

Glial Glutamate Dysfunction in Schizophrenia: 13C Acetate MRS

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Introduction The role of glutamate in schizophrenia¹, has recently been confirmed in patients². With our preliminary data, we provide direct support for a paradigm shift which could alter the drug discovery process for schizophrenia, moving away from dopaminergic inhibitors to glutamatergic stimulants. However, the glutamate/glutamine cycle is a complex pathway occurring between neurons and glia and involving at least eight distinct metabolic processes. Further dissection of the abnormality in schizophrenia is necessary to guide effective therapy. We describe preliminary results of studies distinguishing between neuronal and glial elements of the glutamate glutamine cycle in schizophrenic subjects.

Method In vivo 13C MRS was performed on a clinical 1.5T MR scanner (GE Healthcare LX) using a home-built dual tuned 1H-13C rf head coil and a stand-alone proton decoupling unit, provided with power monitor³. The known glial fuel, sodium acetate, enriched in carbon 1 position (2mg/kg/min over 1 hour = approximately 10g total) was administered intravenously. 13C is traced in the brain and its glial and neuronal compartments to directly determine the in vivo rates of the Krebs Cycle, glutamate-glutamine cycle and oxidative pathways⁴. Peak areas, observer independent data analysis and metabolic flux models developed in this Laboratory, were employed in near-steady-state conditions to quantify all aspects of the aforementioned metabolic cycles *in vivo*⁵. Patients, diagnosed by DSM-IV criteria as schizophrenic and receiving conventional treatment(s) were evaluated by 2 psychiatrists.

Results 1-13C acetate appeared in the brain, with subsequent enrichment of glutamine C5, glutamate C5 and bicarbonate (Fig. 1a, 1b). The time course of enrichments approached steady state after 60 minutes (Fig. 2). In the representative subjects illustrated, no differences between control and schizophrenic subject were apparent in C5 glutamate or C5 glutamine enrichment was identified. However, the schizophrenic subject showed markedly slower rate and decreased final fractional 13C HCO₃ enrichment (Fig. 3). These preliminary results were reproduced in a small series of treated schizophrenic subjects and normal controls.

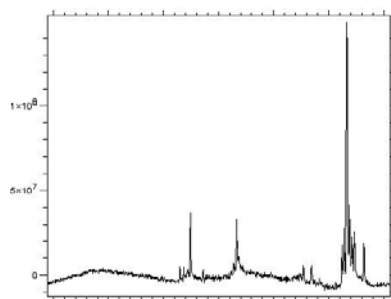


Fig 1a. 13C Full Spectrum

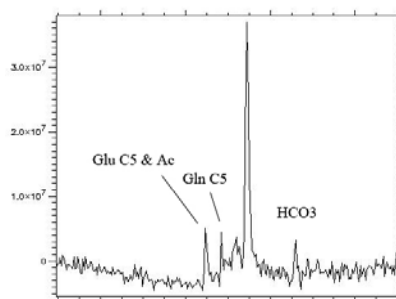


Fig 1b. 13C C5 Region

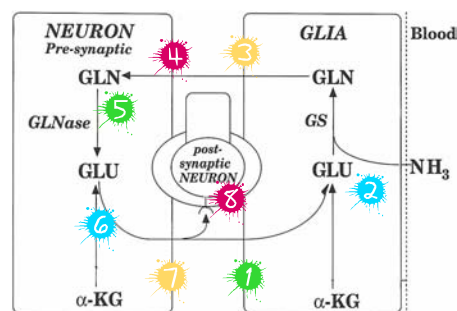


Fig 3. Glutamate Glutamine Cycle

Time Course of Enrichment

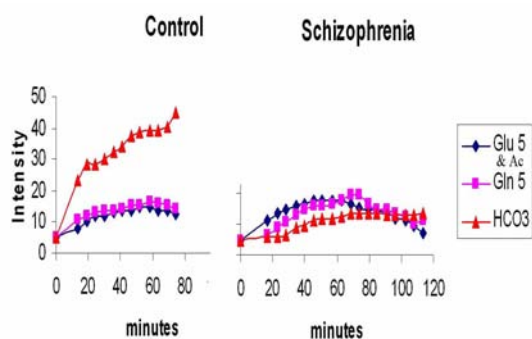


Fig. 2

Acknowledgements KH thanks NARSAD for a Young Investigator Award and HMRI and RSRI for additional funding. BD Ross assisted with intravenous injection of 13C substrates. Dr. George Simpson, University of Southern California provided valuable psychiatric guidance. Study under FDA 59,950 & 56,510. Informed consent HMH IRB. **References** 1) Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. *Harv Rev Psychiatry* 3:241-253, 1996. 2) Harris K, Bhattacharya P, Lin A, Ross BD. (2004) 13C glucose magnetic resonance spectroscopy of human schizophrenia: Impact of medication. *Proc Int Soc Magn Reson Med* 12:66 3) S. Bluml, *In vivo* quantitation of cerebral metabolite concentrations using natural abundance 13C MRS at 1.5 T. *J. Magn. Reson.* **136**, 219 (1999). 4) Moreno A, Ross BD, Bluml S. Direct determination of the Nacetyl-L-aspartate synthesis rate in the human 13C MRS and [1-13C] glucose infusion. *J. Neurochem.* 2001; **77**: 347-350. 5) Shic F, Ross B. Automated data processing of {1H-decoupled} 13C MR spectra acquired from human brain *in vivo*. *J Magn Reson.* 2003 Jun; **162**(2):259-268 6) Lin AP, Shic F, Enriquez C, Ross BD. Reduced glutamate neurotransmission in patients with Alzheimer's disease -- an *in vivo* (13C) magnetic resonance spectroscopy study. *Magma* 2003; **16**:29-42.

Discussion: In earlier studies, we demonstrated significant abnormality in the cerebral metabolism of 1-13C glucose among schizophrenic subjects². Because the impact of schizophrenia differed from that described previously in Alzheimer's Disease⁶, we suggested that disturbance of glial glutamate metabolism may contribute to abnormality of glutamate neurotransmission. The present study attempts to address that hypothesis by providing the purely glial fuel, 1-13C acetate, in place of the neuronal fuel 1-13C glucose. Initial results support the hypothesis that glial metabolism is depressed in schizophrenic subjects. Accordingly we suggest that schizophrenia is a coordinated failure of neuronal and glial metabolism. The glutamate neurotransmitter cycle provides at least 8 identifiable control points (Fig 3) with several potential target genes and transporters. 13C MRS can help to identify schizophrenia phenotype(s) and genotype(s), thereby accelerating effective drug discovery.

Conclusion 1-13C acetate MRS *in vivo* allows further definition of recently identified abnormality of glutamate neurotransmitter rate in schizophrenic subjects.