RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Treating Concussion with Vasopressin Antagonists: A Preclinical MRI Study

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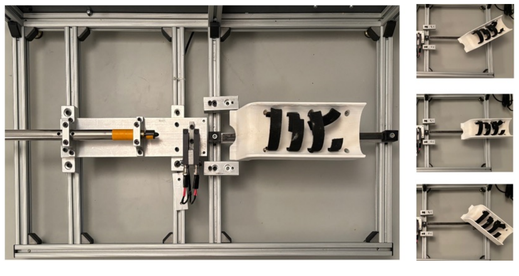
EKAM
THE IMAGE OF DRUG DISCOVERY

Introduction

Concussions are the most prevalent form of traumatic brain injury, affecting individuals of all ages in organized sports, accidents and falls, military service, and everyday life. With over 2 million incidents per year, a $40 billion annual burden to the U.S. health care system, and no clinically approved treatments, there exists a dire need for preclinical research. We hypothesized that vasogenic edema stemming from blood-brain barrier (BBB) leakage and contributing to neuroinflammation after concussion can be treated with vasopressin antagonists AVN849 and SRX251, known to modulate BBB permeability. This presentation will discuss our findings from a longitudinal rodent MRI study.

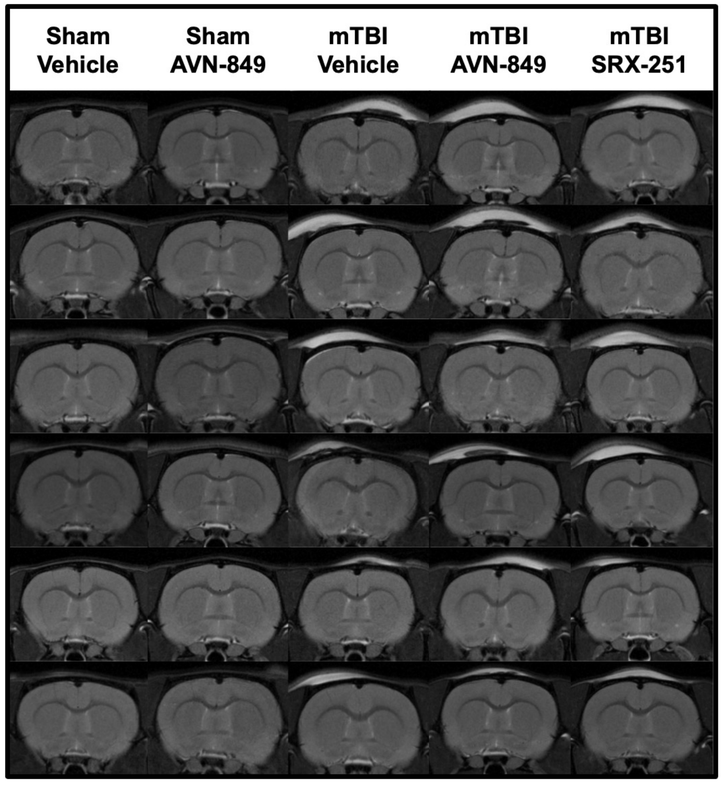
Momentum Exchange Model of mTBI

The momentum exchange method ranks highest among preclinical rmTBI models in translational value for its ability to generate tightly regulated, ethologically valid linear and rotational forces without skull fracture or surgical procedure. The apparatus features a pneumatic rubber-tipped impactor, sensors to verify impact velocity, and a track along which the platform accelerates after impact for longitudinal use with fully awake rats, maximizing translational value.



30 adult rats underwent mTBI or sham procedure once. SRX-251, AVN-849, or vehicle control was administered via intraperitoneal injection 10 minutes post-mTBI. T2-weighted and Diffusion-Weighted MRI scans were acquired within two hours of injury and again three weeks later. After follow-up imaging, tissue was acquired for histological and proteomic quantification of astrocyte and microglia morphology.

