Experimental Neurology 283 (2016) 16–28

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Primary blast injury causes cognitive impairments and hippocampal circuit alterations

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ARTICLE INFO

Article history:
Received 22 January 2016
Received in revised form 14 May 2016
Accepted 20 May 2016
Available online 28 May 2016

Keywords:
Blast induced traumatic brain injury
Concussion
Blood-brain barrier

ABSTRACT

Blast-induced traumatic brain injury (bTBI) and its long term consequences are a major health concern among veterans. Despite recent work enhancing our knowledge about bTBI, very little is known about the contribution of the blast wave alone to the observed sequelae. Herein, we isolated its contribution in a mouse model by constraining the animals' heads during exposure to a shockwave (primary blast). Our results show that exposure to primary blast alone results in changes in hippocampus-dependent behaviors that correspond with electrophysiological changes in area CA1 and are accompanied by reactive gliosis. Specifically, five days after exposure, behavior in an open field and performance in a spatial object recognition (SOR) task were significantly different from sham. Network electrophysiology, also performed five days after injury, demonstrated a significant decrease in excitability and increase in inhibitory tone. Immunohistochemistry for GFAP and Iba1 performed ten days after injury showed a significant increase in staining. Interestingly, a threefold increase in the impulse of the primary blast wave did not exacerbate these measures. However, we observed a significant reduction in the contribution of the NMDA receptors to the field EPSP at the highest blast exposure level. Our results emphasize the need to account for the effects of primary blast loading when studying the sequelae of bTBI.

1. Introduction

Often referred to as the signature injury of the Iraq and Afghanistan conflict, blast-induced traumatic brain injury (bTBI) in the military is a complex biomechanical process wherein the head is subjected to the blast wave (blast loading), possible acceleration from impact, and penetrating injuries from projectiles (DePalma, 2015; Rosenfeld et al., 2013). Although the epidemiology of traumatic brain injury (TBI) in the military population is now clearer (Center, 2012), there remains significant debate about whether the sequelae and underlying etiology of bTBI are distinct from those of non-blast TBI (Wall, 2012). A review of the existing literature shows conflicting reports with some studies finding no differences between the two modes of injury and others reporting that survivors of bTBI show a decline in self-rated health compared with those of non-blast TBI. Determining the differences between non-blast and blast TBI is difficult because the exact biomechanics of each injury is unknown (Heltemes et al., 2012).

Animal models of bTBI offer a direct method for evaluating the effect of primary blast exposure on the brain. In small animal models, either a shock tube or live explosives are most commonly used to deliver an idealized, Friedlander-type shock wave to the animal (Kovacs et al., 2014; Meaney et al., 2014; Nakagawa et al., 2008). It is increasingly recognized that shock tube studies also contain two phases of biomechanical loading to the brain – the blast load on the brain, and the additional head accelerations that occur from the wind forces behind the shockwave front (Dal Cengio Leonardi et al., 2012; Dal Cengio Leonardi et al., 2013; Sundaramurthy et al., 2012). These simultaneous injury mechanisms make the interpretation of shock tube studies difficult. For example, although some recent work suggests that primary blast loading causes no neurological impairment (Goldstein et al., 2012), other studies indicate that it does affect cognition (Budde et al., 2013; Heldt et al., 2014).

In this study, we assess the effects of primary blast loading on the murine brain. We used a system to expose only the head to blast loading, and introduced a method to minimize head accelerations that occur during this simulated blast event. Our results show that primary blast loading

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http://dx.doi.org/10.1016/j.expneurol.2016.05.025
0014-4886/

does not cause gross structural changes but causes changes in hippocampus-dependent behavior that are accompanied by reactive astrogliosis in the tissue and alterations in area CA1 circuitry. Our *in vivo* findings, coupled with our recent *in vitro* work (Effgen et al., 2014; Vogel et al., 2015), emphasize the need to define the unique mechanisms of primary blast, either isolated from or in combination with contact/acceleration injuries that contribute to outcome of TBI in the military environment.

