Diffusion kurtosis and proton MRS changes following mild TBI from blast overpressure using a novel direct cranial blast injury model

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Introduction

Traumatic brain injury resulting from an explosive blast (bTBI) is one of the most serious wounds suffered by warfighters. Experimental models of bTBI provide a useful tool for understanding the microstructural and metabolic changes induced by the damage. In this study we investigated brain alterations using diffusion kurtosis imaging (DKI) and proton magnetic resonance spectroscopy (^{1}H MRS) following a rodent model of direct cranial blast injury (dcBI), in which a blast overpressure could be delivered exclusively to the head, precluding indirect brain injury via thoracic transmission of the blast wave. We investigated microstructural and metabolic changes in dcBI rats at baseline, 24-hours, 7-days, 14-days, and 28-days after bTBI at 7 Tesla.

Materials and Methods:

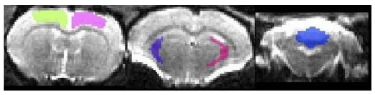

Fig.1. ROI regions used for MD, FA, MK calculations in DTI experiment. Somatosensory cortex (left), internal capsules (middle), and cerebellum (right).

bTBI Model

Six adult male Long-Evans rats (300 ± 10 gms) were subjected to dcBI injury[1]. Rats were anesthetized (60 mg/kg ketamine plus 7.5 mg/kg xylazine, IP), intubated with an endotracheal tube. After exposing the dorsum of the skull of an anesthetized rat, the animal was exposed to a blast overpressure by detonating a 0.22 caliber smokeless powder. Among six rats, three rats received 427 kPa, one received 462 kPa and two received 517 kPa. The blast resulted no other fractures as measured by a glass strain gauge revealed, indicating that no inward flexure occurred. All the rats recovered spontaneous movements from the procedure. The experimental protocol was approved by the Committee for the Welfare of Laboratory Animals of the University of Maryland.

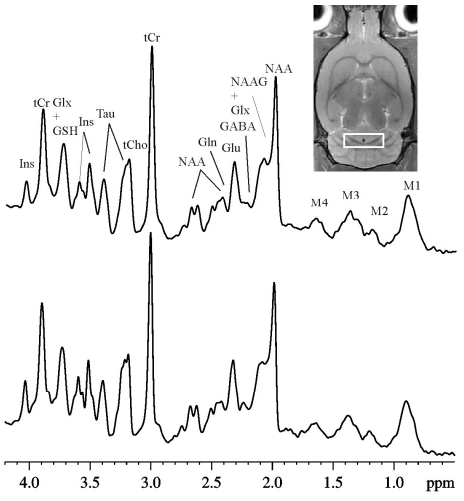

Fig. 3. *In vivo* high resolution proton spectra and corresponding voxel location in cerebellum from a rat at baseline and Day28 after direct cranial blast injury. It is noted that NAA (NAA/tCr) increased at Day28 compared to baseline. GABA=γ-aminobutyric acid, Glu=glutamate, Gln=glutamine, Glx=Glu+Gln, Ins=*myo*-inosital, NAA=*N*-acetylaspartate, Tau=taurine, tCho=total choline, NAAG=*N*-acetylaspartateglutamate

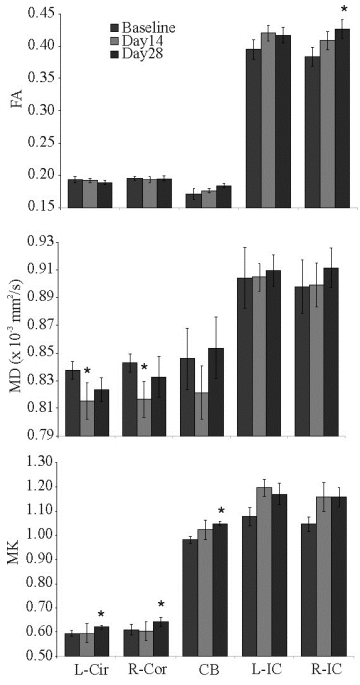

Fig. 2. Regional FA, MD, MK values for baseline and post dcBI; data expressed as mean ± standard error; * P < 0.05 compared to baseline.

