

Targeted Inhibition of Adenine Production Mitigates Brain–Kidney Injury and Enables Biomarker-Guided Care in Prolonged Field Care

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Introduction

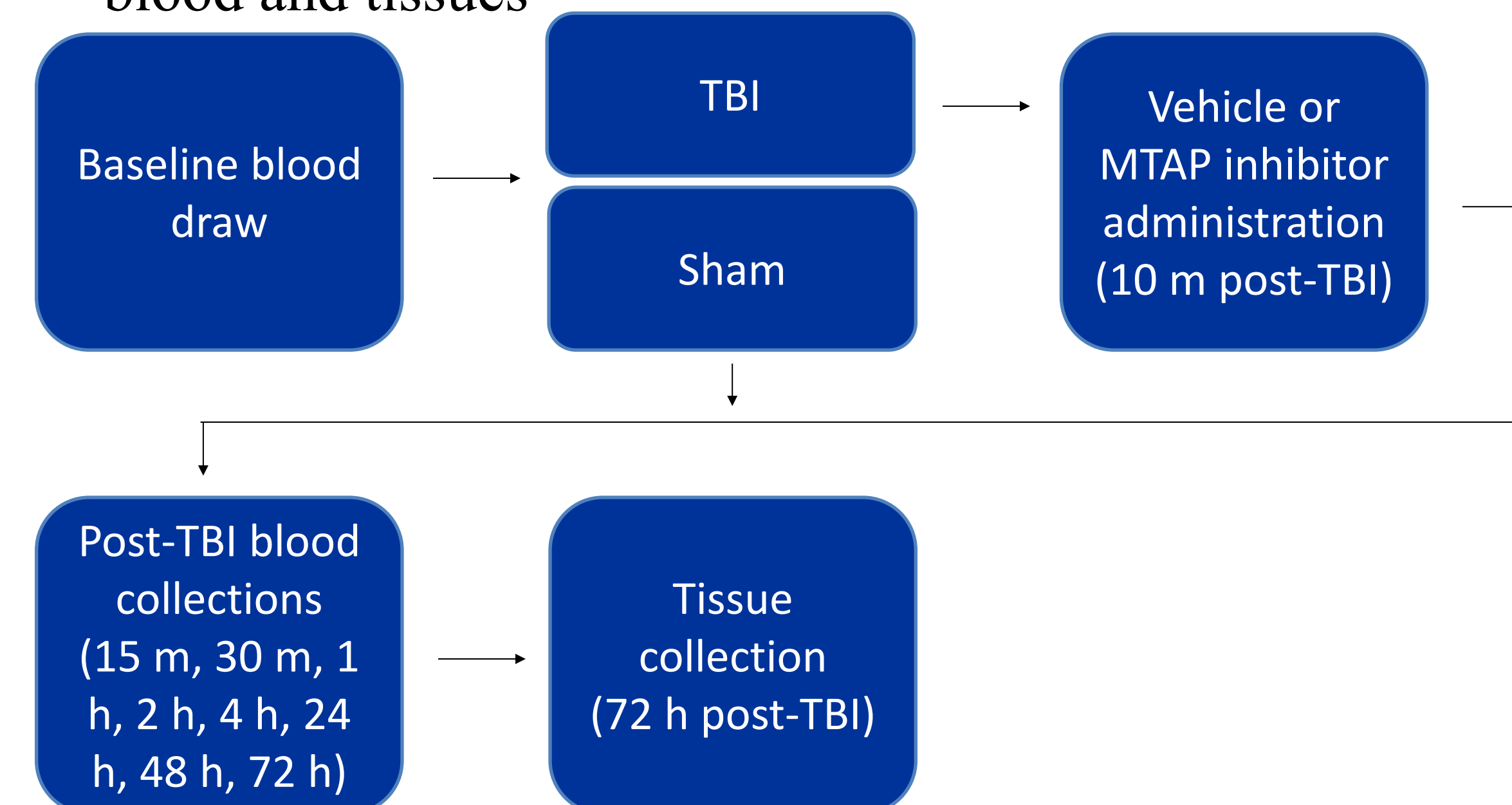
- Combat operations requires prolonged field care (PFC) under conditions of delayed evacuation, increasing the risk of multi-organ failure following polytrauma.
- Traumatic brain injury (TBI) is a driver of systemic pathophysiology, promoting metabolic dysregulation and inflammatory signaling that contribute to organ dysfunction, particularly acute kidney injury (AKI).
- Increase adenine production is a predictor and contributor of acute and chronic kidney injury (*ref 1 and 2*).
- However, field-deployable therapeutics and biomarkers for early detection and mitigation of organ injury remain limited.

