Reduced Glucose Oxidation by Glutamatergic Neurons in Cerebral Cortex during Normal Aging in Mice

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INTRODUCTION: Normal aging is associated with a decline in brain function, including cognitive, memory and sensory processes[1]. Changes in mitochondrial function have been implicated in age-related neurodegenerative diseases and have been suggested to have a role in the loss of cognitive function with healthy aging[2]. However, the changes in mitochondrial function at the cellular level is not fully understood with normal aging. In this study, we have investigated glucose oxidation by glutamatergic and GABAergic neurons and neurotransmitter cycling during healthy aging in cerebral cortex of mice by using ^{1}H-[^{13}C]-NMR spectroscopy together with infusion of [1,6-$^{13}C_2$]glucose.

MATERIALS AND METHODS: All the animal experiments were performed under protocols approved by the Institute Animal Ethics Committee. Two groups of male C57BL6 mice were studied at the age of 6 (adult, n=6) and 24 (aged, n=6) months. Overnight fasted mice were anesthetized with urethane (1.5 g/kg). Body temperature was maintained ~37°C with a heating pad warmed by a temperature-regulated, re-circulated water bath. [1,6-$^{13}C_2$]Glucose (0.225 M dissolve in water) was infused in mice for 10 min via tail vein after 45 min of induction of anesthesia with urethane[3]. In addition both groups were also infused with glucose for 90 min. At the end of the infusion, mice head was frozen in liquid nitrogen and metabolites were extracted from frozen cortical tissue[4]. The Concentration and percent ^{13}C enrichment of metabolites were determined from the ^{1}H-[^{13}C]-NMR spectrum of the cortical extract recorded at 600 MHz Bruker AVANCE spectrometer[5]. Plasma glucose enrichment was measured in ^{1}H MR spectrum.

RESULTS AND DISCUSSIONS: Level of cortical glutamate was found to be reduced significantly ($p=0.045$) in aged mice (12.3±0.3 μmol/g, n=6) compared to adult (13.1±0.8 μmol/g, n=6). Accumulation of ^{13}C label into Gln_{C4} during 10 min of [1,6-$^{13}C_2$]glucose infusion was reduced (adult: 0.26±0.07 μmol/g; aged: 0.18±0.03 μmol/g) significantly ($p=0.037$, n=6,6) suggesting decreased neurotransmission in aged mice. Initial rate of glucose oxidation by glutamatergic and GABAergic neurons was estimated by a nonlinear least-squares fitting to the labeling time course of Glu (Glu_{C4} + 2xGlu_{C3} + Asp_{C3}) and GABA ($GABA_{C2}$ + 2x$GABA_{C3}$ + Asp_{C3}) to a monoexponential function. The time constant of cortical Glu and GABA labeling was higher in aged mice. The glucose oxidation by glutamatergic neurons in cerebral cortex was found to be reduced in aged mice (adult: 0.29±0.03 μmol/g/min; aged: 0.24±0.02 μmol/g/min). GABAergic metabolism seems to be unchanged with normal aging. A detailed metabolic modeling is required to understand changes in glutamatergic and GABAergic neurotransmission with normal aging in different brain regions.

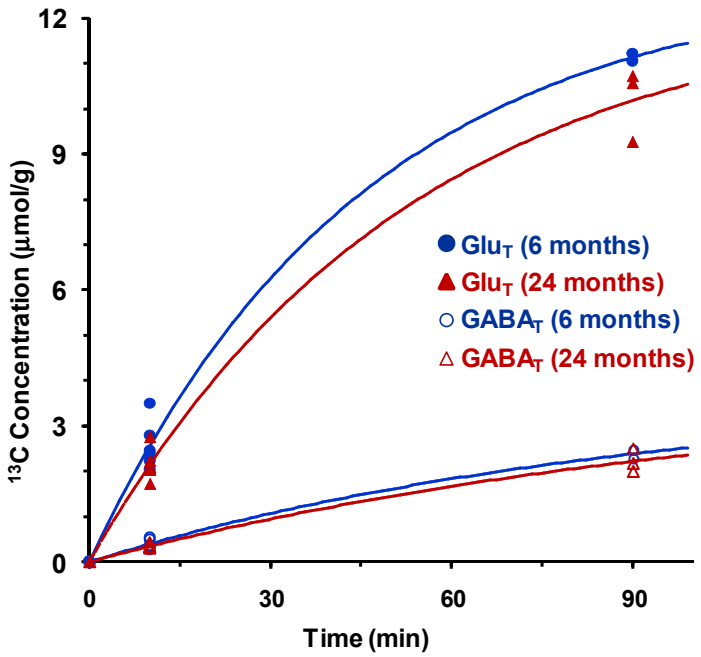

Fig. 1 ^{13}C Labeling of Glu & GABA from [1,6-$^{13}C_2$]glucose

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