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Blast neurotrauma impairs working memory and disrupts prefrontal *myo*-inositol levels in rats

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ABSTRACT

Working memory, which is dependent on higher-order executive function in the prefrontal cortex, is often disrupted in patients exposed to blast overpressure. In this study, we evaluated working memory and medial prefrontal neurochemical status in a rat model of blast neurotrauma. Adult male Sprague–Dawley rats were anesthetized with 3% isoflurane and exposed to calibrated blast overpressure (17 psi, 117 kPa) while sham animals received only anesthesia. Early neurochemical effects in the prefrontal cortex included a significant decrease in betaine (trimethylglycine) and an increase in GABA at 24 h, and significant increases in glycerophosphorylcholine, phosphorylethanolamine, as well as glutamate/creatine and lactate/creatine ratios at 48 h. Seven days after blast, only *myo*-inositol levels were altered showing a 15% increase. Compared to controls, short-term memory in the novel object recognition task was significantly impaired in animals exposed to blast overpressure. Working memory in control animals was negatively correlated with *myo*-inositol levels ($r = -.759$, $p < 0.05$), an association that was absent in blast exposed animals. Increased *myo*-inositol may represent tardive glial scarring in the prefrontal cortex, a notion supported by GFAP changes in this region after blast overexposure as well as clinical reports of increased *myo*-inositol in disorders of memory.

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Introduction

Blast-induced neurotrauma (BINT) has been shown to have deteriorating effects on cognition. Previous animal and clinical studies have shown irreversible damage in cognitive centers of the brain, namely the hippocampus (Bogdanova and Verfaellie, 2012; Kovesdi et al., 2012; Matthews et al., 2011; Säljö et al., 2009; Terrio et al., 2009; VandeVord et al., 2012). Commonly associated clinical issues with BINT include memory deficits and anxiety (McAllister, 2009; Okie, 2005; Rosenfeld and Ford, 2010; Terrio et al., 2009; Vanderploeg et al., 2012). Studies mainly have focused on the role of hippocampal impairment in conjunction with cognitive impairment. These studies have demonstrated neurodegeneration, glial response and inflammation in hippocampus following blast overpressure exposure. However, other major cognitive regions such as the medial prefrontal cortex (PFC), which plays an important role in memory-related cognitive functions, may also be affected (Cernak et al., 2011; Elder et al., 2010; Hayes et al., 2011; Koliatsos et al., 2011; Säljö et al., 2009).

The association of PFC, perirhinal cortex and hippocampus plays an important role in working memory, decision making, and short term memory. In addition, PFC contributes to the potentiation of long term memories due to its direct innervation of axonal fibers with the hippocampus (Brown, 2011; Goldstein et al., 1996; Groenewegen et al., 1997; Koenigs, 2012; Rushworth et al., 2011; Stuss, 2011; Thierry et al., 2000; Vertes, 2006). Although animal behavioral tests demonstrated impaired cognition in an acute phase, paradigms specific for working and short term memory issues have not been evaluated following blast neurotrauma. Recent pre-clinical and clinical reports have shown injury in PFC after blast exposure (Hayes et al., 2011; Mao et al., 2012; Säljö et al., 2009). These factors indicate the need for behavioral studies that test cognition and short term memory governed by the PFC.

It is hypothesized that working memory impairment after blast exposure is due to acute metabolic neurochemical changes and neurodegeneration in the medial prefrontal cortex. To test this hypothesis, novel object recognition paradigm was used to evaluate working memory and the PFC tissue from these animals was used to assess

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metabolic and neurochemical changes by high-resolution magic angle spinning (HRMAS) proton magnetic resonance spectroscopy (^{1}H-MRS) ex vivo and neurodegeneration using FluoroJade B and NeuN staining. Collectively, these data address memory impairment issues mediated by early neurochemical alterations, neurodegeneration and gliosis in the PFC following blast overpressure exposure and thereby provide novel insight that is amenable to clinical translation.

Results

Object recognition behavior and short-term memory

While no differences in NOR behaviors during T1 or T2 were observed at 72 h following blast exposure compared to sham, a significant decrease ($F_{1,17} = 8.46$, $p < 0.01$) in time spent with the novel object between sham and blast-exposed rats during T2 was observed 168 h (7 days) after exposure (Fig. 2). Furthermore, the sham group, but not the blast-exposed group, showed a significant increase ($F_{1,17} = 9.12$, $p < 0.01$) in time spent with the novel object in T2 relative to T1 and the location where the novel object would be placed in T2, which is consistent with learned behavior in the controls and a deficit in blast exposed rats at 168 h.

Neurochemical assessment by ^{1}H-MRS

Following blast overpressure exposure, a significant decrease in glutathione (GSH) (1.08 ± 0.06 vs. 0.92 ± 0.03 nmol/mg) and *myo*-inositol (Ins) (5.65 ± 0.23 vs. 4.93 ± 0.18 nmol/mg) were observed at 3 h. Decreased levels of betaine (BET) (5.03 ± 0.44 vs. 4.02 ± 0.13 nmol/mg) and increased levels of γ-amino butyric acid (GABA) (8.52 ± 0.31 vs. 9.62 ± 0.34 nmol/mg) were seen at 24 h. Increased levels of glycerophosphocholine (GPC) (2.81 ± 0.12 vs. 3.22 ± 0.17 nmol/mg), phosphorylethanolamine (PEA) (9.93 ± 0.35 vs. 10.99 ± 0.39 nmol/mg), glutamate/creatine ratio (Glu/Cre) (1.97 ± 0.03 vs. 2.08 ± 0.02), and lactate/creatine (Lac/Cre) (1.68 ± 0.04 vs. 1.79 ± 0.03) ratio was found at 48 h. Finally, increased levels of Ins (4.59 ± 0.25 vs. 5.30 ± 0.18 nmol/mg) were observed at 168 h (7 days) (Fig. 3).