In Vivo DKI and ^{1}H MRS

All experiments were performed on a Bruker Biospec 7 T scanner using a Bruker ^{1}H surface coil array as the receiver and a Bruker 72 mm linear-volume coil as the transmitter. After obtaining a set of axial proton density-weighted and T_2-weighted images, DKI images were acquired with single shot spin-echo EPI sequence. Following 5 images acquired using b = 0 s/mm^2, three separate b-values (1000, 1500, 2000 s/mm^2) were acquired for 30 direction (δ/Δ=4/20 ms). Similar slice coverage was obtained as the T_2-weighted images but with a matrix resolution of 128×128, at a TR/TE of 6000/50 ms respectively. Images were motion corrected and Gaussian smoothed with a FWHM of 0.3mm to improve the signal-to-noise ratio. Mean Diffusivity (MD), Fractional Anisotropy (FA) and Mean Kurtosis (MK) maps were generated using a previously published method[3]. Manually drawn regions of interest (ROI) were placed in the left and right somatosensory cortex (L-Cor and R-Cor), left and right internal capsules (L-IC and R-IC) and cerebellum (CB) (Fig. 1) to obtain values for MD, FA, and MK. A short-TE PRESS pulse sequence (TR/TE = 2500/10 ms)[2] was used for MRS data acquisition with voxel centered on the hippocampus (HP, 2.0 x 7.0 x 3.0 mm^3) , L-IC and R-IC (3.0 x 3.0 x 3.0 mm^3), and CB (3.0 x 6.0 x 2.0 mm^3). MRS data was fitted using the LC Model package and only results from metabolites with standard deviations (SD) % < 20 were included for further analysis. Paired T-test was used for statistical analysis.

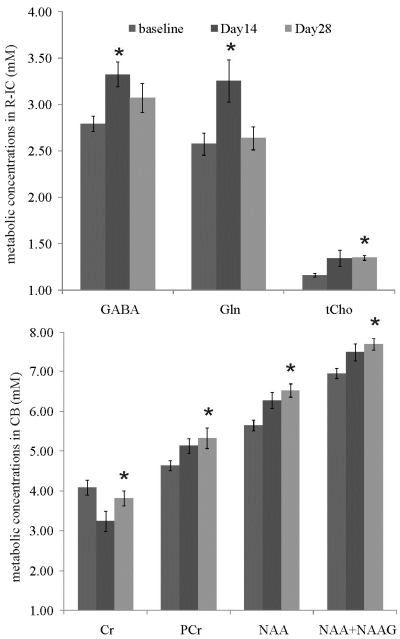

Fig. 4. Regional metabolic concentrations for baseline and post dcBI; data expressed as mean ± standard error; * P < 0.05 compared to baseline.

Results & Discussion

The overpressure blast did not create any MR visible injuries using conventional sequences even at 28 days. The reduced MD and increased MK in the cortex and cerebellum at 14 to 28 days post injury may be an indication of cell swelling and possible cytotoxic edema. Increased MK at 28 days may also indicate a delayed microglial activation or activation that elevate high enough to be detectable through changes in MK and also through changes in key metabolites such as NAA. NAA is a neuronal osmolyte and a source of acetate for lipid and myelin synthesis in oligodendrocytes, and its increase at 28 days suggests existence of active repair process. The alterations of Cr and PCr in CB may indicate a mitochondrial malfunction. Taken together, the results from MRS and MRI are consistent with mTBI using the controlled bTBI model which show delayed structural changes using advanced imaging techniques on animals where conventional MRI is negative.

References

1. Kuehn R et al, J Neurotrauma 2011; 28:2155-2169.**2.** Xu et al. *Magn Reson Med* 2012 [Epub ahead of print]. **3.** Zhuo et al., Neuroimage. 2012; 59:467-477.