Reduced Glutamatergic Activity Under Acute Alcohol Exposure

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INTRODUCTION: Alcohol abuse is one of the major health problem leading to 2.5 million deaths annually. Alcohol causes impairment of cognitive, psychological functions and neural activities[1]. Ethanol has been shown to act as an allosteric inhibitor of N-methyl-D-aspartate receptor at behavioral intoxicating doses[2]. Binding of ethanol to $GABA_A$ receptors may have implications for its anxiolytic, anaesthetic and sedative effects[3]. It is hypothesized that exposure with ethanol will alter the energetics of glutamate and GABA, the major excitatory and inhibitory neurotransmitters, respectively in the mature central nervous system. In this study, we have investigated the effect of acute alcohol in mouse on glutamatergic and GABAergic pathways 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. Measurements were carried out in two month old C57BL6 mice treated with ethanol (2.5 g/kg, i.p, n=8) and control mice treated with normal saline (n=8). Overnight fasted mice were anesthetized with urethane (1.5 g/kg) after 20 minute of ethanol/normal saline administration (2.5g/kg, 20% v/v) and [1,6-$^{13}C_2$]glucose was infused after 45 min of anesthesia induction[4]. Alcohol treated mice and control mice were also infused with ^{13}C labeled glucose for 90 min to evaluate labeling at steady state. Cerebral metabolites were extracted from different brain regions[5]. The concentrations and percent ^{13}C enrichment of metabolites were determined from the ^{1}H-[^{13}C]-NMR spectrum of the extract recorded at 600 MHz NMR spectrometer (Bruker AVANCE)[6].

RESULTS AND DISCUSSIONS: A typical ^{1}H-[^{13}C]-NMR spectrum recorded from cortical extract is presented in Fig. 1A. Level of glutamate was found to be significantly lower in cerebral cortex (Control: 13.4±0.9, Alcohol: 11.9±0.6; p<0.01) and olfactory bulb (Control: 12.1±0.5, Alcohol: 11.0±0.6; p<0.01) regions of brain of mice exposed with alcohol. ^{1}H-[^{13}C]-NMR spectrum exhibit lower ^{13}C labeling of amino acids from [1,6-$^{13}C_2$]glucose during 10 min in alcohol treated mouse compared to normal saline treated control (Fig. 1B). This together with no change in steady state labeling of Glu_{C4} suggests impairment in glutamatergic activity. Glucose oxidation associated with glutamatergic neurons is decrease in alcohol treated mice (Fig. 1C). However no significant change in $GABA_{C2}/GABA_{C3}$ labeling suggests acute alcohol does not affect glucose oxidation by GABAergic neurons. Further, decrease in Gln_{C4} labeling in cortex implies reduction of total (Glu+GABA) neurotransmitter cycling. These findings indicate that acute exposure of alcohol perturbs only excitatory functions without affecting the inhibitory activity.

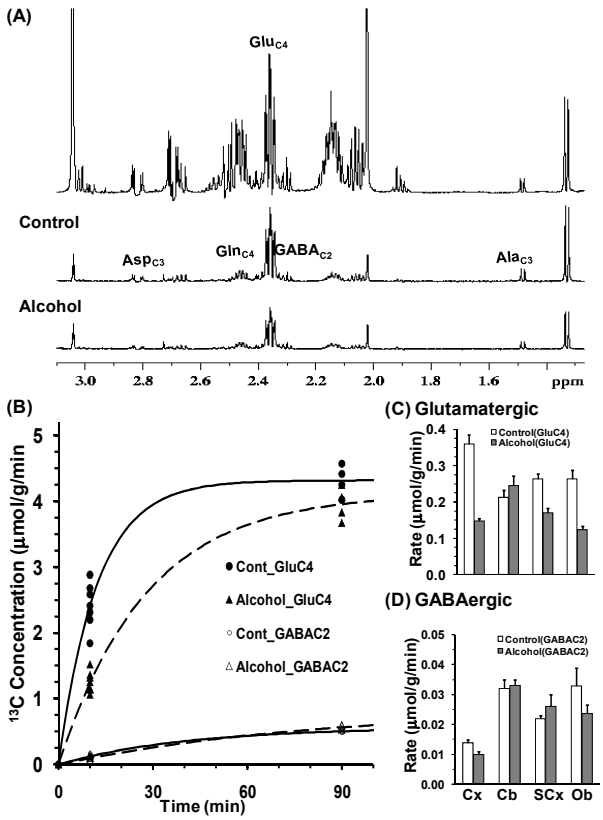

Fig.1 (A) Typical ^{1}H-[^{13}C]-NMR spectra from cortical extract. (B) Turnover of Glu_{C4} and $GABA_{C2}$ from [1,6-$^{13}C_2$]glucose in cerebral cortex. Rate of glucose oxidation by glutamatergic (C) GABAergic neurons in different regions of brain of APP-PS1 and Wild Type mice

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