13C Glucose Magnetic Resonance Spectroscopy of Human Schizophrenia: Impact of Medication

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Aims: Determine neuronal TCA cycle rate in treated schizophrenics (SZ).

Background: N-acetyl aspartate (NAA), a recognized neuronal marker of function, is possibly reduced in concentration in the brains of SZ human and in some animal models. NAA is synthesized in an energy dependent process requiring ATP and intact neuronal mitochondria. We hypothesized that glutamate neurotransmitter rate, neuronal TCA cycle or glucose oxidation rates might therefore be altered in SZ. Because drug naïve SZ may not tolerate prolonged MRS after IV 13C glucose infusion, this preliminary study was performed in stable, treated SZ and age matched controls.

Methods: We performed MRI, ^{1}H MRS and ^{13}C MRS after 1-^{13}C glucose infusion in 3 treated SZ patients and 5 age-matched healthy controls, using a routine clinical GE 1.5 T LX MR spectrometer fitted with a stand-alone decoupler and a custom-built ^{1}H-^{13}C MR head coil and fast, semi-automated analysis of the ^{13}C data (1). SZ patients were diagnosed by DSM IV and SCID criteria and their medication recorded. Each received I-V infusion of approximately 20g. 20% w/v of 99% enriched 1-13C glucose (Cambridge Isotopes Laboratory, Mass) over 10-12 minutes (FDA, IND 56, 510).

Results: MRI, localized ^{1}H MRS and ^{13}C MRS with broadband decoupling was continued for 90 – 120 minutes after 1-^{13}C glucose administration, in all SZ and controls. Enrichment of cerebral glucose was maximum after approx. 20 minutes and similar in SZ and controls (not shown). However, representative ^{13}C difference spectra of SZ and control subjects showed reduced incorporation of ^{13}C into the principal neuronal metabolites, glutamate, glutamine and aspartate (Figure 1). The time course of enrichment of glutamate (Glu2) was delayed (Figure 2) while that of $H^{13}CO_3^-$ overlapped with control (Figure 3).

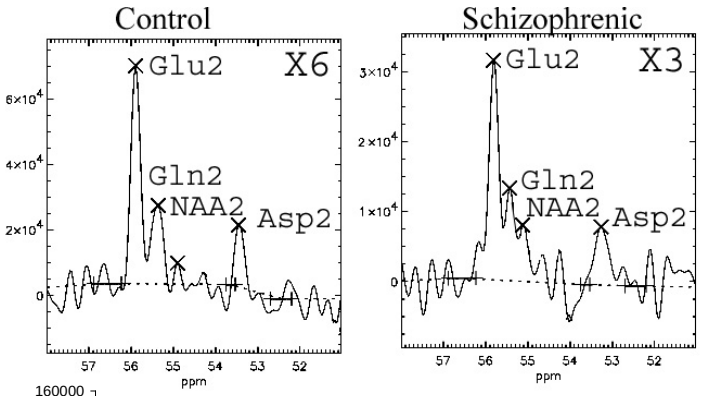
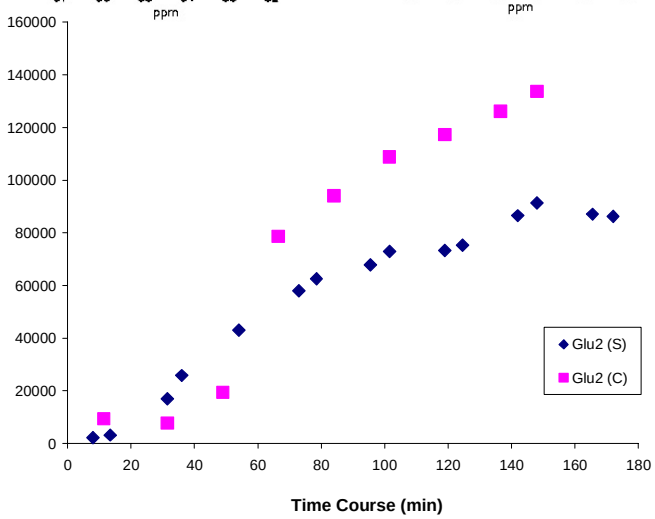
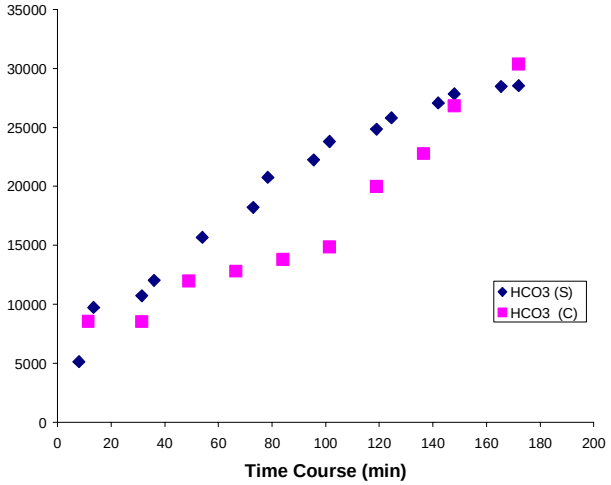


Figure Legend: Fig. 1 Part of ^{13}C difference spectra showing C2 resonances of glutamate, glutamine and aspartate, from control (left) and SZ (right) acquired after 90 minutes. Note the scaling indicates metabolites achieved only half the signal intensity in the SZ compared to control.

Figs. 2 and 3. Time courses of metabolite enrichment were constructed from spectra acquired at 5 minute intervals using data processing of (1).





Discussion and Conclusions: 1. Feasibility of clinically informative ^{13}C MRS in a complex human brain disorder, using a standard clinical MR scanner at 1.5 Tesla is established.

2. Significant metabolic abnormalities observed in this preliminary study are consistent with reduced neuronal TCA cycle or glutamate neurotransmission in a small group of treated SZ.
3. Whether these effects are due to SZ or to therapy, can only be established by studies in drug-naïve SZ.

References:

1. Shic F, Ross B. Automated data processing of {^{1}H-decoupled} ^{13}C MR spectra acquired from human brain in vivo. J Magn Reson. 2003 Jun;162(2):259-268.

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