CB1/TRPV1 Antagonism Ameliorates Lateral Perforant Pathway STP/LTP Deficits in a rmTBI Young Adolescent Rat Model

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INTRODUCTION

- Mild Traumatic Brain Injuries (mTBI) make up 85% of all TBIs[1]. They can often be repetitive (rmTBI) in young adolescents.
- mTBIs can be associated synaptic plasticity deficits in preclinical models.
- The role of Endocannabinoids (ECs) in mTBI is underexplored in rmTBI cases[2,3].

METHODS

Lateral Impact Model (LIM)

- 53 Sprague-Dawley (PND30) rats received 3x Shams or mTBIs 72-hours apart, using LIM.
- Rats sacrificed 7 days after final injury (PND 43)
- Time-to-Right is a metric for loss of consciousness

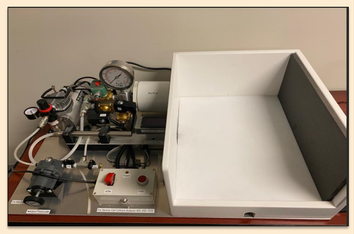

Figure 1. Image of LIM, used to deliver mTBI to subjects. Injuries were done on Post-Natal-Day 30, 33, 36, and animals were sacrificed on PND 43

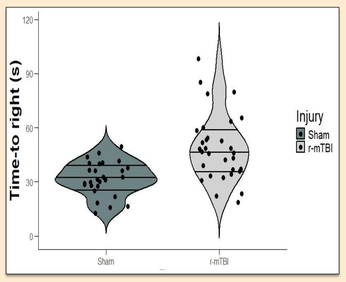

Figure 2. Violin plot of TIR. Used for confirmation of concussion deliverance.

Electrophysiology

- Field electrophysiological recordings from the medial perforant path (MPP) of the dentate gyrus (DG).
- LTP: 4 x 100 Hz

A) 10 uM BIC
B) 4 uM AM251 + 10 uM BIC
C) 3 uM AMG9810 + 10 uM BIC

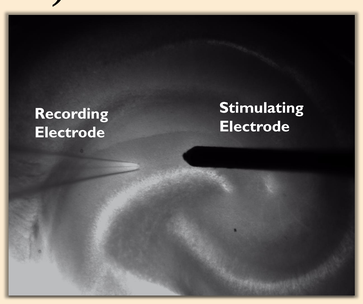

Figure 3. Image of electrode positioning for electrophysiological recordings in the medial perforant pathway. Slices were cut at 400 µM with a sagittal orientation