Hypothesis

We hypothesized that inhibition of adenine production, a metabolite implicated in nephrotoxicity and vascular injury, via a small molecule methylthioadenosine phosphorylase (MTAP) inhibitor mitigates brain–kidney crosstalk and enables biomarker-based detection of organ dysfunction in austere environments.

Study Design

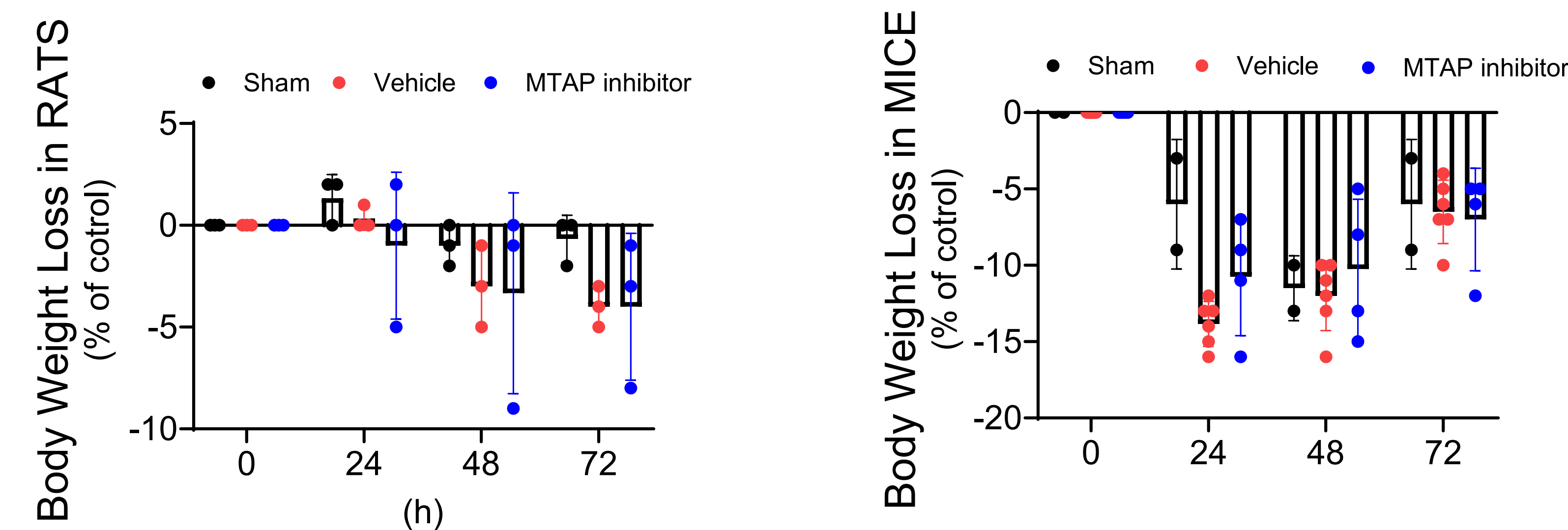
- 350-500 g male CD rats and 3-5 months male WT mice were randomized to sham group, TBI + vehicle, or TBI + MTAP inhibitor (MTAP inhibitor, 20 mg/kg, intramuscular, 10 min post-TBI) (n=2-6 per group).
- TBI induction: controlled impact to right cortical hemisphere via impactor by 3.5 (mice) or 5 (rats) m/s speed, 50 (mice) or 250 (rats) msec dwell time, 1 (mice) or 2 (rats) mm depth.
- Blood collection: baseline, then 15 m, 30 m, 1 h, 2 h, 4 h, 24 h, 48 h, and 72 h post-TBI.
- Tissue collection: 72 h post-TBI.
- Adenine and MTA levels were measured by LC-MS.
- Metabolic and histopathological changes analyzed in blood and tissues