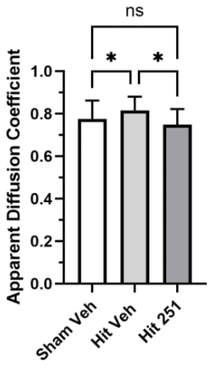
Mild Head Injury Model Without Fracture or Contusion

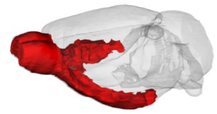


T2-weighted MRI verifies the model absent of fracture or contusion, consistent with the clinical mTBI phenotype.

Olfactory Microstructure is Restored by SRX-251

Olfactory System

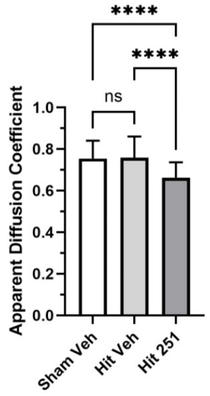


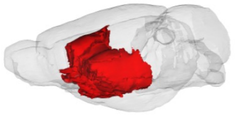


ADC of the olfactory system is significantly elevated above baseline 4 hours post-mTBI and returned to control levels by SRX-251 treatment.

$p = 0.0292$

Basal Ganglia

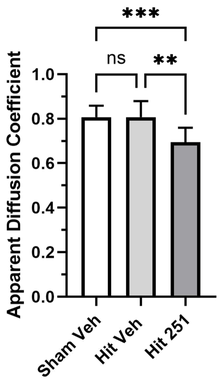


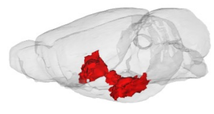


ADC of the basal ganglia is not significantly altered 4 hours post-mTBI, though diffusivity is reduced by SRX-251 treatment.

$p < 0.0001$

Amygdala

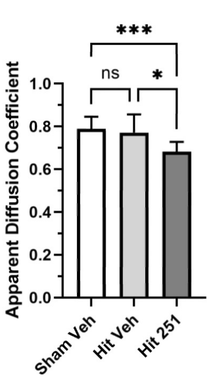


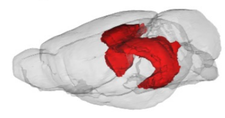


ADC of the amygdala is not significantly altered 4 hours post-mTBI, though diffusivity is reduced by SRX-251 treatment.

$p = 0.0002$

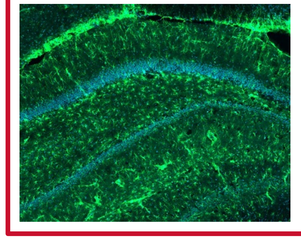
Hippocampus





ADC of the hippocampus is not significantly altered 4 hours post-mTBI, though diffusivity is reduced by SRX-251 treatment.

$p = 0.0005$

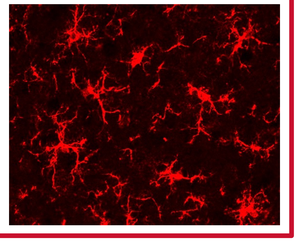


Future Directions

Three weeks post-injury and treatment, tissue was collected for proteomic and histological analysis of lasting microstructural changes. Changes in astrocytic aquaporin channel expression is associated with blood-brain barrier modulation regulated by vasopressin V1a receptors. Lasting changes to populations of astrocytes and microglia, key indicators of neuroimmune activation, will undergo further analysis.

We recommend further investigation of SRX-251 for treatment of BBB-compromising small vessel disruptions, including mTBI.

Further investigation of the novel candidate AVN-849 is not recommended, as no changes were observed in this model.



Discussion

The validity of preclinical models in guiding the development of new therapeutics for the treatment of head injury has been called into question on account of the many failed clinical trials for TBI. To that end, we have employed the momentum exchange model of mTBI for its high translational value, further adding to it by adapting its holster for use with conscious rats. The olfactory system, basal ganglia, amygdala, and hippocampus have been identified as areas sensitive to microarchitecture alteration, which may be treated with vasopressin V1a antagonists administered after impact.

Acknowledgements

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