Decreased Cerebral Metabolism in Mice Exposed with Alcohol During Developmental Period

Anant Bahadur Patel[1], Vivek Tiwari[1], and Dev Ketan Thacker[1]
[1]*NMR Microimaging and Spectroscopy, Centre for Cellular and Molecular Biology, Hyderabad, Andhra Pradesh, India*

INTRODUCTION: Alcohol crosses the placental barrier, damages neurons and brain structures which might result in psychological or behavioral problems. Neural development continues throughout prenatal and postnatal period. Lactation period, in rats and mice lasts for approximately 21 days after birth, is a period of rapid brain development marked with increase in excitatory and inhibitory synapses[1]. Ethanol has been shown to bind NMDA and $GABA_A$ receptors[2,3]. Therefore, exposure of alcohol during gestation and lactation period might alter the development of glutamatergic and GABAergic neurons and associated functions. Current study investigates the glutamatergic and GABAergic metabolism in the pups of dams treated with alcohol during gestation and lactation period.

MATERIALS AND METHODS: All animal experiments were performed under approved protocols by Institute Animal Ethics Committee. Female C57BL6 mice were used for (i) Gestation, (ii) Lactation and (iii) Control. Group (i) mouse was fed alcohol (2.5 g/kg, 15% v/v, i.g.) from the day of plugging till the parturition. Mouse in Group (ii) was fed alcohol from the P4 to P21 and Group (iii) mice received normal saline. The pups were separated from dams on the P23 and cerebral metabolic study was carried out on P25. Mice were anesthetized with urethane and [1,6-$^{13}C_2$]glucose was infused for 15 min using bolus variable infusion rate[4]. Blood was collected and head was frozen *in situ* into liquid nitrogen at the conclusion of experiment. Metabolites were extracted from frozen cortical tissue[5]. ^{1}H-[^{13}C]-NMR spectra of cortical extracts were acquired at 600 MHz spectrometer (Bruker AVANCE II)[6].

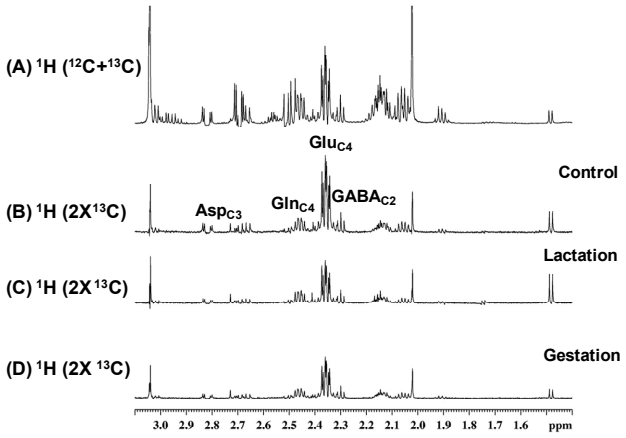

Fig. 1 ^{1}H-[^{13}C]-NMR spectra of cortical extract

RESULTS AND DISCUSSION: Level of cortical Glu, Asp and Cho was significantly lower in mice exposed to alcohol during lactation period whereas exposure to alcohol during gestation period did not exhibit any perturbation in level of cortical metabolites. ^{13}C Labeling of amino acids Glu_{C4}, $GABA_{C2}$, Gln_{C4}, Glu_{C3} and Asp_{C3} from [1,6-$^{13}C_2$]glucose was significantly lower in mice exposed with alcohol during prenatal and postnatal period than with normal saline treated controls (Fig. 1). Reduction in ^{13}C labeling of amino acids from [1,6-$^{13}C_2$]glucose implies impairment in glucose oxidation in the mice exposed to alcohol during prenatal or postnatal periods (Fig. 2). Further, reduction in Gln_{C4} labeling suggests impaired neurotransmitter cycling as a consequence of exposure with alcohol during developmental periods. These findings suggest that exposure with alcohol during prenatal and postnatal period has profounding effect on brain development.

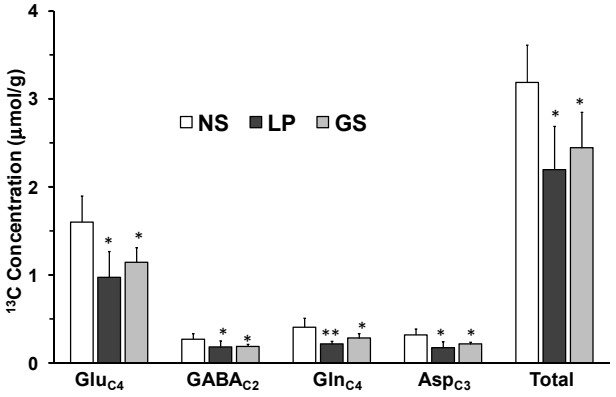

Figure 2. Concentration of ^{13}C labeled amino acids from [1,6-$^{13}C_2$]glucose, **p<0.01, *p<0.05

REFERENCES: 1.Woodward JJ (2000) *Crit Rev Neurobiol* **14**:69; 2. Suzdak et al (1987) *Psychopharmacol Bull* **23**:445 ; 3. Paul et al (2006) *Proc Natl Acad Sci* **103**:8307 ; 4. Fitzpatrick et al (1990) *J Cereb Blood Flow Metab* **10**:170; 5. Patel et al (2001) *Brain Res* **919**:207; 6. De Graaf *et al* (2003) *Magn Reson Med* **49**:37.

ACKNOWLEDGEMENTS: This study was supported by funding from Council for Scientific and Industrial Research, India.