Chronic Exposure to Lead Impairs Neuronal Metabolism in Mouse Brain: A ^{1}H-[^{13}C]-NMR Study

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Introduction: Lead is a highly toxic heavy metal, shown to inhibit the Ca^{2+} dependent release of acetylcholine, dopamine and amino acid neurotransmitters and increases their basal level even at low levels of exposure[1]. Neurotoxic actions of lead include apoptosis, excitotoxicity, neurotransmitters storage and release, and damage to the astroglia and oligodendroglia[2]. Impact of lead toxicity on brain energy metabolism is yet elusive. In this study, we investigated the effects of chronic exposure of lead on the glutamatergic and GABAergic metabolism in cortical and hippocampal regions in mouse by using ^{1}H-[^{13}C]-NMR spectroscopy in conjunction with infusion of [1,6-$^{13}C_2$]glucose.

Material and methods: Male C57BL6 mice (2 months) were divided into two groups: Group (i) Control (n=14), Group (ii) Lead treated (n=15). Mice in Group (ii) were given lead acetate in drinking water (500 ppm/day) while the control mice received sodium acetate in water for 60 days. For metabolic study, overnight fasted mice were anesthetized with urethane and [1,6-$^{13}C_2$]glucose was administered (i.v.) for 10, 45 and 90 min[3]. At the end of the infusion, head was frozen *in situ* in liq. N_2 and metabolites were extracted from frozen brain tissue[4]. The concentration and percent ^{13}C enrichment of metabolites were determined from the ^{1}H-[^{13}C]-NMR spectra[5] of tissue extracts acquired at 600 MHz (Bruker AVANCE II) NMR spectrometer (Fig 1). The ^{13}C labeling of amino acids was analyzed using a three compartment metabolic model for the determination of absolute metabolic fluxes[6].

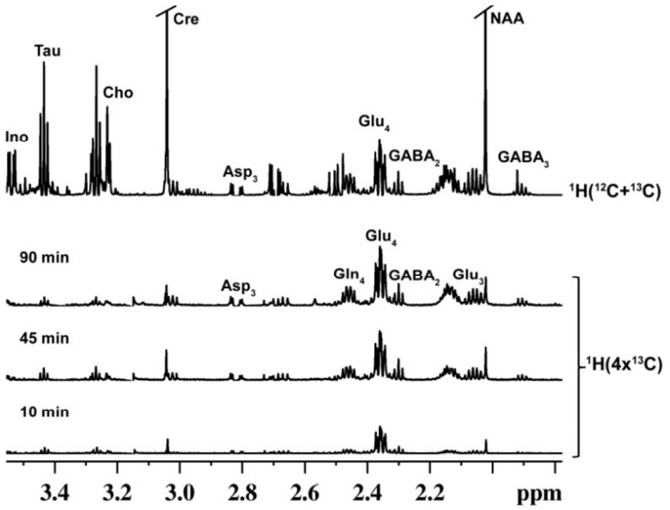

Fig. 1 ^{1}H-[^{13}C]-NMR spectra from mouse cortical extract

Results and Discussion: Level of inositol was found to be elevated in hippocampus with chronic lead exposure suggesting astrogliosis due to neuroinflamation. Increasing ^{13}C labeling of amino acids with time is evident in the ^{1}H-(^{13}C)-NMR spectra. The ^{13}C turnover curve of amino acids were constructed based on the measurement of percent ^{13}C enrichment with time. The analysis of turnover data using a three compartment metabolic model indicated deficit in TCA cycle and neurotransmitter cycling associated with glutamatergic neurons in cortical and hippocampal regions while GABAergic fluxes were perturbed only in the hippocampus. These findings indicate that chronic exposure to lead causes widespread impairment of the excitatory activity and total neurotransmission while inhibitory function is impaired only in the hippocampus (Fig. 2). These results explain the reduced activity[7], and modulation in neurotransmitter systems[8] on chronic exposure of lead.

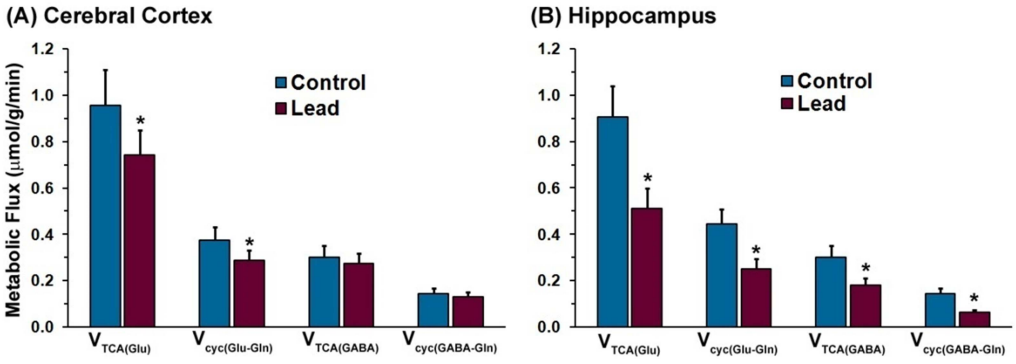

Fig. 2 Glutamatergic and GABAergic fluxes in (A) Cerebral cortex, (B) Hippocampus of mice exposed with lead

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