Is Human Glial TCA Cycle Rate Faster than We Thought?

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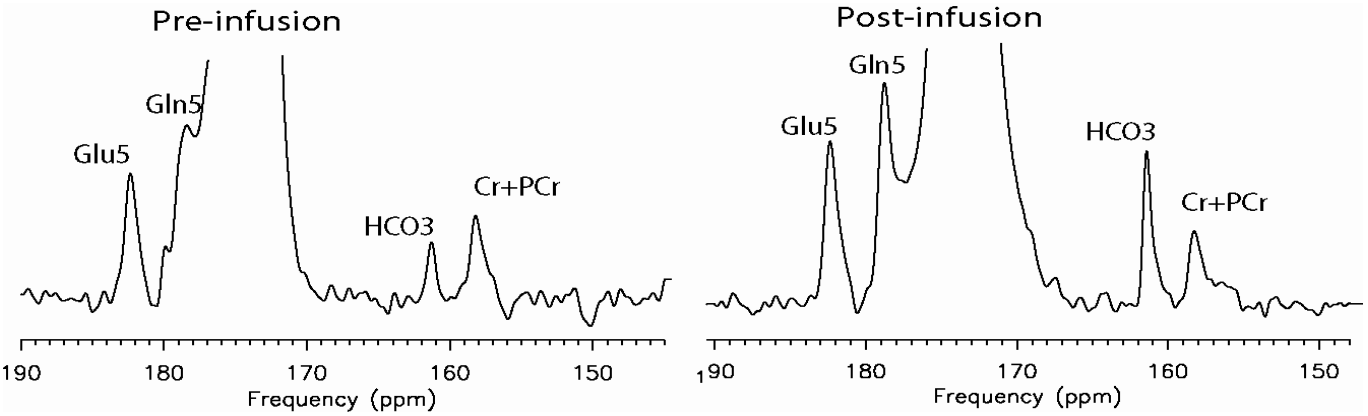
Purpose: Supported by the widely held view that acetate is transported into glia but not neurons, it may be possible to separately quantify neuronal and glial glutamate cycle and TCA in a wide range of disease states. Accordingly we have attempted to improve the accuracy with which in vivo cerebral metabolic rate for glia in the human brain is calculated.

Background: In the present study we enrich cerebral metabolic pathways of glia from 1-13C acetate and demonstrate glial TCA cycle rate, avoiding all modeling in favor of a two steps calculation, acetate -> HCO3.

Human Subjects and Methods: Six subjects received 1-13C acetate intravenous infusions, followed by direct 13C MRS of the posterior brain region as previously described [1]. Time courses were constructed to demonstrate increasing 13C enrichment of the principal metabolic products. In separate examinations, the same subjects were examined without 13C infusion in order to quantify the initial pool size of brain bicarbonate (HCO3). Natural abundance 13C spectra were analyzed to obtain relative peak areas of Cr+PCr, glutamate C5 and bicarbonate, all of which were readily observed in spectra summed over 20 – 40 minutes.

Results: Natural abundance 13C brain spectrum (Figure below, left) shows adjacent resonances for Cr+ PCr (158ppm), bicarbonate (161ppm) and C5 glutamate (182ppm) as well as the extra-cerebral glycerol lipid peak (172ppm). A representative spectrum acquired after enrichment with 1-13C acetate (Figure below, right) demonstrates the marked increase in peak-height of 13C bicarbonate compared to the adjacent 13C Cr + PCr, which does not become enriched by systemic 13C acetate over the short time frame of the in vivo study. While 1-13C acetate is not observed, steady state input function was readily observed from enriched C5 glutamate. The absolute number of added micromoles of 13C bicarbonate is readily derived and calculation of the glial TCA cycle rate is accomplished directly. Assuming [Cr + PCr] = 11 mM, glial TCA in normal brain obtained in this way = 0.54 µmoles/min/g.



Discussion and Conclusions: The directly determined value for glial TCA rate is higher than either of the earlier published values and also higher than that more recently obtained in this Laboratory, using the Bluml method [1]. Two approaches have been used in human subjects, to imaging and then quantifying metabolic rates in the glutamate-glutamine cycle, TCA cycle and other processes assigned to the glial cell rather than the neuron. Starting with 1-13C acetate, followed the enrichment of C5 glutamate and glutamine and of the final oxidative produce CO2 (as 13C bicarbonate). Glial flux was then expressed as a fraction of the neuronal metabolic flux of 1-13C glucose published by others [2, 3]. Starting with 2-13C acetate, Lebon et al [4] followed 13C label into C2-3 and 4 glutamate and glutamine and compared this directly with the parallel study in which the same metabolites were enriched by the neuronal fuel 1-13C glucose. Metabolic models were necessary to both methods. Given that total brain metabolic rate for oxygen consumption (1.3 µmoles/min/g) [5] must be accounted for by the sum of neuron and glia TCA cycle rates, neuron: glial TCA ~ 4:1, and that a recent in vitro TCA cyle rate for glia = 0.4 µmoles /min/g [6], it appears likely that the higher estimate of glial TCA emerging will prove to be correct. A re-evaluation of the models used in previous estimates appears timely.

References: [1] S. Bluml, A. et al. NMR Biomed 15 (2002) 1-5. [2] G.F. Mason, et al. J Cereb Blood Flow Metab 15 (1995) 12-25. [3] J. Shen, et al. Proc Natl Acad Sci U S A 96 (1999) 8235-40. [4] V. Lebon, et al. J Neurosci 22 (2002) 1523-31. [5] F. Xu, et al. MRM (2009) 62, 141-148. [6] R.A. Waniewski, J Neurochem (1998) 18, 5225-5233.
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