A Novel Countermeasure to Improve Recovery Following Traumatic Brain Injury (TBI)

University of Colorado Anschutz

Matthew F. Palmer, BA, CVT, ALAT[1], Genna M. Nault, CVT[1], Katharine Warner, MS[1], Dora Pisula-Litoff[1], Jacob Altholz, MD[1], Dylan Rodriguez, MS[7], MAJ Steven G. Schauer, DO[3], Patrick Ng, MD[4], Maria Castenada, MS[4], James E. Orfila, PhD[5], Paco S. Herson, PhD[5], Col Joseph K. Maddry, MD[2,6], Maj William T Davis, MD, MPH, FACEP[2,7],Col Vikhyat S. Bebarta, MD[1], Tara B. Hendry-Hofer, MSN, RN[1]

1. University of Colorado Anschutz Medical Campus, Aurora, CO, USA. 2.Office of the Chief Scientist, Wilford Hall Ambulatory Surgical Center, 59th Medical Wing, JBSA-Lackland, TX 3.US Army Institute of Surgical Research, San Antonio, Texas. 4.UT Health San Antonio, San Antonio, TX, USA.. 5. Department of Neurological Surgery, The Ohio State University College of Medicine, Columbus, OH, USA.. 6. Department of Clinical Investigation, Brooke Army Medical Center San Antonio Texas USA. 7.En route Care Research Center, 59th Medical Wing, Science & Technology, Defense Health Agency, San Antonio, Texas

Introduction

- A field deployable therapeutic to treat traumatic brain injury (TBI) early in the course of injury is a high priority for multi-domain operations.
- Transient receptor potential melastatin 2 (TRPM2) is a calcium-permeable channel activated by adenosine diphosphate ribose metabolites and oxidative stress.
- TRPM2 contributes to neuronal injury in the brain caused by stroke, cardiac arrest, and TBI.
- In prior efforts, using a mouse model of TBI, we found the novel TRPM2 channel inhibitor, tatM2NX, improved hippocampal synaptic plasticity and memory function.

Objective

The objective of this study is to determine the therapeutic effect of tatM2NX in a clinically relevant, porcine model of TBI.

Methods

After induction of anesthesia, swine (N=10) were intubated and sedation maintained with inhaled isoflurane. Central venous and arterial access was obtained for blood sample collection and invasive hemodynamic monitoring. TBI was induced using a modification of the TBI model established by the 59MDW/ST. For these studies, two sequential controlled cortical impact (CCI) strikes via actuated piston to an aluminum disk placed on the center of the head 10 minutes apart was used. At 1 and 4 hours after insult, swine were treated with 2 mg/kg tatM2NX (n=5) or saline control animals (n=5). Swine were recovered from anesthesia, and a 15-minute timed novel object recognition test was used to measure cognitive behavior at 72 hours post TBI. A novel object recognition test is used to evaluate memory by using the natural tendency of an animal to spend more time exploring a new (novel) object than a familiar object.

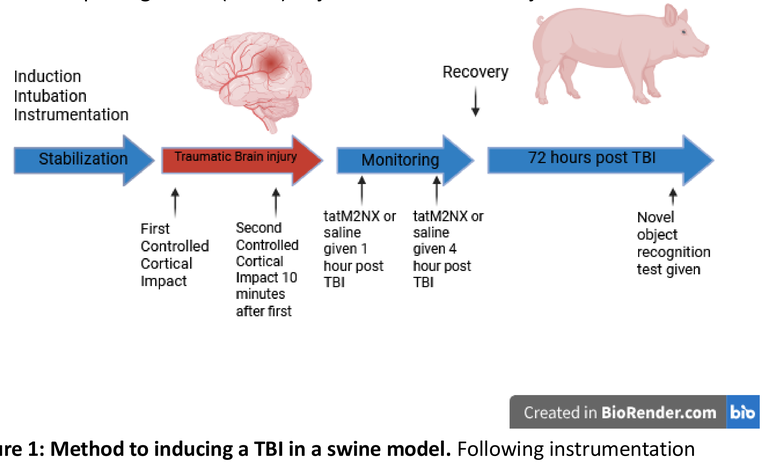

Figure 1: Method to inducing a TBI in a swine model. Following instrumentation and stabilization TBI was induced via 2 sequential CCI 10 minutes apart. At 1 and 4 hours after TBI, animals received treatment with 2 mg/kg tatM2NX or saline control. Swine were recovered from anesthesia and monitored for 72 hours post TBI. Prior to euthanasia a 15-minute novel object recognition test was used to quantitively assess cognitive behavior.