RESULTS

Controls

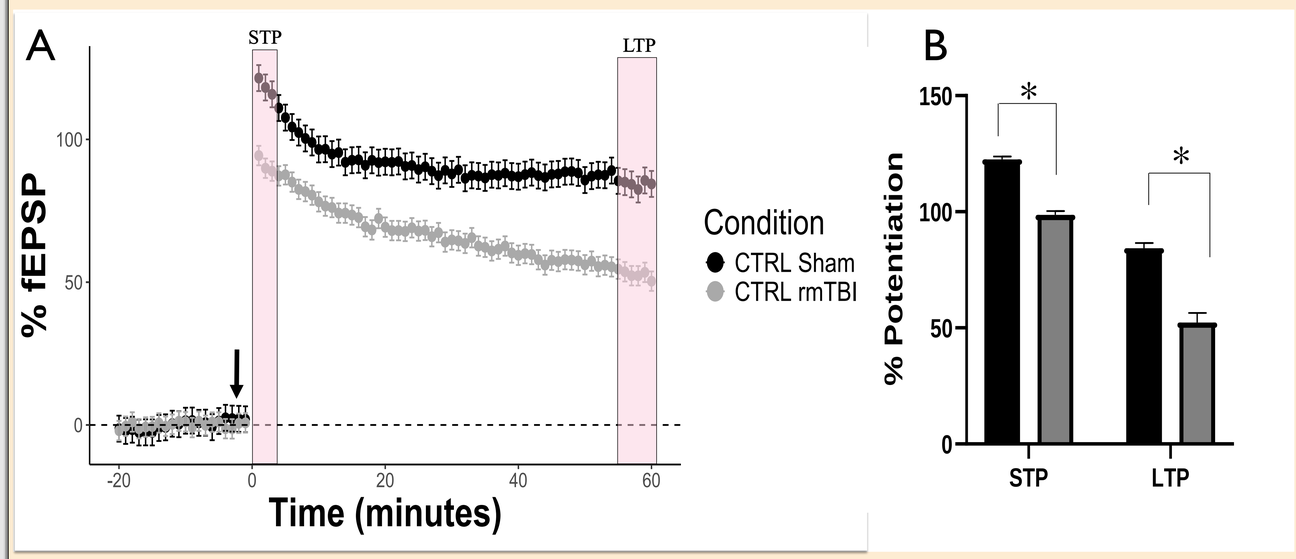

Figure 4. A) Graphical depiction of 1-hour long LTP decay recordings. Black arrow indicates HFS delivery (4x 100Hz). All points are averages of 4 stimulations, one every 15 seconds (i.e. 1 minute of decay). STP and LTP were defined as the first 3 minutes/points, and the final 5 minutes/points, respectively. Control groups contained 10 Sham rats, and 12 rmTBI. **B)** Histogram comparing the differences potentiation between groups across all conditions. Groups were compared using Welches T-Tests. Figures were created in RStudio/GraphPad PRISM 10.

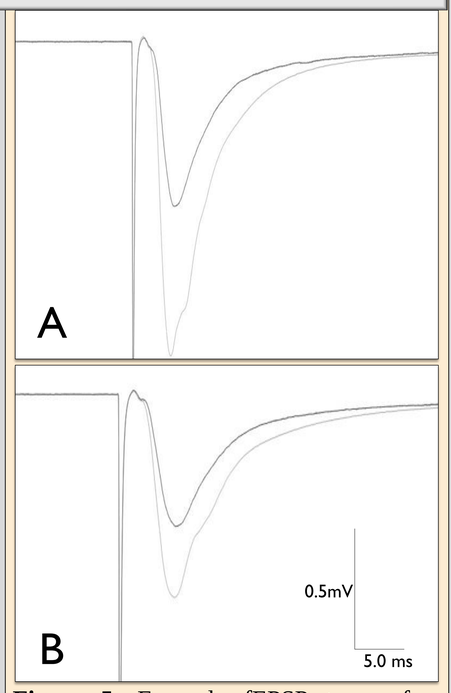

Figure 5. Example fEPSP traces for Control slices, A) Sham, B) rmTBI. Baseline recordings are shown in black, and post-condition in grey. Traces are averaged.

