Blast traumatic brain injury induced increase in neuronal excitability, Tau levels, and Tau phosphorylation
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Introduction

The relationship between traumatic brain injury (TBI) and Alzheimer’s disease (AD) has been a matter of debate for many years. TBI seems to increase the probability of developing AD by unknown mechanisms [1]. Here we explored blast TBI-induced changes in Tau protein. Tau hyperphosphorylation and posterior aggregation in neurofibrillary tangles are hallmarks of AD, where it seems to work in a prion-like matter facilitating the aggregation of more Tau and accelerating AD spreading throw the brain [2]. Wu et al. [3] have observed that Tau can be transported from one neuron to another in an activity-dependent matter, propagating Tau pathology. Since TBI is known to increase neuronal activity [4], blast injury-induced changes in Tau might be related to changes in neuronal excitability. Our results seem to corroborate with this hypothesis.

Abstract

Blast TBI-induced changes in neuronal excitability is an understudied subject. Nonetheless, other forms of TBI are well-known to induce increase in neuronal activity and induce seizures [4, 5]. Blast TBI has been shown to result in hyperphosphorylation of Tau in phosphorylation sites that are related to AD [6]. We have established a mouse model to explore a possible relationship between blast-induced changes in Tau and neuronal excitability. Our results show that mice subjected to 3 consecutive blast TBI present post-TBI seizures, increased excitability in DG pyramidal cells, and higher levels of total Tau and phosphorylated Tau. Future experiments will be performed to test if these concomitant Blast TBI-induced changes are related to each other. We believe that Blast TBI-induced increase in neuronal excitability might facilitate changes in Tau protein that can lead to a higher risk of developing AD.

Materials and Methods

Results

Figure 2. EEG setup demonstrating the efficacy of our TBI seizure model. (A) Diagram of epidural screw electrodes used for recording EEGs. (B) Image of a mouse with an electrode head mount and preamplifier.

Figure 3. Slice patch-clamp recording, in whole-cell mode, were performed in DG granule cells. Adapted from Cell Physiology Source Book, 4th ed., 2011.

Figure 4. Samples collected for Immunoblot. Levels of GAPDH, Tau, pTAU (PHF1), and pTAU (CP13) were semiquantified.

Figure 5. Incidence of seizures in mice after Blast TBI. (A) 2/6 mice subjected to two blast injuries had focal seizures, while three Blast TBI subjects induced 3/24 focal and 9/24 generalized seizures. (B) The majority of the seizures occurred in the first 2 days after TBI. (C) Examples of EEG recordings.

Figure 6. Quantification of action potential properties (A) and spontaneous PSCs (B) in sham (2) and Blast (6) mice. A) Comparison of AP parameters measured by 200 pA, 600 msec constant current injections. B) Comparison of spontaneous postsynaptic currents measured at -80 mV holding potential. Recordings are from 1 sham treated mouse (25 cells) and 3 blast-TBI mice (32 cells).

Conclusion

We have established a valid model to study Blast-induced changes in neuronal excitability and Tau protein. Future experiments will aim to test for a connection between these two TBI-induced deleterious effects. This study was supported by DoD CDMRP grants W81XWH-15-1-0284 (J.L., M.S., and R.B.).

References