Reduced Glutamatergic Metabolism in Mice Cortex with different Level of Alcohol Exposure

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INTRODUCTION: Alcohol has a broad range of actions on a number of neurotransmitters receptor such as glutamate, GABA, dopomine and serotonine[1]. Alcohol produces dose dependent pattern for changes in the cerebral activity[2]. Low doses of alcohol have been shown to increase functional activity in motor structure while higher alcohol level decreases functional activity in number of sensory regions. The majority of animal studies have investigated the effects of alcohol on central nervous system functional activity via intraperitoneal or intravenous routes of administration. To study the neurobiological consequences of alcohol use in animal models, it is important to use parameters that closely approximate conditions in which humans consume alcohol. The present study investigates glutamatergic and GABAergic metabolism under different level of alcohol exposure via oral route in mice brain by using ^{1}H-[^{13}C]-NMR spectroscopy in conjunction 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. Four groups of two month old male C57BL6 mice were studied. Group (i) control mice (treated with normal saline, n=7), Group (ii) mice treated with 0.5 g/kg alcohol (n=6), Group (iii) mice treated with 1.5 g/kg alcohol (n=4) and Group (iv) mice treated with 2.5 g/kg alcohol (n=7). Overnight fasted mice were administered alcohol orally. Mice were anesthetized with urethane (1.5 g/kg) 20 min after alcohol/normal saline administration. [1,6-$^{13}C_2$]Glucose was infused in mice for 10 min via tail vein after 45 min of induction of anesthesia with urethane[3]. 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 Hz Bruker AVANCE spectrometer[5]. Plasma alcohol level and glucose enrichment was measured in ^{1}H NMR spectrum.

RESULTS AND DISCUSSIONS: Level of cortical neurometabolites did not change with acute treatment of 0.5 g/kg alcohol. However, cortical GABA level was found to be increased significantly ($p<0.05$) in mice exposed with alcohol 1.5 g/kg (2.7±0.2 μmol/g) and 2.5 g/kg (2.9±0.3 μmol/g) as compared to control (2.4±0.3 μmol/g). Although, 0.5 g/kg alcohol did not affect labeling of cortical amino acids, exposure with higher doses of alcohol (1.5 and 2.5 g/kg) reduces ($p<0.02$) ^{13}C labeling of Glu_{C4} and Gln_{C4} from [1,6-$^{13}C_2$]glucose without any change in $GABA_{C2}$ labeling (Fig. 1). These data suggest that acute alcohol selectively attenuate excitatory activity without much changes on inhibitory function. Furthermore, labeling of Glu_{C4} correlates negatively with plasma alcohol contents suggesting that the cognitive function decreases with increase in level of blood alcohol.

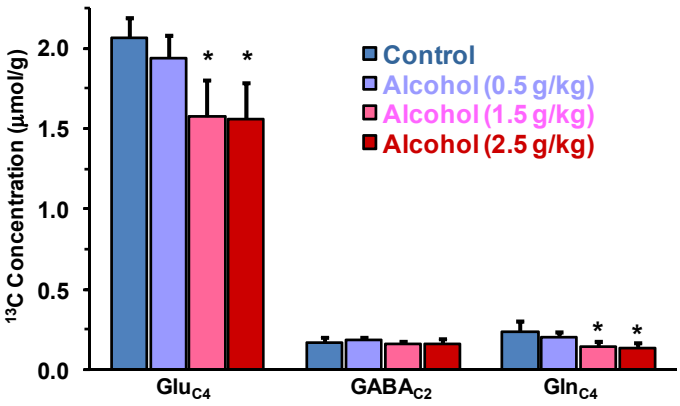

Fig. 1 Concentration of ^{13}C labeled cortical amino acids after acute alcohol exposure

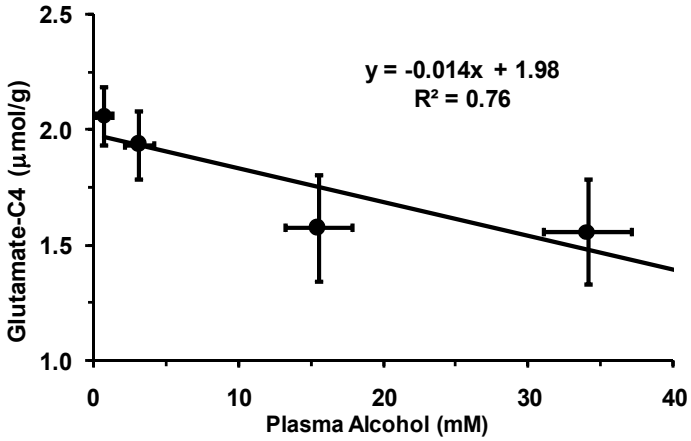

Fig. 2 Correlation of Glu_{C4} labeling with plasma alcohol

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