Blast-induced dysregulation of tryptophan metabolism in the liver: implications in blast-induced neuropsychiatric disorders

Chetan Pundkar, PhD[1,2]; Manoj Govindarajulu, PhD[1,2]; Rex Jeya Rajkumar Samdavid Thanapaul, PhD[1,3]; Gaurav Phuyal, MS[1,2]; Matthew L LoPresti, PhD[1]; Peethambaran Arun, PhD[1]

[1]Blast-Induced Neurotrauma Branch, Center for Military Psychiatry and Neuroscience, Walter Reed Army Institute of Research, Silver Spring, MD20910, USA
[2]Oak Ridge Institute for Science and Education, Oak Ridge, TN 37831, USA
[3]The Geneva Foundation, Tacoma, WA 98402, USA

Background

Blast-induced traumatic brain injury (bTBI) often leads to neuropsychiatric and cognitive impairments. Tryptophan metabolism plays a major role in inflammation and neuropsychiatric disorders. No systematic studies have been carried out to determine the effects of blast exposure on tryptophan metabolism and the associated synthesis of serotonin, which plays a major role in neuropsychiatric disorders. Previous studies have shown that stress-induced corticosterone release can upregulate tryptophan-2,3-dioxygenase (TDO2), the rate limiting tryptophan catabolizing enzyme present in the liver, leading to depression through tryptophan and serotonin deficiency. This study investigated the effect of blast exposure on liver TDO2 gene and protein expression at acute (2-h, 24-h) and sub-acute (1-month) time points in a rat model.

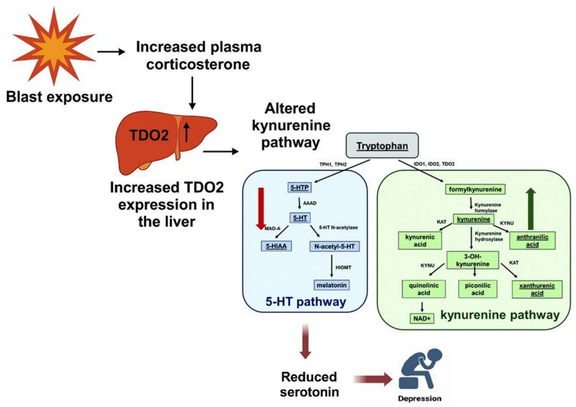

Figure 1

Methods

- Adult Sprague Dawley rats were exposed to a single blast (20psi) using an advanced blast simulator under isoflurane anesthesia.
- Animals were euthanized at 2-h, 24-h, or 1-month post-blast under isoflurane anesthesia, and blood and liver tissue were collected.
- Plasma corticosterone levels were quantified by ELISA.
- TDO2 gene and protein expressions in the liver were assessed using qRT-PCR and Western blotting respectively.

1. Effect of blast exposure on plasma corticosterone levels at 2-h, 24-h and 1-month post-blast injury.

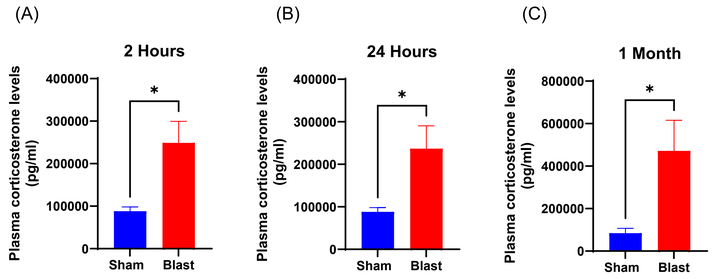

Figure 2: Plasma corticosterone levels following a single 20psi blast exposure. Corticosterone concentrations were measured at (A) 2-h post-injury, (B) 24-h post-injury, and (C) 1-month post-injury in rats subjected to blast (Red), compared to sham controls (blue). Results are expressed as means ± SEM (n = 6). Statistical significance was determined using Student's *t*-test. *$p < 0.05$ for sham versus blast group.

