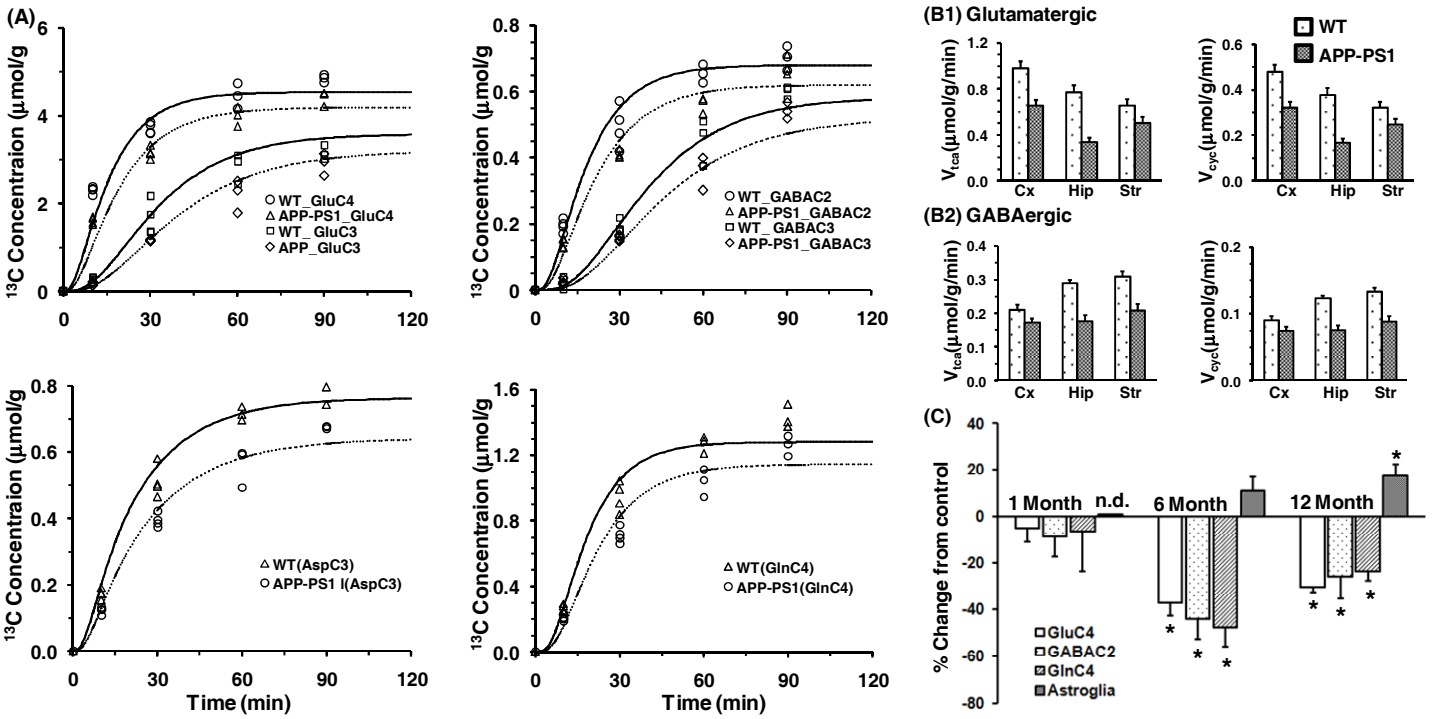

Fig. 1. (A) Fit of the metabolic model to ^{13}C turnover of amino acids from [1,6-$^{13}C_2$]glucose. (B1) Glutamatergic and (B2) GABAergic fluxes in different regions of brain at the late age. (C) Changes in Glutamatergic, GABAergic and Astroglial activity with progression of disease in APP-PS1 mice compared to age matched control

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