Results

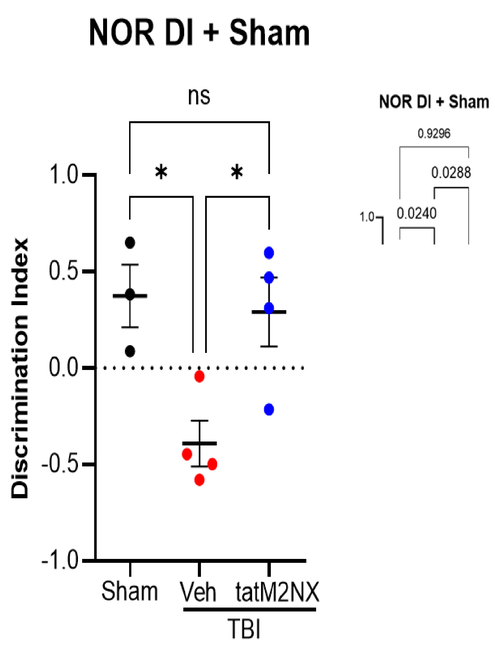

Figure 3. Novel object recognition (NOR) test. Animals in the tatM2NX and sham group showed similar scores on the discrimination index (DI) indicating rescued cognitive function.

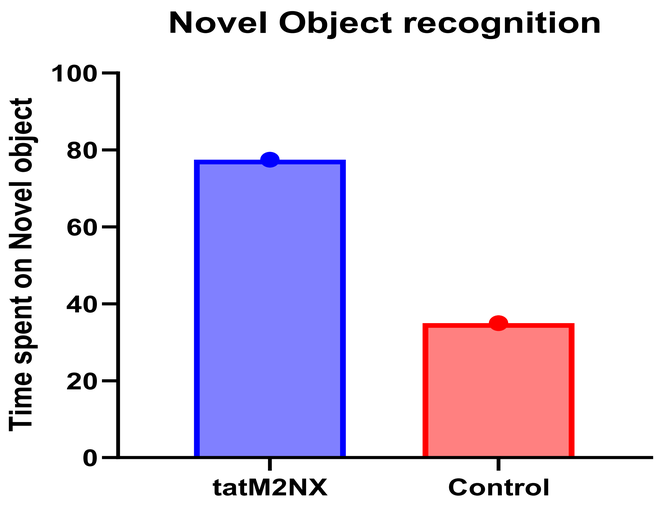

Figure 3. Novel Object Recognition (NOR) Treatment vs Control. Following TBI swine in the control group explored the novel object for 35.0 ± 14.1% of the time compared to the tatM2NX group which explored the novel object for 77.5 ± 13.4%.

Results

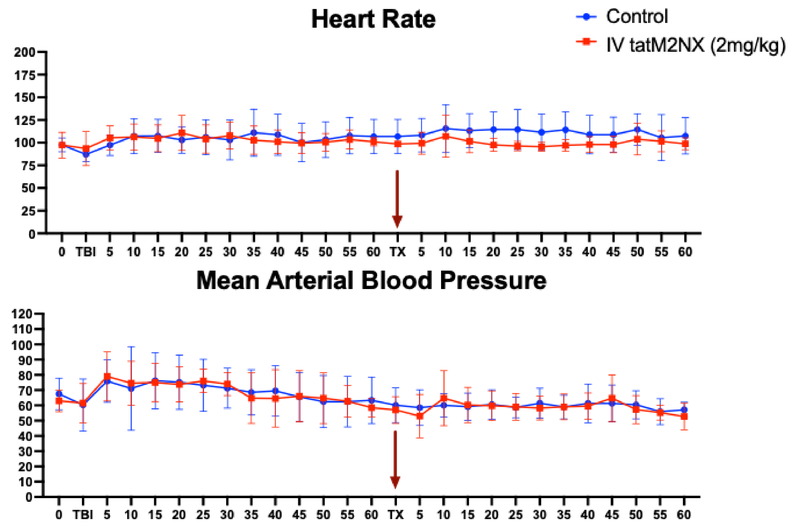

Figure 4. Hemodynamics after treatment. There were no observed adverse physiological effects following treatment as indicated by heart rate and mean arterial blood pressure.

Conclusion

Treatment with tatM2NX reduced TBI-induced memory impairment compared to control treated animals

Future Directions

- Determine the minimal efficacious dose of of tatM2NX to intervene to prevent TBI in a swine model.
- Compare histological outcomes between tatM2NX and saline control treated outcomes.
- Evaluate long term cognitive outcomes (14-28 day) with tatM2NX treatment compared to saline control.

Disclaimer

The views expressed in this poster are those of the authors and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of Defense, nor the U.S. Government. This work was supported by funding from the DHA FY23 RESTORAL Program. The study protocol was approved by the University of Colorado Institutional Animal Care and Use Committee (IACUC) and reviewed by AFOSR in compliance with all applicable Federal regulations governing the protection of animal subjects. The experiments reported herein were conducted in compliance with the Animal Welfare Act and per the principles set forth in the "Guide for the Care and Use of Laboratory Animals, Eighth Edition", The National Academies Press, 2011.