[1-13C] acetate MRS to study glial glutamate dysfunction in methamphetamine users

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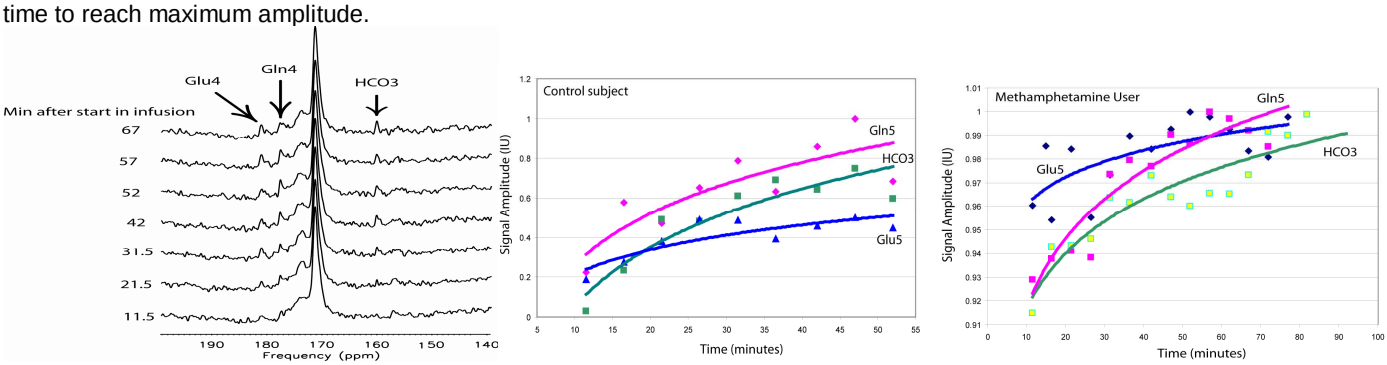
Purpose: With the recent demonstration of elevated steady-state glutamate concentration in abstinent MA we hypothesized that Glu contributes to addiction by a long-lasting adaptation of glutamate neurotransmission (GNT) (1). Numerous lines of evidence indicate that neurons play an essential role in the regulation of glutamatergic neurotransmission (2) However, much less is known about the involvement of glia in addiction behaviors. In this study, we employed [1-13C] acetate, a glial fuel, together with 13C MRS to study dynamics of glial GNT in abstinent MA users.

Methods: Localized 1H MRS and proton decoupled 13C MRS were performed on a clinical 1.5T MR scanner using a home-built dual tuned half head coil and standalone decoupling accessories (2). The known glia fuel, acetate, enriched in carbon 1 position (2mg/kg/min over 15 min) was administered via arm vein. Three abstinent MA and two normal controls participated in the studies. Six minutes block of 13C MRS were acquired for approx. 120 min (non-localized pulse and acquire data acquisition scheme, 1024 data point, 5000 Hz spectral width, TR=2sec: ref 4 Bluml/Moreno).

Results: 1. Steady state [Glu] increased 18% in frontal WM (P<0.01); [NAA] and [ml], the latter a glial marker, were unaltered (p=ns). 2. 1-13C acetate was rapidly taken up and metabolized in normal and in MA brain. The appearance of Glu4, Gln4 and HCO3 resonances after start of infusion is shown as stack plot in the left figure below. C1 acetate was metabolized in glia to Gln5, Glu5 and bicarbonate. 13C enriched resonances of glutamine C5 at 178ppm was observed within 20 min and HCO3 resonance at 161 ppm was also identified. For the MA user, the Gln5 resonance was constant at 70-80 min after start of the infusion while in the control takes longer time to reach maximum amplitude.



3. As expected from the localization of glutamine synthetase to glia, 13C glutamine appeared earlier and more prominently that glutamate in both MA and in Controls. Time for Gln5 to reach maximum amplitude appeared to be reduced compared to the control group. Taken together, the preliminary results suggest a faster acetate turnover rate in MA than control.

Discussion: In order to accumulate elevated [Glu] at steady state there must be excessive synthesis or reduced catabolism. Two cell types (neuron 80% and glia 20%) account for brain glu; similarly two metabolic pathways (TCA-cycle and glutamate-glutamine cycle) account for 80% of glutamate turnover. The present study is the first to our knowledge to explore a biochemical and neuroanatomical hypothesis to account for drug abuse in MA. Preliminary results point to acceleration in glial portion of the glutamine-glutamate cycle (believed responsible for glutamate neurotransmission GNT) as a possible mechanism for elevated brain [Glu] and the resulting neuropsychological abnormalities.

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