Differential Cellular Metabolism Following Traumatic Brain Injury

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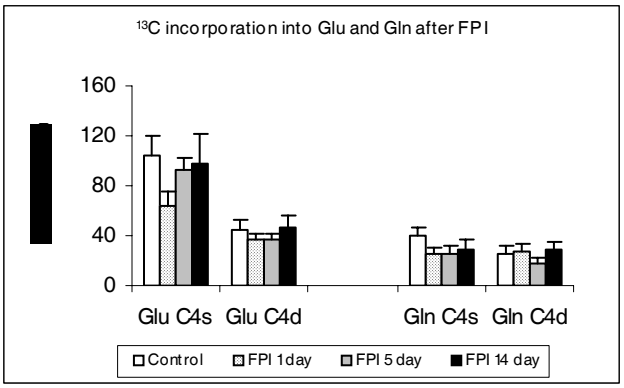
Introduction: Various lines of evidence point to the cellular compartmentalization of metabolism within the brain yet few studies have examined potential differences in neuronal versus glial metabolism after TBI. Results from our previous study examining the metabolic fate of [1,2 $^{13}C_2$] glucose after a lateral FPI suggested cell type specific changes in metabolism (Bartnik et al., 2005). In addition, the FPI model of experimental TBI produces characteristic changes in cerebral metabolic rates of glucose (CMRglc), where an early and transient increase is followed by an extended period of metabolic depression (Yoshino et al., 1991; Kawamata et al., 1992). Thus, we hypothesized that in the period of metabolic depression after FPI, glucose metabolism would be reduced and metabolism within the astrocyte compartment increased in support of reduced neuronal metabolism.

Methods: Fifteen, male rats (300-350g) underwent a moderate FPI with an additional 13 rats receiving a craniotomy only (Control). At one (n=5), 5 (n=5) and 14 days (n=5) after injury the animals were infused, via femoral vein catheter, with an equimolar concentration of [1 ^{13}C] glucose and [1,2 $^{13}C_2$] acetate for 60 minutes. Following the infusion, animals were anesthetized and euthanized by a focused microwave beam and extracts of the left (injury) and right hemisphere 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° 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, the injured hemisphere showed an increase in the ^{13}C-labeled glucose pool at 1 and 5 days, which returned to control levels by 14 days. This was accompanied by decreases in the glutamate (Glu) and glutamine (Gln) pools within the injured hemisphere at 1 and 5 days. The amount of ^{13}C enrichment in the lactate (Lac) pool of the injured hemisphere did not differ between groups, until decreasing at 14 days post-injury. ^{13}C incorporation into newly synthesized NAA was reduced in the injured hemisphere at all time points after injury. Glu enrichment of the C4 isotopomer via the oxidative metabolism of both glucose (singlets) and acetate (doublets) were reduced in the injured hemisphere 1 day after FPI (see Fig). After 5 days, enrichment of the Glu singlets returned to sham levels. Gln enrichment from the metabolism of glucose was reduced in the C4 singlet of the injured hemisphere 1 and 5 days after FPI. ^{13}C labeling of Gln from acetate was not significantly altered in the injured hemisphere at any time point after FPI.



Discussion: Despite a decrease in glucose metabolism, lactate enrichment was not affected at 1 or 5 days indicating that glycolytic metabolism was not altered by FPI at these time points. At 1-day post-FPI, the total pool of ^{13}C-labeled Glu, Gln, Asp. GABA, and NAA were decreased, suggesting an overall reduction in the oxidative metabolism of both neurons and astrocytes. Decreased labeling in the singlet resonances of Glu and Gln supported this finding. At 5 and 14 days post-FPI, Glu C4 singlet enrichment returned to sham levels, while labeling of the Gln C4 singlets remained below sham levels. This may indicate that glucose metabolism had recovered in neurons while the astrocytic metabolism of glucose remained impaired. It is also possible that the mismatch between recovered Glu C4 singlet labeling and decreased Gln C4 singlet labeling at 5 and 14 days post-FPI is the result of enhanced Gln shuttling to the neurons. This would suggest altered astrocyte metabolism in response to the decreased glucose metabolism in neurons. Despite the changes in glucose metabolism within the neurons and astrocytes at 1 day post-FPI, acetate metabolism in astrocytes was relatively unaffected by injury. This observation might suggest that glucose metabolism is inhibited at some point between its uptake, glycolytic metabolism, and/or entry into the TCA cycle since acetate enters the TCA cycle as acetyl CoA bypassing these metabolic pathways.

References:

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