No changes were found in alanine, N-acetyl aspartate (NAA), N-acetyl aspartate glutamate, succinate, aspartate, choline, inositol, taurine, glycine or phosphorylethanolamine at any time points.

NOR versus Ins correlation

A negative correlation between NOR behavior (time spent with the novel object in T2) and levels of Ins, measured at 7 days following blast exposure ($R = -0.759$, $p < 0.05$) was observed in the sham group while the same correlation was not observed in the blast group ($R = 0.202$) (Fig. 4).

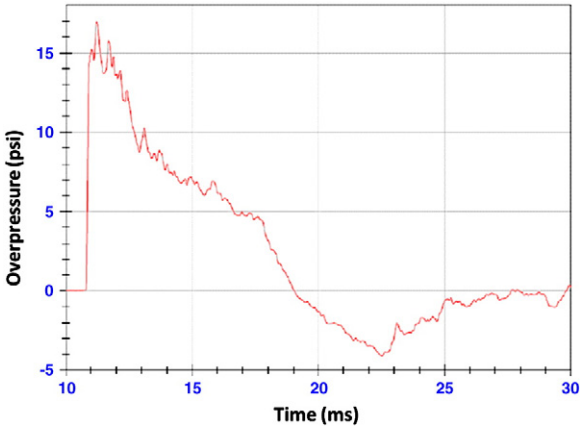

Fig. 1. Representative pressure profile of calibrated shock wave to which animals are exposed with a resultant peak positive overpressure at 117 kPa.

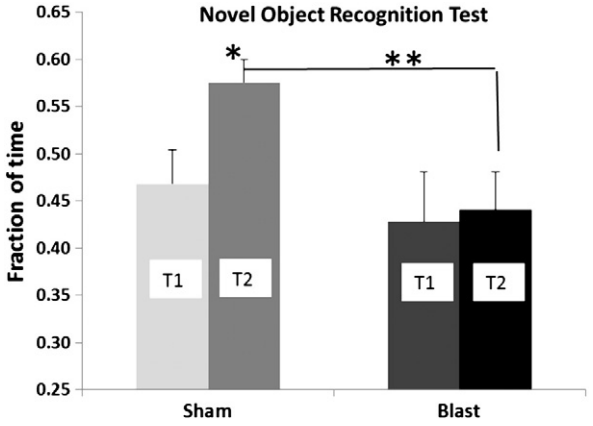

Fig. 2. Sham rats learn the behavior and show good working memory (T1–T2 sham), while blast exposed rats do not show learning (indicates impaired working memory) and are significantly different from sham rats in T2 from learning at 168 h post blast. T1 — trial with familiar objects; T2 — trial with a novel object; *$p < 0.05$, **$p < 0.002$.

FJB, Iba-1, GFAP and NeuN

A significant increase in FJB+ staining was observed at 3, 48 and 168 h following blast overpressure exposure compared to the sham group, *$p < 0.05$ (Fig. 5). A significant decrease in NeuN+ staining was observed in the blast group when compared to sham at 3, 48 and 168 h following blast exposure (Fig. 6). No changes were observed in GFAP at 3 and 48 h following blast overpressure in PFC between the sham and the blast groups; however, a significant increase was observed at 168 h following blast overpressure exposure compared to sham, *$p < 0.01$ (Fig. 7). The levels of Iba-1, a marker of microglia, remained unaltered at all the time points evaluated.

Discussion

Injury to the PFC in the field of blast neurotrauma research has been understudied. Most of the studies that focused on examining cognitive defects and injury were confined to the hippocampus after blast trauma. The PFC mediates and is involved in the processing of working memory and the transition of short term memories into long term memories via neurotransmission. This study demonstrates the significant injury that occurs to the PFC in a blast neurotrauma animal model that causes working memory impairment. These novel data provide fundamental knowledge on the underlying mechanisms of blast neurotrauma that may be relevant to clinically reported memory issues.

Behavioral outcome

Many clinical studies have reported deficits in attention and memory following BINT (Belanger et al., 2009; Bhattacharjee, 2008; Bogdanova and Verfaellie, 2012). Although some studies describe cognitive deficits associated with BINT using animal models, none thus far have evaluated the short-term/working memory deficit following blast overpressure. Working memory is impaired at 168 h (7 days) following blast overpressure in the exposed group compared to the sham group; however, we did not observe any behavioral deficits at 72 h following blast exposure. This delayed onset of symptoms (i.e., compromised memory) following blast overpressure exposure is similar to clinical reports (Kovesdi et al., 2012). Although the delayed onset of the symptoms is reported after blast, no specific brain region or neuropathological outcome in relation to cognition were identified for the prognosis of injury. Here, to further understand the molecular

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