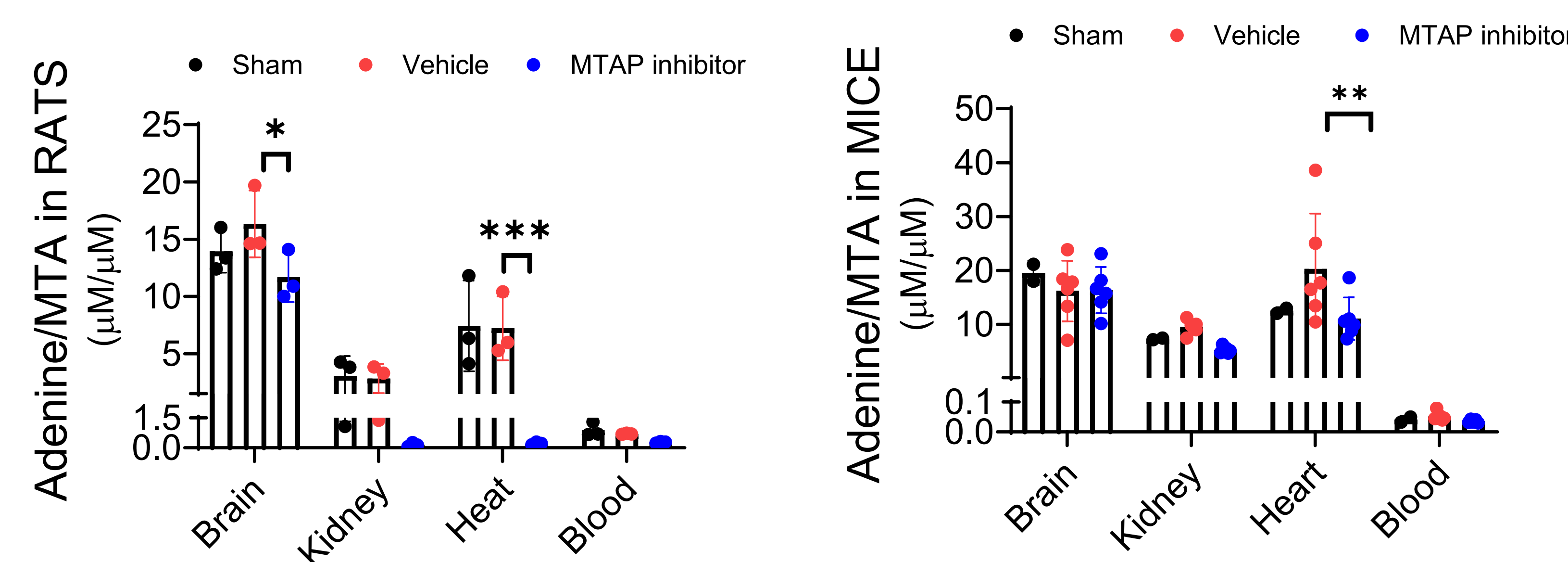
- Data were expressed as mean ± SD and analyzed by one-way or two-way ANOVA (Tukey's multiple-comparisons test), or Pearson correlation. * p<0.05, ** p<0.01, ****p<0.0001.