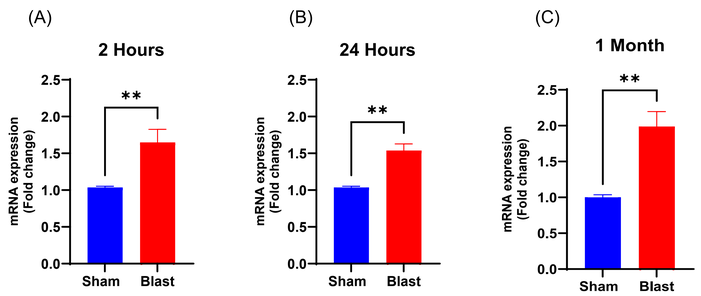

Figure 3: Blast exposure alters expression of *TDO2* gene in the liver. Fold changes in mRNA expressions were quantified for (A) 2-h post-injury, (B) 24-h post-injury, and (C) 1-month post-injury in rats subjected to blast (Red), compared to sham controls (blue). Results are expressed as means ± SEM (n = 6). Statistical significance was determined using Student's *t*-test. **$p < 0.01$ for sham versus blast group.

3. Effect of blast exposure on TDO2 protein expression in the liver at 2-h, 24-h and 1-month post-blast injury.

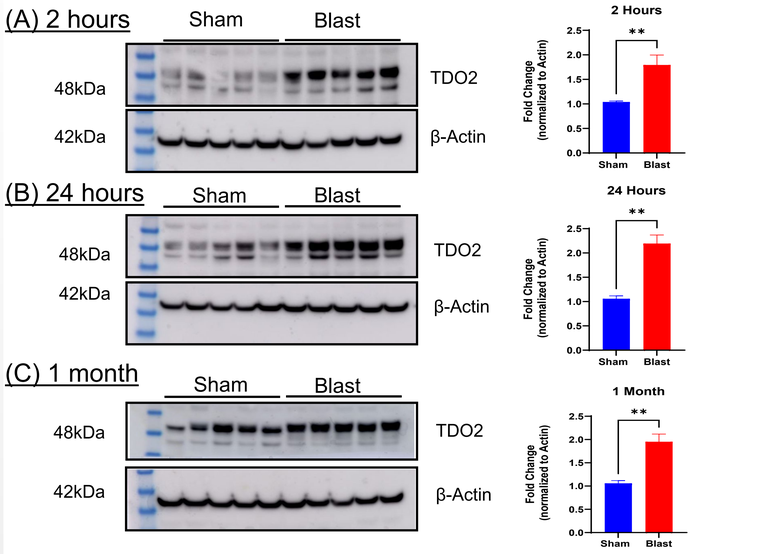

Figure 4: Effect of blast exposure on protein expression of TDO2 in the liver of rats exposed to single 20psi blast. Representative Western blots for TDO2 protein levels are shown, with protein levels normalized to β-actin and presented as fold change relative to the sham controls (mean ± SEM). Sample size (n): 5 animals/group/time point. Statistical significance was determined using Student's *t*-test; ** $p < 0.01$ for sham versus blast group.

Conclusions

Blast exposure induced a sustained upregulation of hepatic mRNA and protein expression of tryptophan-2,3-dioxygenase (TDO2), suggesting a potential depletion of tryptophan and thereby serotonin levels, which can play a major role in the neuropsychiatric sequelae of bTBI. Ongoing analyses include plasma and CSF levels of tryptophan, serotonin, and kynurenine metabolites. Future multicenter longitudinal studies are warranted to validate TDO2 as a biomarker and therapeutic target in blast-induced neuropsychiatric disorders.

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Disclaimer: The experiments reported herein were conducted in compliance with the Animal Welfare Act and per the principles set forth in the "Guide for Care and Use of Laboratory Animals," Institute of Laboratory Animals Resources, National Research Council, National Academy Press, 2011.

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