

Juvenile Traumatic Brain Injury Results in Cognitive Deficits Associated with impaired ER Stress and Early Tauopathy

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Results

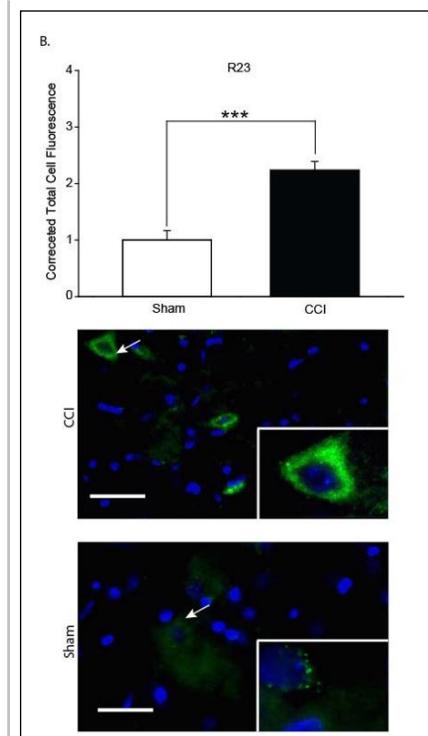
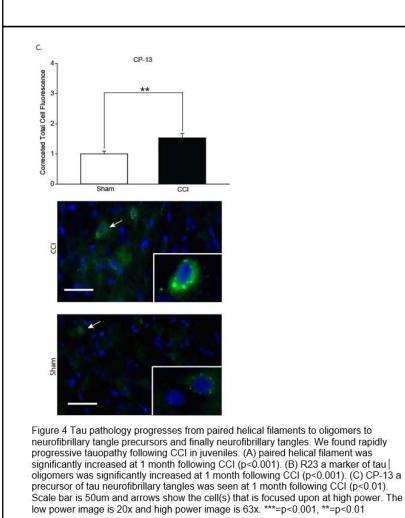
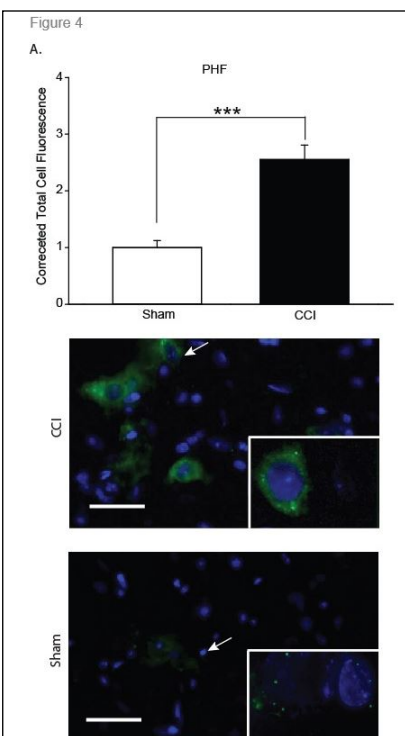
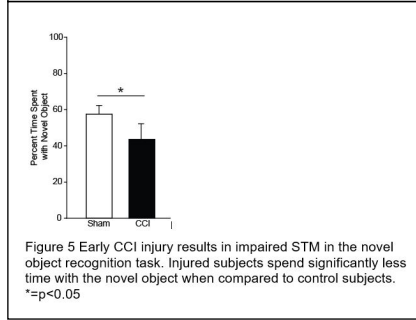
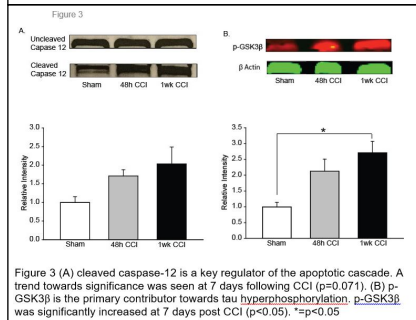
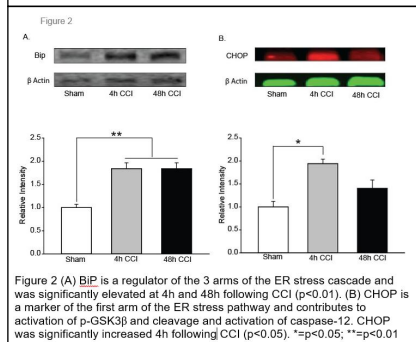
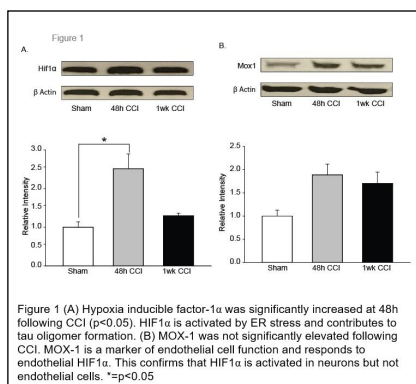
At 4 hours following injury, BiP and CHOP were significantly elevated ($F_{2,4} = 8.319, p=0.039$) in rats exposed to TBI. Hypoxia inducible factor 1a was also significantly upregulated at 48h following TBI ($F_{2,4} = 18.451, p = 0.01$) indicating that early ER stress activation contributed to the activation of the tau kinase GSK3 β ($F_{2,4} = 9.855, p = 0.028$) by 1 week. Tau oligomers measured with R23 were significantly increased by 30 days following TBI ($t_{18} = -5.435, p < 0.001$). These post-TBI changes were associated with increased impulsive behavior measured with elevated plus maze ($t_{10} = 2.287, p = 0.0452$), deficits in short term memory measured with novel object recognition ($t_{23} = -2.321, p = 0.029$), and deficits in spatial memory measured with Morris water maze ($F_{4, 24} = 2.898, p = 0.026$).