Results

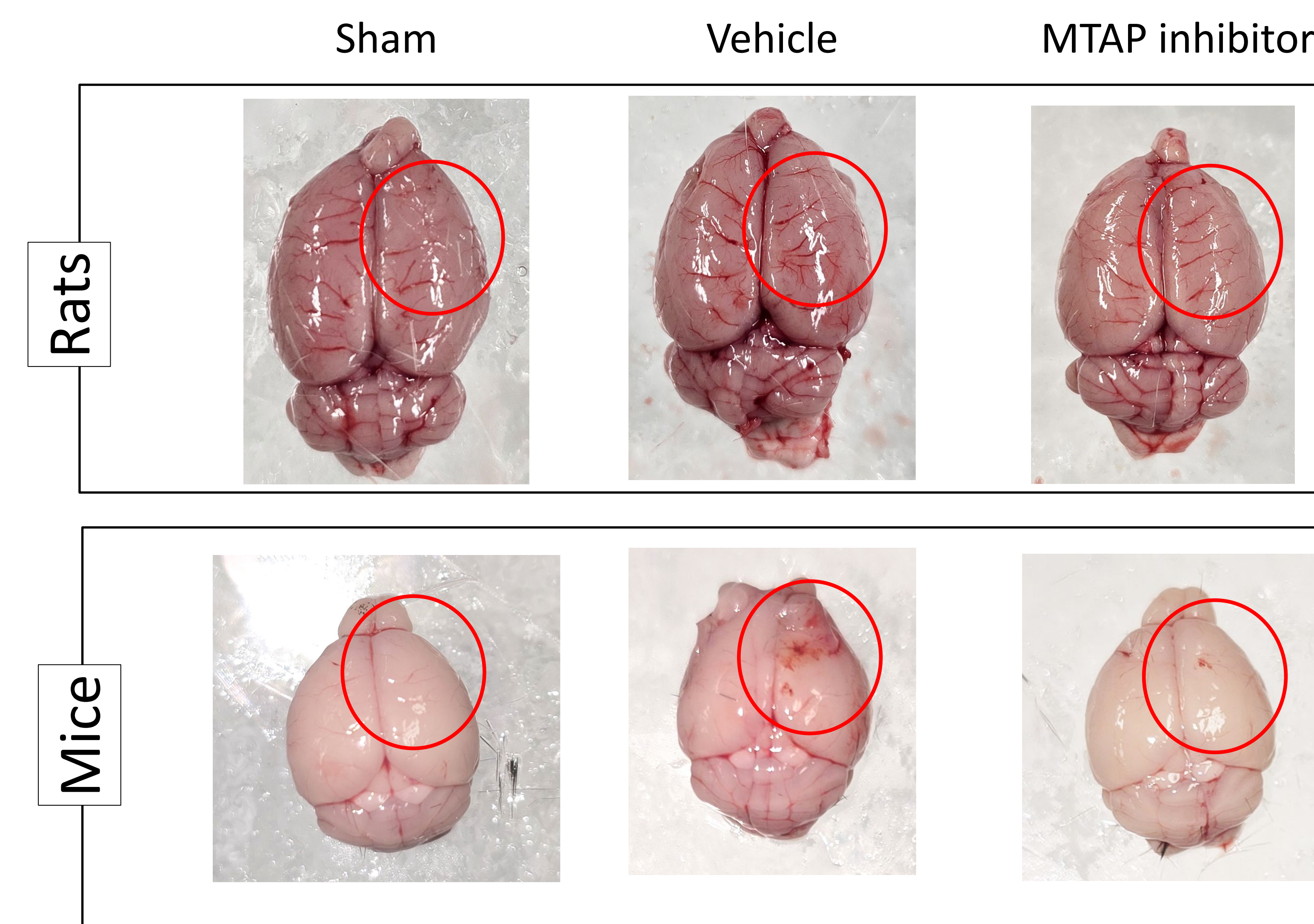
TBI induces body weight loss which is not affected by MTAP inhibition.



MTAP inhibition decreases Adenine/MTA ratio in the brain, kidney and heart.

