Glucose Metabolism in Animals with a Traumatic Brain Injury: a 13C NMR Study

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Introduction: Traumatic brain injury (TBI) is associated with cellular alterations that may contribute to metabolic dysfunction and energy crisis. Experimental studies have identified an early, transient increase in cerebral glucose uptake, followed by a decrease in ATP synthesis and glucose metabolic depression (Yoshino et al., 1991). These observations suggest that the increase in glucose utilization may not be directed towards maintaining the cell's energy state, but metabolized through alternative metabolic pathways. The present study was designed to explore the metabolic fate of glucose in the rat cortex 3.5h and 24h after a fluid percussion injury (FPI). We hypothesized that glucose metabolism after FPI would be shifted away from oxidative metabolism towards pathways associated with regenerative and/or anaplerotic processes.

Methods: The metabolic fate of [1,2 $^{13}C_2$] labeled glucose was determined in control (n=10) and male rats (300-350g) after a moderate lateral FPI to the left parietal cortex at 3.5h (n=5) and 24h (n=4) after injury. Following glucose infusion, animals were anesthetized and euthanized by a focused microwave beam and extracts of the left (injury core) and right cortices were deproteinated, neutralized, and prepared for NMR. Proton decoupled ^{13}C NMR spectra were obtained on a Bruker AM 360 MHz spectrometer using a 45 degree flip angle, 10 kHz spectral width, 2 sec acquisition time, 3 sec relaxation delay, and 15 000 acquisitions. All peaks were integrated and the amount of ^{13}C in each metabolite isotopomer was quantified using sodium 3-(trimethylsilyl) propionate (TSP) as an internal reference. All values are reported as mean ± SEM and a one-way ANOVA was used to test for an overall difference with a post-hoc Bonferrroni comparison to determine individual group differences.

Results: After a FPI, there was an increase in the ^{13}C-labeled glucose pool at both 3.5h and 24h. This was accompanied by a decrease in both the glutamate (Glu) and glutamine (Gln) pools at 3.5h and a decrease in the Gln pool only after 24h. The amount of ^{13}C enrichment in the lactate (Lac) pool did not differ between groups, however a Lac C3 singlet was identified in the injured cortex of both injury groups (Fig. 1). In the injured cortex, the percentage of lactate that was produced via the pentose phosphate pathway (PPP) was 13.2 ± 6.42% at 3.5h and 9.4 ± 6.4% at 24h post-injury. ^{13}C labeling of the Glu C3 and C4 doublet was significantly reduced in the injured cortex at 3.5h ($p < 0.05$; Fig. 2). By 24h the Glu enrichment in the injured cortex had recovered to control levels. The percentage of Glu that is recycled through pyruvate was calculated using the C4 singlet/doublet ratio. In the control group, 14.1 ± 1.9% of the Glu pool was recycled through this pathway. At 3.5h after FPI, this ratio significantly increased to 28.7 ± 5.5% ($p < 0.05$). By 24h post-FPI, the amount of Glu recycling also returned to control levels. A significant decrease in the ^{13}C enrichment of all Gln isotopomers was detected in the injured cortex at 3.5h after injury ($p < 0.05$; Fig. 3). By 24h the injured cortex continued to show a reduced enrichment in many of the Gln isotopomers.

Figure 1: mean ^{13}C enrichment of lactate

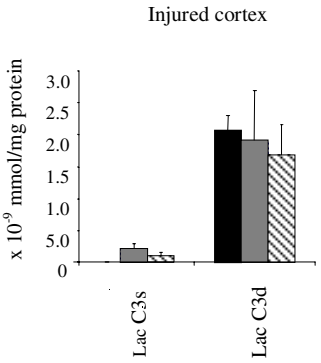


Figure 2: mean ^{13}C enrichment of glutamate

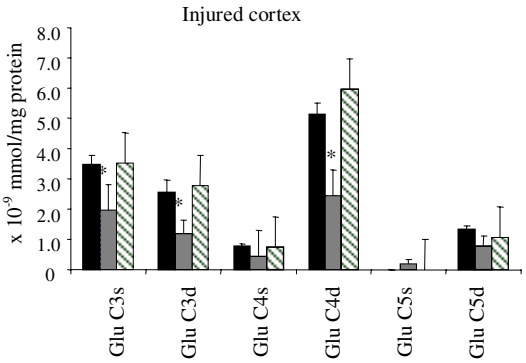
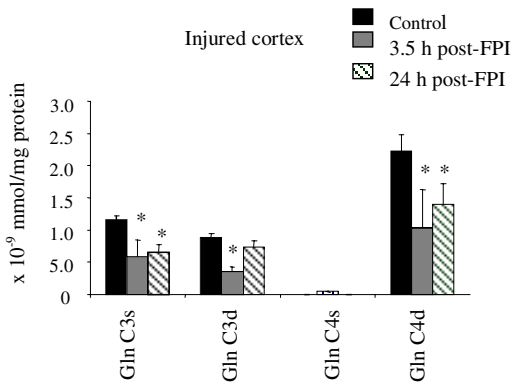


Figure 3: mean ^{13}C enrichment of glutamine



Discussion: The increased tissue glucose and decreased glutamate and glutamine enrichment at 3.5 h after injury suggests a decrease in glucose oxidation in the TCA cycle of both neurons and astrocytes. The increase in pyruvate recycling at this time may be an adaptive response to the injury-induced metabolic alterations. An increase in PPP activity was observed in the injured cortex at 3.5 h. Increased glucose metabolism through both the PPP and the pyruvate recycling pathways generate NADPH, suggesting an injury-induced need for reducing equivalents. The increase in PPP activity occurs in the absence of significant changes in the lactate pool at either time after FPI. By 24 h the decreased glucose metabolism (i.e. increased tissue glucose enrichment) in the injured cortex is accompanied by a decrease in glutamine enrichment and the normalization of glutamate levels. The mismatch between glutamate and glutamine enrichment may indicate a disruption of the glutamate-glutamine cycle or an inhibition of glucose oxidation within the astrocytic compartment.

References:

1. Yoshino A., Hovda D.A., Kawamata T., Katayama Y., Becker D.P. (1991) *Brain Research* 561:106 - 119.

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