Introduction

The leading cause of death in the juvenile population is neurotrauma. Endoplasmic reticulum (ER) stress has been shown to contribute to injury expansion and behavioral deficits in adult rodents and humans. Whether ER stress contributes to injury expansion in juveniles with traumatic brain injury (TBI) is poorly delineated. We proposed that ER stress would be significantly increased in juvenile rats following TBI and that this would contribute to behavioral deficits.

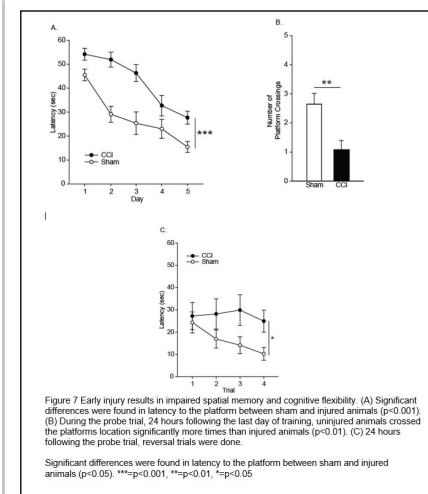
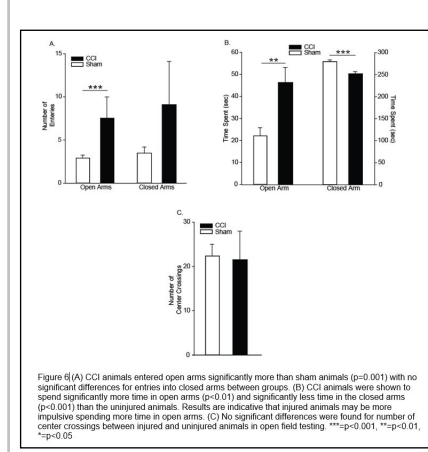
Methods

A juvenile rat (post-natal day 28) controlled cortical impact model was used with 14 rats in the TBI group and 14 rats in the sham. BiP and CHOP (ER stress markers) were measured at 4 hours in the ipsilateral peri-contusion cortex. HIF 1 alpha was measured at 48 hrs, tau kinase measured at 1 week, and tauopathy at 30 days.



Learning Objectives

- ER stress is a significant contributor to injury in juvenile rodents
- ER stress activation after injury in juvenile rodents contributes to delayed hypoxia and tauopathy.
- Biochemical changes following traumatic brain injury are associated with behavioral deficits.



Conclusions

These results show that ER stress is a significant contributor to injury in juvenile rodents, and that pharmacologically targeting ER stress may prevent the long-term sequelae associated with TBI.

References

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- Mearns GP, Mines MA, Beurel E, Eom TY, Song L, Zmijewska AA, Jope RS: Glycogen synthase kinase-3 regulates endoplasmic reticulum (ER) stress-induced CHOP expression in neuronal cells. *Exp Cell Res* 2011;317:1621-1628.
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