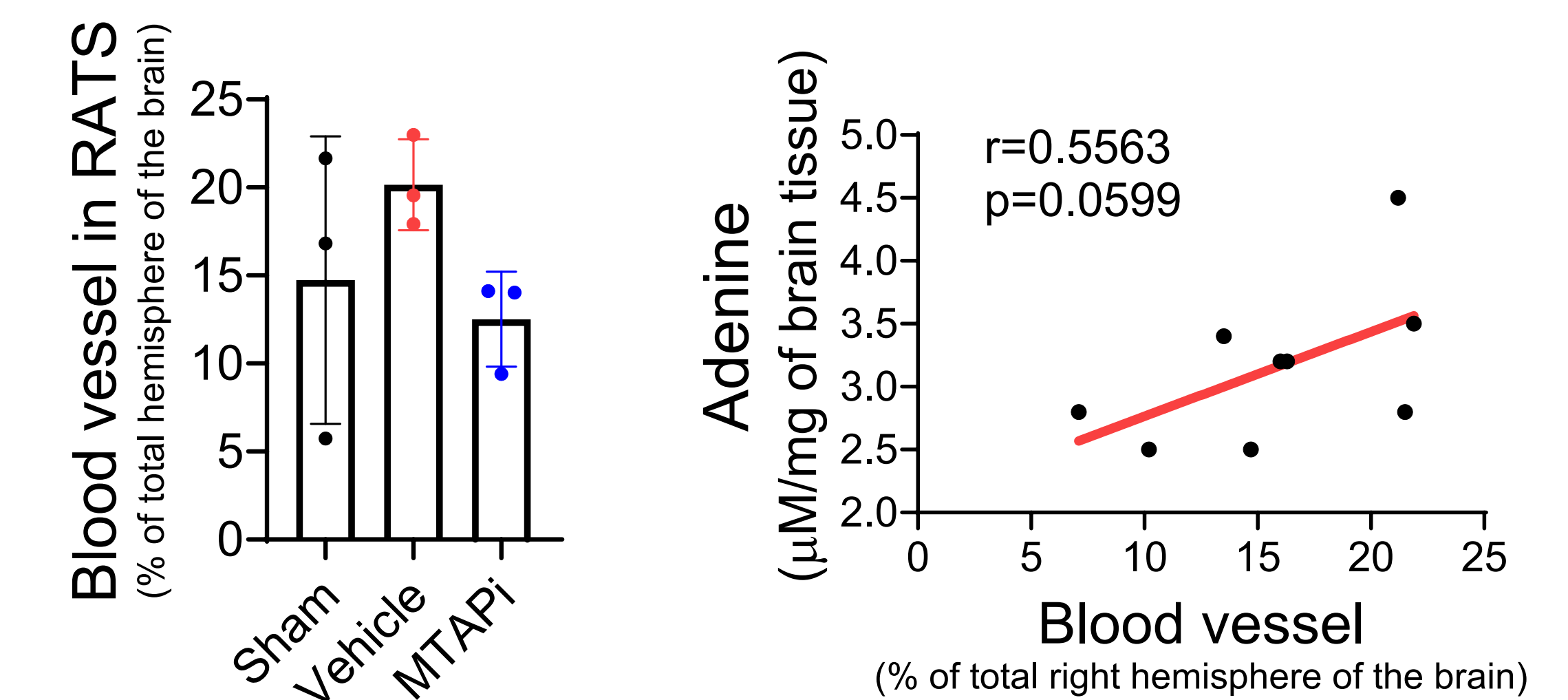


MTAP inhibition ameliorates TBI-induced hemorrhage on the brain.



Inhibition of adenine production decreases TBI-induced brain hemorrhage and NfL and plasma NGAL

NfL (Neurofilament Light chain) and NGAL (Neutrophil Gelatinase-Associated Lipocalin) are indices of brain and kidney injury markers, respectively



Summary

1. TBI induced body weight loss and no MTAP inhibitor adverse safety signals in body weight and blood glucose levels were observed.
2. Administration of MTAP inhibitor decreased adenine production in the brain, kidney, and heart.
3. Inhibition of adenine production ameliorated TBI-induced hemorrhage on the brain of animals.
4. TBI-increased adenine production was associated with brain hemorrhage.
5. Brain injury marker was correlated with acute kidney injury marker in animals with TBI.

Conclusion

This combined therapeutic–diagnostic approach provides a scalable, clinically relevant solution to improve survival and outcomes in combat casualties with complex organ injury when evacuation is delayed or unavailable.

References

1. Sharma, K., et al. Endogenous adenine mediates kidney injury in diabetic models and predicts diabetic kidney disease in patients. *J Clin Invest* 2023, 133(20): 170341.
2. Saliba, A., et al. Quinolinic acid potentially links kidney injury to brain toxicity. *JCI Insight* 2025, 10(6):e180229.