Exploring the Effects of TBI and Alcohol in Inducing TDP-43 Proteinopathy in the Lumbar Spinal Cords of Rats

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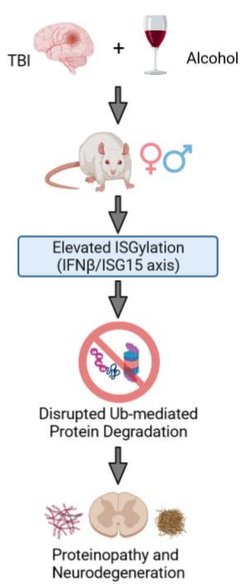
Introduction

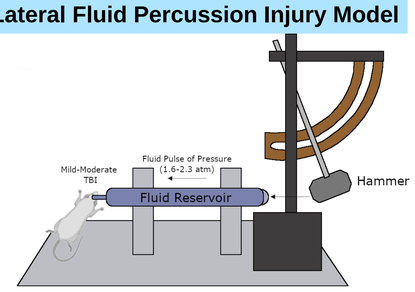
Although considered as a rare neurodegenerative disorder, veterans who have served in the military are at a nearly 60% greater risk of being diagnosed with Amyotrophic Lateral Sclerosis (ALS) than those with no history of military service. Traumatic brain injury (TBI) has been identified as one of the major risk factors for ALS development in veterans. Alcohol and TBI are a deadly pair; while alcohol increases one's risk for TBI, TBI also increases one's likelihood of alcohol abuse. Currently, the knowledge of the mechanism(s) underlying TBI-mediated neurodegeneration and whether alcohol modulates these mechanism(s) is not known.

Approximately 97% of ALS cases exhibit a common neuropathology known as TDP-43 (TAR DNA binding protein 43) proteinopathy, which is characterized by the accumulation of non-degraded TDP-43 proteins in nerve cells, potentially due to impaired ubiquitin-mediated protein degradation. Interferon stimulated gene 15 (ISG15), a ubiquitin-like protein, has previously been shown in our lab to antagonize ubiquitin-mediated protein degradation. Notably, we have demonstrated that the ISG15 pathway (free ISG15 and its protein conjugates (ISGylation)) is elevated in the lumbar spinal cords (LSCs) of ALS veterans, a region of the spinal cord that is commonly affected in ALS patients. We have also found that levels of ISGylation are significantly increased in the LSCs from female vs male ALS veterans. TBI induces ISG15 expression in other experimental model(s). Based on these results, we hypothesize that TBI-induced activation of the IFNβ/ISG15 axis impairs the ubiquitin-mediated turnover of neuronal proteins (e.g., TDP-43) in the spinal cord. Toxic accumulation of non-degraded proteins leads to neurodegeneration, and alcohol exacerbates this mechanism.

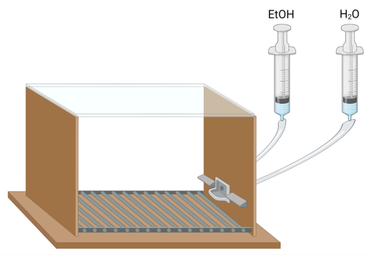
Hypothesis and Models



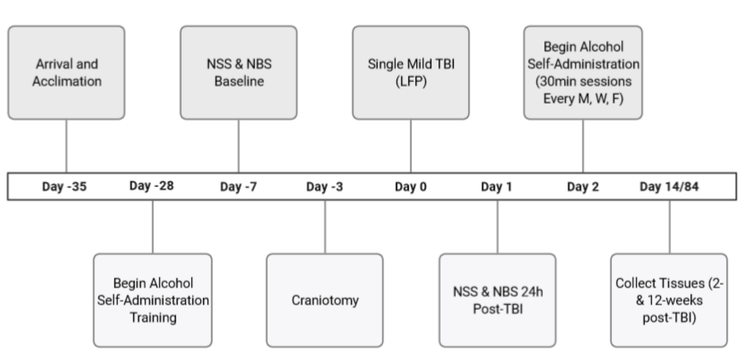
Lateral Fluid Percussion Injury Model



Self-Administration Alcohol Model



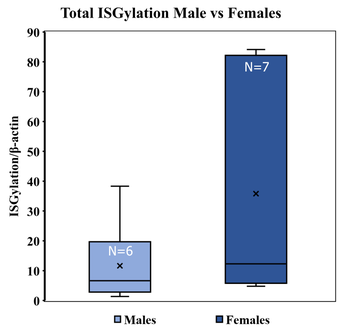
Timeline

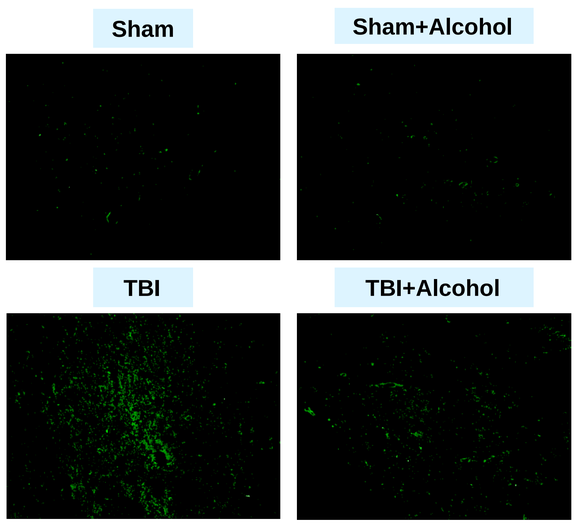


Results

♀ TBI induces neurodegeneration in LSCs

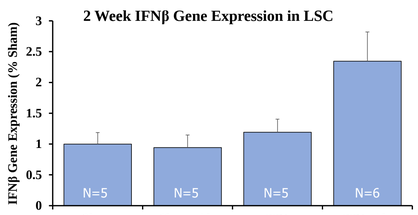
ISGylation is increased in female ALS veterans

