

Methamphetamine Abuse Impacts Glial Metabolism

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Purpose: Use ¹³C MRS to define specific glial metabolic rate in humans recovering from methamphetamine abuse.

Background: Drug abuse severely impacts cognitive functions associated with frontal lobe structures. Conventional PET and fMRI have been used to map the anatomical extent of abnormalities but throw little light on the possible underlying mechanism of drug addiction, craving or recovery. ¹³C MRS provides unique distinction between neuronal and glial compartments and, with recent technical advances (1), can now safely be applied to address the question of glial dysfunction in frontal brain of human subjects.

Human Subjects, Patients and Methods: Ten human subjects were recruited for the ¹³C MRS study, 5 recently (3 – 8 weeks since last use) abstinent methamphetamine dependent (AMD) and 5 age and gender matched normal controls. DVM-IV, SCID and neuropsychological as well as complete drug history were provided. The 10 subjects received sterile intravenous 1-¹³C acetate (IND 59,960) 3 gm/kg body weight over 1 hour. Using GE 1.5 Tesla broad-band clinical MR scanner with a conforming dual tuned proton/carbon RF coil applied to the forehead, low power NOE ¹³C spectra were acquired in 6 minute blocks for 120 minutes. Data was processed as previously described to yield peak intensities for glutamate (182ppm) and glutamine C5 (178ppm), glutamine+glutamate C1 (175ppm) and bicarbonate (161ppm) (2). For the present study, the flux rate of 1-¹³C acetate to ¹³C bicarbonate = glial TCA cycle rate was calculated and expressed as $\mu\text{moles/g/minute}$.

Results: Localizer MRI from the dual tuned RF coil defined the volume of interest of approximately 100cc to include prefrontal cortex and frontal white matter in approximately equal proportions, which did not differ between AMD and Controls. Glial TCA cycle rate for frontal brain in normal subjects was $0.11 \pm 0.01 \mu\text{moles/g/minute}$. The rate in AMD was only half of that in normal subjects ($0.04 \pm 0.01 \mu\text{moles/min/g}$; $P < 0.001$).

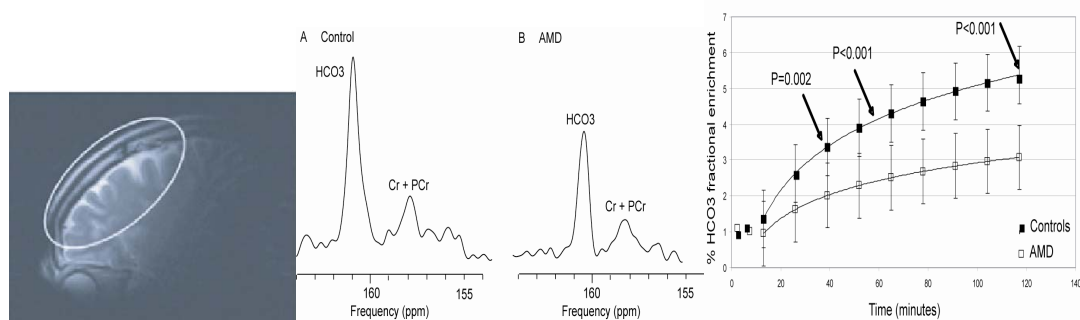


Figure 1, left, shows MRI of the frontal brain. Comparison of ¹³C MRS spectra of HCO₃ and Cr plus phosphocreatine at 120 min after the infusion in control (left) and AMD (right) subject is shown in figure 2 (middle figure). The un-enriched Cr + PCr peak intensities indicate that their concentration is very similar while substantial differences in HCO₃ peak intensities was observed between control and AMD subject.

Logarithmic fits of the averaged % fractional enrichment of HCO₃ (%E) is plotted as a function of time after start of the infusion shown in figure 3 (right). %E in AMD (lower trace) was shown to be lower than the controls (upper trace) with significant P values calculated between 7-40min ($P=0.002$), 60 min ($P<0.001$), and 120 min ($P<0.001$) after start of the infusion.

Discussion and Conclusions:

Drug abuse, a major neuropsychiatric challenge of our times has resisted a clear definition in neurochemical terms. The present study represents a 'first' at several levels: First clinical ¹³C MRS study of frontal brain in humans. First demonstration that in vivo glial activity is under metabolic control. First evidence that methamphetamine abuse may impact the glutamate neurotransmitter system. The ¹³C MRS technique appears to be robust and reproducible and therefore suited to more detailed longitudinal studies in patients necessary to unravel the complex cycle of drug abuse, craving, relapse and recovery.

Reference: (1) Sailasuta N, et al. J Magn Reson 2008;195(2):219-225. (2) Bluml S, et al. NMR Biomed 2002;15(1):1-5. The author thanks NIH for financial support (K25DA21112, NS)