Is Glutamate or Glutamine Elevated Following Traumatic Brain Injury?

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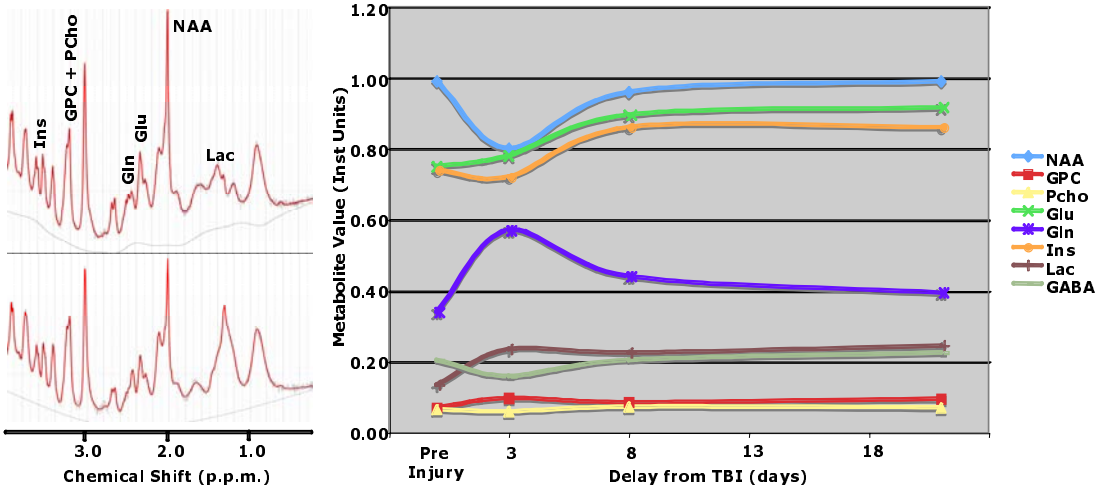
Introduction

Traumatic brain injury (TBI) affects more than 2 million people per year in the United States. Many of these suffer cognitive deficits and become permanently impaired. Despite the enormous social and financial costs (estimated at >$US50 billion/yr) few treatments have proven helpful in enhancing recovery. Previous studies have shown that magnetic resonance spectroscopic measurements of N-acetylaspartate (NAA) and choline (Cho) can predict cognitive outcome following TBI [1]. Moreover, the temporal evolution patterns of such biomarkers have been associated with patterns of recovery [2]. Such studies link cognitive and behavioral recovery to specific molecular pathways and ultimately to mechanisms of injury and recovery.

Further results [3] showed that MRS measurements might be helpful in discriminating severe from mild/moderate TBI in human patients. In particular, short echo MR spectroscopic imaging at 3T indicated that glutamine (Gln), but not glutamate (Glu), was significantly elevated in the brains of severely injured patients but not in mild TBI. However, since Gln and glutamate (Glu) signals are overlapping at 3T leading to possibly ambiguous quantitation, we used a rat model of TBI at 9.4T to confirm these observations. Given that Glu has been implicated in excitotoxic pathways following TBI, elaboration of which entity is elevated might be important for clinical management.

Methods

A linear-motor-based impactor was used to create controlled cortical impact injury [as in 4] in adult rats. The parameters were impactor tip size = 5mm, velocity = 1.5m/sec, penetration = 1.5mm, and contact time = 300ms or 100ms for severe vs. mild injury, respectively. MRS was carried out prior to and at 3, 8, and 21 days post-injury with a Varian 9.4T system. First and second order shims were adjusted using FASTMAP [5]. A 4x3x4mm^3 voxel adjacent to the contusion site was examined using ultra-short echo time STEAM (TE=2ms, TR=5s, TM=20ms) for localization [6]. The water signal was suppressed using VAPOR [6]. Spectra were analyzed using LCModel [7] (all Cramer-Rao lower bounds below 15%) and expressed as institutional units. Metabolites such as NAA, Gln, Glu, glycerophosphocholine (GPC), phosphocholine (PCho), myo-inositol (Ins), and lactate (Lac) were quantified.



Results

High quality spectra were obtained at 9.4T. Fig 1 shows a pre-injury spectrum (upper) and the altered spectral pattern 3 days after a 300ms contact time injury (lower). In general, the patterns of metabolite alterations over time were similar to those observed in previous studies in humans [2]. At 9.4T, Gln and Glu are each well resolved and can be fitted with high reliability using LCModel. NAA is clearly reduced and Gln is elevated by >60% 3 days after injury and continue to increase over 1 week. Glu and Ins were elevated at about 1 week following injury and remained elevated for an extended period. Patterns in the less severe injury (contact time = 100ms) were similar although the magnitude of change was lower. Quantitative LCModel analysis of variations in neurometabolites over 21 days are plotted in Fig 1 (right).

Discussion

Treatment of TBI could be enhanced by a better understanding of the mechanisms involved with injury progression and recovery. In this study we applied a translational approach to explore the mechanistic underpinnings of altered biomarkers seen by MRS after head injury in human patients. In a rat model of TBI, we were able to discriminate Gln from Glu using ultra-short echo-time MRS at 9.4T and found that Gln signals appeared to be transiently increased prior to Glu elevation. This is thought to be a result of rapid glutamate uptake and conversion to glutamine by astrocytes (Glu-Gln cycling). Since the astrocyte Gln pool is considerably larger than the extracellular space where free glutamate is measured following TBI, this would be consistent with our observations of elevated Gln following severe human TBI. It is also consistent with previous MRS observations in humans at 4T of apparently elevated Gln in a ketamine-induced model psychosis wherein Glu is known to be released [8]. The eventual elevation of Glu might be the result of saturation of the astrocyte uptake capability or from astrocyte demise [9]. Our second observation was that GPC, and not PCho, was elevated following injury. In MRS studies of humans at field strengths of 3T and below these compounds are not resolved and are commonly labeled Cho (total choline). The specific mechanistic significance of GPC alterations requires further investigation.

References

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