2. Materials and methods

2.1. Blast exposure

All experiments were performed on adult male (12–16 weeks old) C57BL/6 mice (Charles River, Wilmington, MA). Animal care and use followed guidelines specified by the Institutional Animal Care and Use

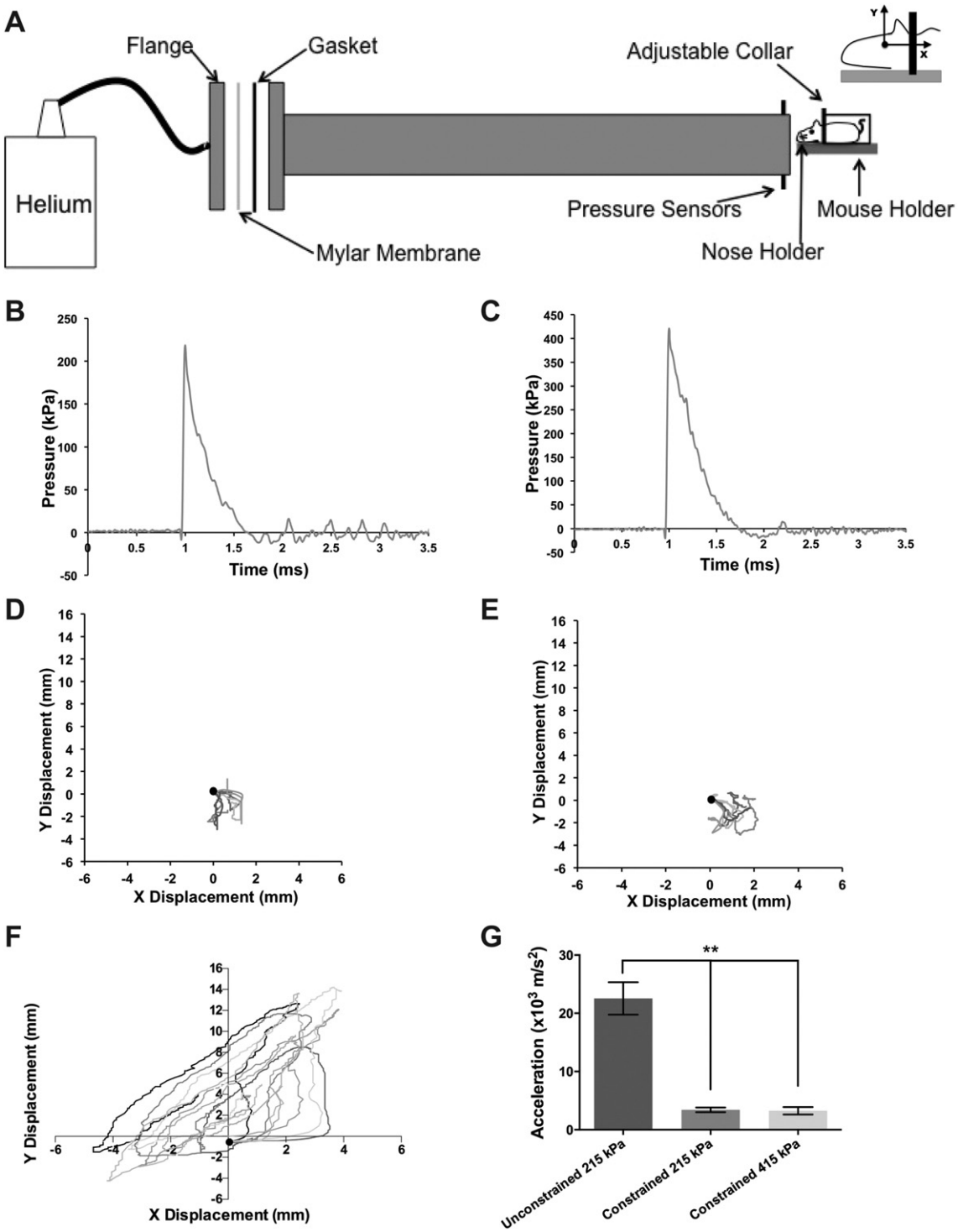

Fig. 1. Constraining the head significantly reduces the acceleration experienced by it upon impact. (A) Schematic of the shock tube configuration used to create the blast wave exposure. The animal was placed 1 cm outside the exit end of the shock tube in a protective body holder with its head either constrained or unconstrained. (B, C) Representative shockwaves for mild blast (215 kPa peak overpressure) and moderate blast (415 kPa peak overpressure) loading. (D, E) Constraining the head minimizes its displacement during both mild (D) and moderate (E) blast loading. (F) Displacement of the head when it is unconstrained ($n = 13$) during mild blast loading. Exposure to moderate blast loading in this kinematic condition was lethal. (G) The acceleration is significantly larger than when the head is unconstrained under the same loading condition ($p < 0.0001$, Student's *t*-test). There was no significant difference in the accelerations produced by mild ($n = 8$) and moderate ($n = 5$) blast loading ($p = 0.97$; Student's *t*-test).