Screening potential TBI therapeutics in a Pre-Clinical Model of Repetitive mild TBI

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Background

Mild traumatic brain injury (mTBI) constitutes 75% of all TBIs that occur in the US. The sequelae of mTBI persist long after the primary insult and increase the risk for neurodegenerative diseases later in life. Our group has developed a model of mild repetitive head injury in mice which shows chronic neuroinflammation. Administration of an anti-inflammatory compound over a chronic time period has shown significant improvement in outcome, and delayed administration in a cross-over design has shown positive indicators of reduced inflammation as well.

Methods

Male wild type C57BL/6 mice received 5 hits with an inter-mTBI injury interval of 48 hours, while anesthesia controls were matched for time spent under anesthesia. We administered anatabine, a naturally occurring minor alkaloid with anti-inflammatory properties, in water to a group of injured and sham mice (n = 12 per group) for 9 months after TBI while an additional 12 mice group were untreated (receiving regular water alone). Outcome was evaluated by neurobehavioral testing at both an acute and 6 month timepoint. At 9 months after TBI an n of 4 per group were euthanized for pathological analysis. Remaining untreated mice began receiving anatabine and anatabine treated mice began receiving regular water.

Results

Anatabine treated mice showed no significant differences from untreated mice by Barnes maze testing of spatial memory at an acute timepoint, but at 6 months after TBI anatabine treated mice showed significantly less latency to find the target hole in the probe trial of the Barnes maze. Immunohistochemistry revealed significantly lower signs of inflammation and phospho STAT3 at 9 months after TBI. At 12 months post-TBI, 3 months post-crossover, mice originally untreated with anatabine continued to show a significantly higher latency to find the target hole. Mice originally treated with anatabine continued to show no significant impairment compared to sham animals. At 18 months post-TBI, 9 months post-crossover, no significant effect of injury was seen in any group. Immunohistochemistry showed a significant increase in the inflammation present in the corpus callosum of mice originally treated with anatabine, but a significant reduction in the inflammation of mice who originally received no treatment.

Conclusions

Our pre-clinical model of repetitive mild TBI has been characterized up to 24 months post-injury and consistently shows chronic neuroinflammation, particularly in the white matter of the corpus callosum.

Treatment with an anti-inflammatory compound for a chronic period of time either in an acute or delayed administration paradigm significantly reduced the inflammation seen in the corpus callosum by IBA1 staining, as well as phospho STAT3 signaling. Anatabine shows promise as a potential treatment for repetitive mild TBI. Future studies will evaluate minimum effective dose for future human clinical trials.