Can Early 1H-MRS Predict Tissue Loss in Traumatic Brain Injury?

Janna L Harris[1], In-Young Choi[1,2], Phil Lee[1,3], Hung-Wen Yeh[4], and William M Brooks[1]

[1]*Hoglund Brain Imaging Center, University of Kansas Medical Center, Kansas City, KS, United States,* [2]*Department of Neurology, University of Kansas Medical Center,* [3]*Department of Molecular and Integrative Physiology, University of Kansas Medical Center,* [4]*Department of Biostatistics, University of Kansas Medical Center*

Introduction

Traumatic brain injury (TBI) is a leading cause of death and permanent disability worldwide. The initial physical impact of TBI is followed by a cascade of secondary injury mechanisms responsible for the progressive neurodegeneration that develops over days to weeks after the injury. In the present study, we used a contusive model of TBI in rats which evolves over several weeks into a well-defined lesion cyst. We used high field ^{1}H-MRS to characterize the very early metabolic effects of TBI in two brain regions that would subsequently meet with different ultimate fates: tissue proximal to the impact site which would degenerate over time into a lesion cyst, and tissue slightly more distal that would not develop any overt MR-visible lesion. Our goal was to determine whether the spectroscopic profile of these two regions very early after TBI could differentiate brain tissue destined to die from tissue destined to be preserved.

Methods

Adult male F344 rats (n=12) were subjected to unilateral controlled cortical impact (CCI) of the sensorimotor cortex. Injury parameters were: impact tip size = 5mm; velocity = 3.5m/s; depth = 2.0mm; contact time = 300ms. A Varian 9.4T spectrometer was used to collect water-suppressed STEAM MR spectra (TE=2ms, TR=4000ms; [1]). Spectra were acquired before TBI (<2 weeks) and immediately following TBI (1 hour) in two brain regions: proximal to the cortical impact (2.7 x 1.3 x 2.7 mm^3 VOI over sensorimotor cortex) and more distal to the impact site (3 x 2.5 x 3 mm^3 VOI over hippocampus and dorsal thalamus). VOI positioning was accomplished with T2-weighted RARE images (TE/TR=18/4000ms; matrix=256 x 256, slice thickness=1mm). First and second order shims were adjusted using FASTMAP [2]. Spectra were analyzed with LCModel [3]. Fitted metabolites with Cramér-Rao lower bounds (CRLB) ≤ 30% were accepted. For sample points with metabolite concentrations below the detection sensitivity of our instrument (typically data with CRLB >30%), values were imputed by a uniform distribution between zero and the minimum reliably detected value. TBI effects were analyzed with a linear mixed-effects model, using the Benjamini-Yekutieli's procedure to control the false discovery rate at 0.05.

Results

One hour after TBI, we observed significant neurometabolic changes in both the proximal and the distal VOI. For several metabolites the magnitude of change reflected proximity to the site of trauma. For example, N-acetylaspartate fell to 55% (proximal, p<0.0001) and 89% (distal, p<0.0001), and glutamine increased to 205% (proximal, p<0.0001) and 108% (distal, p<0.05) of pre-injury levels. By contrast, other metabolites were altered only in the proximal VOI (**Figure 1**), i.e., tissue destined to degenerate into the lesion cyst. Glucose (Glc), glutathione (GSH), and N-acetylaspartylglutamate (NAAG) fell significantly at 1 hour, while lactate (Lac) was sharply increased. T2-weighted imaging 2-4 weeks after TBI confirmed that all animals developed cortical lesions in the location of the proximal VOI, observed as a cyst filled with necrotic debris and cerebrospinal fluid.

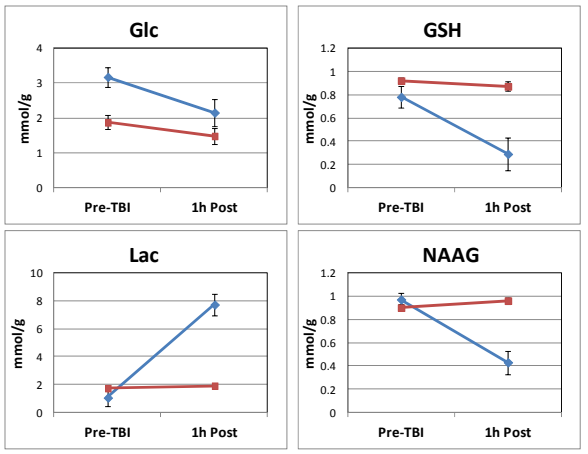

Figure 1. One hour after TBI, changes in Glc, GSH, Lac, and NAAG differentiate tissue that will later degenerate into a frank lesion cyst (proximal VOI; blue) from tissue that will be preserved (distal VOI; red).

Discussion

The present study documents significant changes in the spectroscopic profile of the brain very early (1 hour) in TBI pathogenesis, both close to the injury site and more remotely. Our data support and extend recent studies of neurometabolic changes 1-4h after TBI [4, 5]. Most metabolites showed similar changes in both locations, although of different magnitude, consistent with an injury severity effect. In addition, four metabolites were altered only in the proximal location. In sum, our results demonstrate a different pattern of acute changes in brain tissue destined to progressively degenerate, compared with tissue destined to survive. Moreover, the metabolic profiles of these two regions suggest distinct mechanisms associated with TBI: tissue loss was associated with significant changes in i) glucose and lactate suggesting altered energy metabolism, ii) glutathione indicating oxidative stress, and iii) N-acetylaspartylglutamate suggesting altered neurotransmission. If replicated in human TBI survivors, these findings suggest that early MR spectroscopic imaging could be useful for predicting the extent and location of ultimate brain damage, providing valuable information for prognosis and targeted interventions.

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