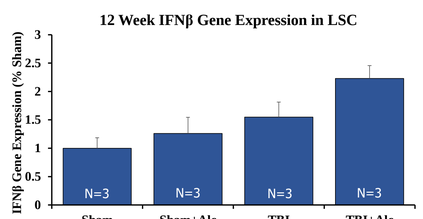




2-Way ANOVA: Main Effect of TBI (p= 0.0042)

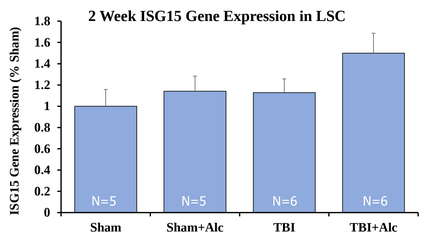
♀ TBI induces IFNβ gene expression and alcohol use exacerbates this response in LSCs

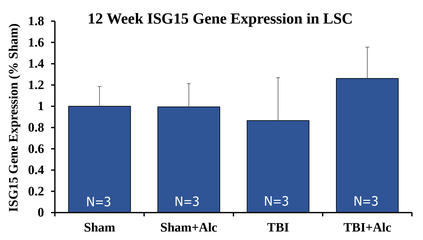


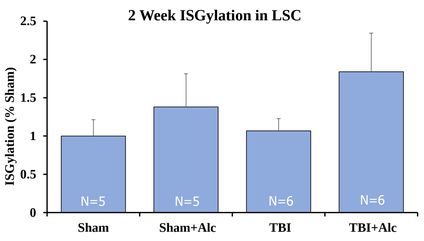


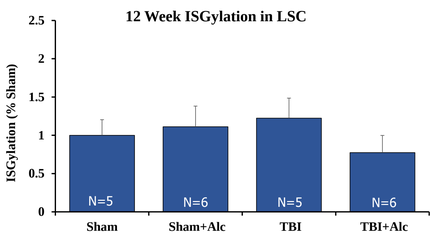
2-Way ANOVA: Main Effect of TBI (p= 0.0121)

♀ TBI appears to have no significant effect on ISG15 gene expression and ISGylation in LSCs



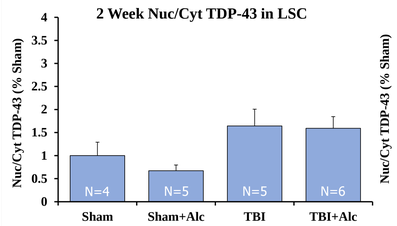


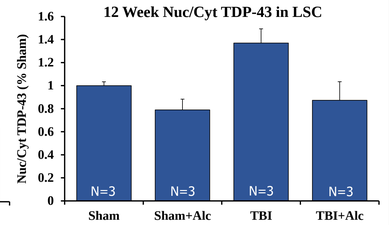




Results

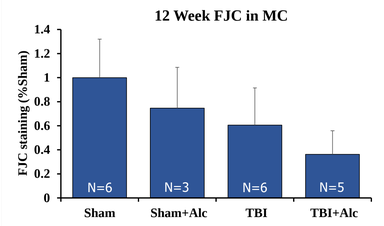
♀ TBI induces nuclear localization of TDP-43 in a time-dependent manner in LSCs

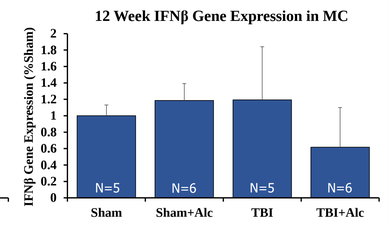


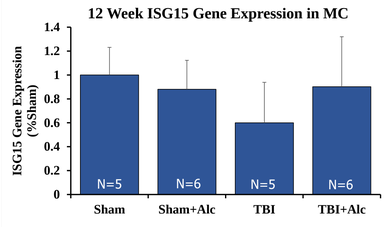


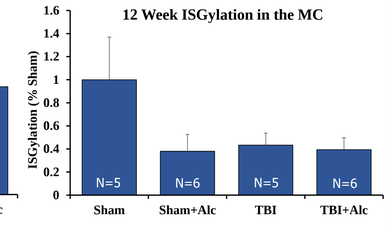
2-Way ANOVA: Main Effect of TBI (p= 0.0118)

♀ TBI appears to have no significant effect on neurodegeneration, IFNβ and ISG15 gene expression, and protein ISGylation in MCs









Conclusions/Future Studies

Conclusions

- TBI induces neurodegeneration in LSCs
- TBI induces IFNβ gene expression and alcohol use appears to exacerbate this response in LSCs
- TBI had no significant effect on ISG15 gene and ISGylation expression in LSCs
- TBI induces nuclear localization of TDP-43 in a time-dependent manner in LSCs
- TBI appears to have no significant effect on neurodegeneration, IFNβ and ISG15 gene expression, and protein ISGylation in MCs

Studies Underway:

- Conducting similar assays in the brains collected from both male and female rats at 2- and 12-weeks post-TBI
- Staining tissue sections in the brain and spinal cord to examine inclusion bodies positive for ubiquitin and TDP-43
- Exploring ISG15-independent mechanisms underlying detected TDP-43 proteinopathy and neurodegeneration post-TBI in LSCs (e.g., deregulation of the proteasome activity post-TBI)

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