Improved Oxidative Metabolism and Cellular Redox State Following Sodium or Ethyl Pyruvate Supplementation after Experimental Traumatic Brain Injury

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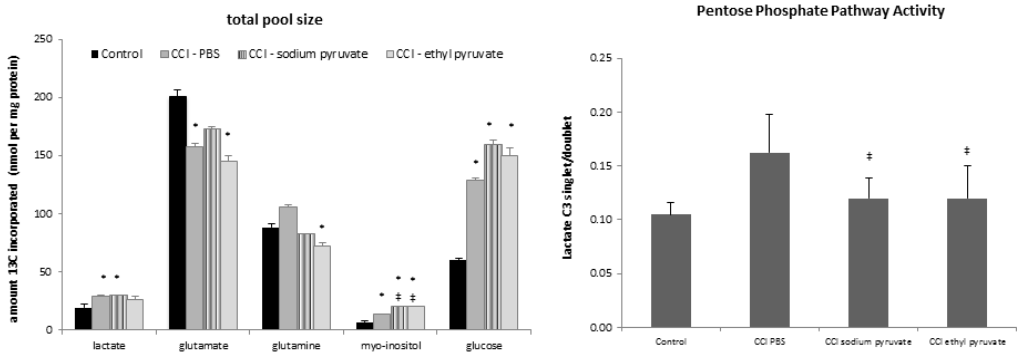
Target Audience: The target audience for this research is basic science and clinical researchers in the field of traumatic brain injury.

Purpose: Previous studies have shown that traumatic brain injury (TBI) initiates ionic and neurotransmitter perturbations and increases oxidative stress that results in an initial increase in the cerebral metabolic rate for glucose (CMRglc), followed by a generalized metabolic depression associated with reduced ATP production [(1-5)]. Both sodium and ethyl pyruvate have been shown to reduce cell death, attenuate reductions in cytochrome oxidase activity, and improve recovery following experimental TBI [(6)]. The purpose of this study is to determine if sodium or ethyl pyruvate supplementation is sufficient to meet increased metabolic demands following injury by influencing the activity of metabolic pathways associated with the intracellular redox state and oxidative metabolism. We hypothesized that in the period of metabolic depression after a controlled cortical impact (CCI) injury, supplementation with sodium or ethyl pyruvate would increase oxidative metabolism and decrease metabolism through the pentose phosphate pathway (PPP) owing to a decreased need for reducing equivalents as a result of improved redox state.

Methods: Thirty male rats (300-350g) underwent a moderate-severe CCI with an additional 10 rats receiving anesthesia only (Control). CCI-injured animals received an i.p. injection of sodium pyruvate (CCI-SP; 1000 mg/kg, n=10), ethyl pyruvate (CCI-EP; 40 mg/kg, n=10), or phosphate buffered saline (CCI-PBS; n=10) at 0, 1, 3, 6 and 23 hours post-injury. At 24 hours post-injury animals were infused, via femoral vein catheter, with [1, 2 $^{13}C_2$] glucose for 60 minutes. Following the infusion, animals were anesthetized and euthanized by a focused microwave beam and extracts of the left (injury) and right cortex and hippocampus underwent chloroform/methanol extraction and prepared for NMR. Proton decoupled ^{13}C NMR spectra were obtained on a Bruker Avance 500 MHz spectrometer using a 45° flip angle, 10 KHz spectral width, 2 sec acquisition time, 3 sec relaxation delay, and 18 000 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 ± SD 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: Compared to naïve controls, the injured cortex of all CCI-injury groups showed an increase in the ^{13}C-labeled glucose and myo-inositol pools at 24 hours post-injury. The increase in the ^{13}C-labeled myo-inositol in the CCI-SP and CCI-EP groups was significantly higher than the CCI-PBS group ($p < 0.05$). The total amount of ^{13}C labeled glutamate in the injured cortex of the CCI-PBS and CCI-EP groups was significantly lower than controls ($p < 0.05$). In contrast, only the CCI-EP group showed reduced significant reduction in the ^{13}C labeled glutamine pool in the injured hemisphere compared to controls ($p < 0.05$). The total amount of ^{13}C labeled lactate was increased in all CCI-injury groups, reaching significance in the CCI-PBS and CCI-SP groups ($p < 0.05$). Glucose metabolism via the PPP, as assessed by the lactate C3 singlet/doublet ratio, was reduced in both the CCI-SP and CCI-EP groups compared to the CCI-PBS group.



* = p < 0.05 vs. control and ‡ = p < 0.05 vs. CCI-PBS

Discussion: Sodium pyruvate supplementation following CCI injury improves oxidative metabolism in neurons and astrocytes. In addition, both sodium and ethyl pyruvate supplementation reduce the amount of glucose metabolized through the PPP compared to CCI-injured animals without fuel supplementation, which suggests improvements in the intracellular redox state due to pyruvate supplementation.. These findings may explain, in part, the mechanisms responsible for the beneficial effects of pyruvate supplementation following experimental TBI.

References:

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