Impaired Glutamatergic and GABAergic function at Early Age in APPswe-PS1dE9 Mice: Implications for Preclinical Diagnosis of Alzheimer's Disease

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INTRODUCTION: Alzheimer's disease (AD) is one of the very common neurodegenerative disorders, characterized by neuritic plaques and neurofibrillary tangles marked with loss of cognitive functions and memory impairment[1]. As there is no effective treatment available for AD, a paradigm shift in AD research is towards the early diagnosis and interventions for delay of the disease. APP-PS1 mice exhibit increase in amyloid plaques with age and more closely match the neurochemical profile and pathology of human AD[2]. Moreover, these mice show occasional deposits of amyloid plaques at the age of 5-6 months without significant memory impairment and neuronal loss- characteristics typical of AD pathology at an early stage of the disease[3]. The objective of the present study is to investigate neuronal metabolism in APP-PS1 mice at 6 month to find out biomarker for the early diagnosis of AD.

MATERIALS AND METHODS: All animal experiments were performed under approved protocols by the Institute Animal Ethics Committee. Overnight fasted APP-PS1 (6 month, n=6) and age matched wild-type (n=6) mice were anesthetized with urethane (1 g/kg, ip). [1,6-$^{13}C_2$]Glucose was infused for 10 min through tail vein using bolus variable infusion rate[4]. In addition, mice were also infused with [1,6-$^{13}C_2$]glucose for 90 min to evaluate labeling at steady state. Blood was collected and head was frozen *in situ* into liquid nitrogen at the end of infusion. Metabolites were extracted from frozen brain tissue[5]. Concentration and percentage ^{13}C enrichment of cerebral amino acids were measured in ^1H-[^{13}C]-NMR spectra of tissue extracts acquired at 600 MHz spectrometer[6].

RESULTS AND DISCUSSIONS: Neurometabolites level was not significantly different in APP-PS1 and wild-type mice. ^{13}C Labeling of cortical amino acids, Glu_{C4}, $GABA_{C2}$, Gln_{C4}, Glu_{C3} and Asp_{C3} from [1,6-$^{13}C_2$]glucose was significantly ($F[1,4]= 52.54$, $p<0.01$) lower in APP-PS1 mice than age matched wild-type (Fig. 1A). This together with no significant differences in the steady state labeling of amino acids suggest that glutamatergic TCA cycling is reduced in APP-PS1 mice. Nonlinear least-squares fitting to the time courses of Glu_{C4} and $GABA_{C2}$ (Fig. 1B) to monoexponential function revealed that glucose oxidation associated with glutamatergic (Fig. 1C) and GABAergic neurons (Fig. 1D) is severely reduced in cerebral cortex of APP-PS1 at the early age of AD. Similar results were observed in the hippocampal and striatal regions of brain. These findings may have implications in the preclinical diagnosis of AD

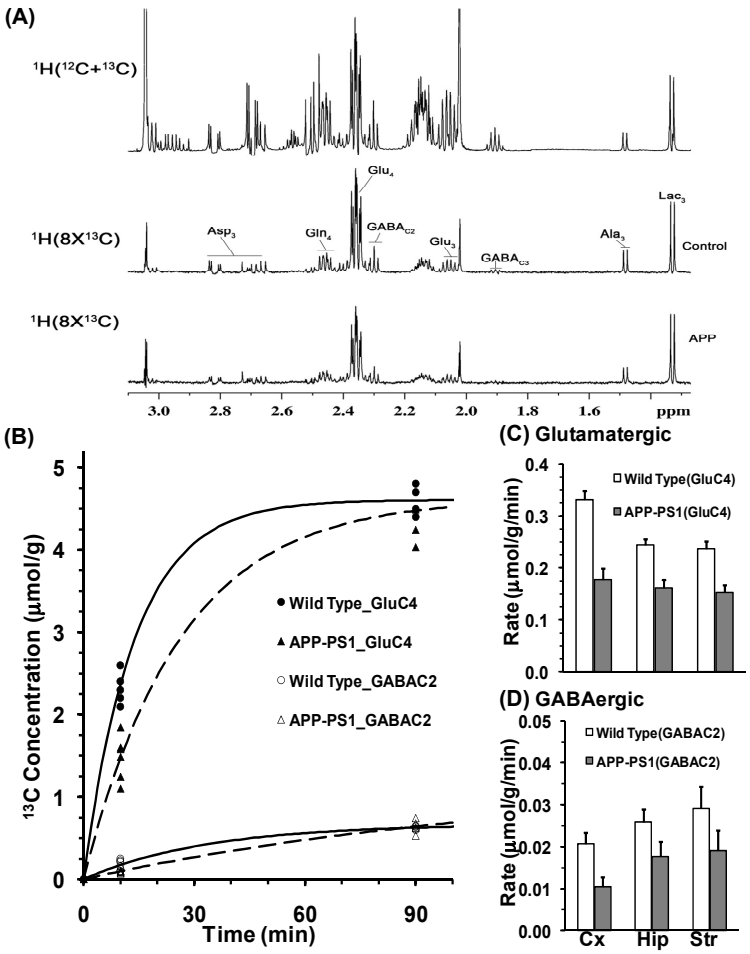

Fig.1 (A) Typical ^1H-[^{13}C]-NMR spectra from cortical extract. (B) Turnover of Glu_{C4} and $GABA_{C2}$ from [1,6-$^{13}C_2$]glucose in cerebral cortex. Rate of glucose oxidation by glutamatergic (C) GABAergic neurons in different regions of brain of APP-PS1 and Wild Type mice

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ACKNOWLEDGEMENTS: This study was supported by funding from Department of Biotechnology, India.