AM251 Trials

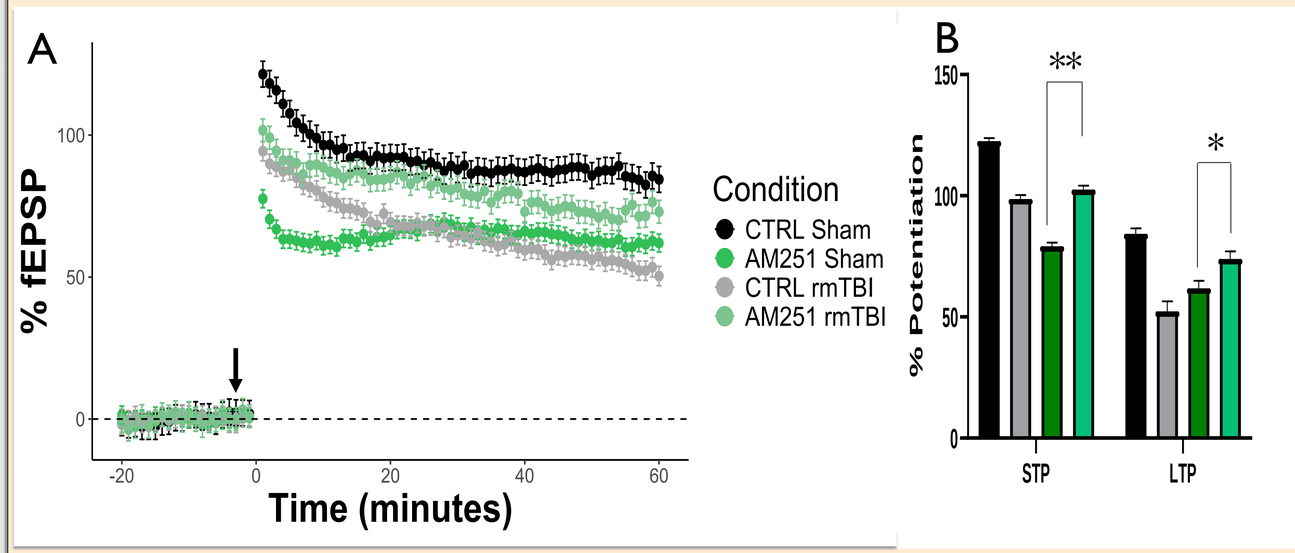

Figure 5. A) LTP decay of AM251 (CB1 inverse agonist) trials (12 total recordings, 6 control/ 6 rm-TBI). All procedure was the same as controls **B)** Histogram comparing the differences potentiation between groups conditions. Note LTP alleviation seen in Sham Am251 trials versus rmTBI Am251. Groups were compared using Welches T-Tests. Figures were created in RStudio/GraphPad PRISM 10. *=significantly different, nd= no statistical difference.

AMG9810 Trials

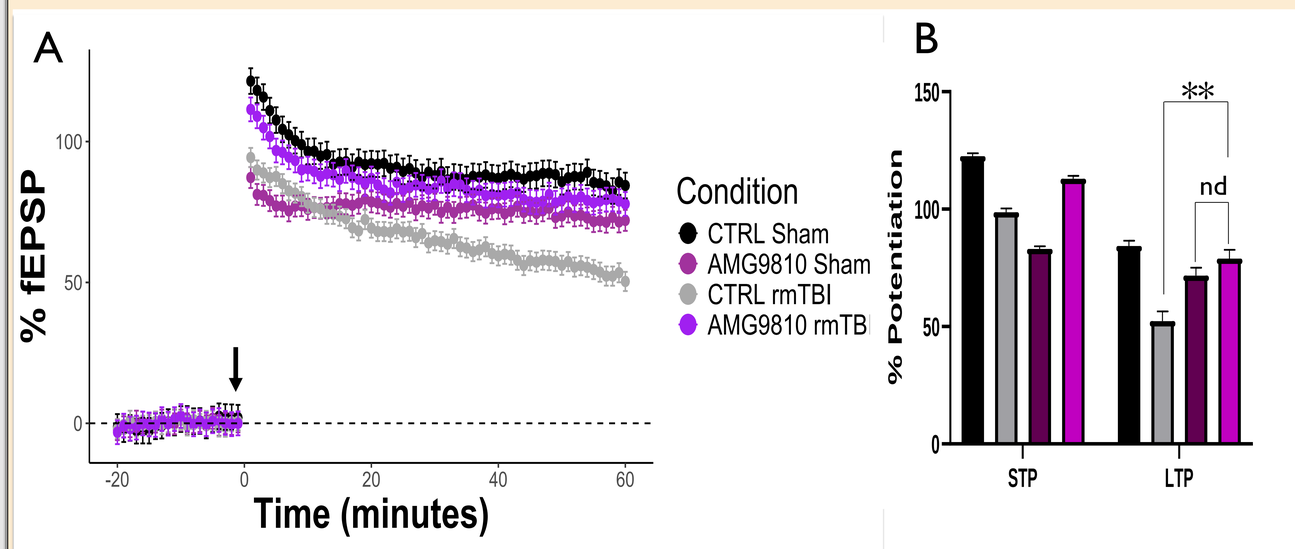

Figure 6. A) LTP decay of AMG9810 (TRPV1 antagonist) trials (18 total recordings, 8 control/10 rm-TBI). All procedure was the same as controls **B)** Histogram comparing the differences potentiation between groups across all conditions. Groups were compared using Welches T-Tests. Figures were created in RStudio/GraphPad PRISM 10. *=significantly different, nd= no statistical difference.

DISCUSSION

- mTBI reduces the capacity for DG LTP
- AM251 normally reduces DG LTP in control animals
- AM251 increases DG LTP following mTBI

CONCLUSIONS

- mTBI alters the role of CB1 receptors in synaptic plasticity in the DG
- Future research should examine whether blocking CB1 receptor has benefits for cognition following mTBI

REFERENCES

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3. Laviola, W. Adriani and R. Cuenoe. 2018. Inside the Developing Brain to Understand Teen Behavior From Rat Models: Metabolic, Structural, and Functional-Connectivity Alterations Among Limbic Structures Across Three Pre-adolescent Stages. *Frontiers in Behavioral Neuroscience* 12.

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