

SUR1-TRPM4 is Upregulated in Mouse Model of Epilepsy

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Introduction:

- Despite best medical management, 30% of epilepsy patients have refractory seizures and significant side effects to current antiepileptics¹.
- In an *in vitro* model of epilepsy, we recently showed that upregulation of glycolysis and LDHA were mediated by the AMPK/HIF1 α pathway
- In other CNS pathologies, HIF1 α activation leads to SUR1-TRPM4 channel upregulation.² This channel, also shown to upregulate during acute status epilepticus,³ may lead to further seizures through increased sodium conduction.

Objective:

- To determine SUR1-TRPM4 channel expression in a chronic epilepsy model.

Methods:

- Six mice were injected with an IP sub-convulsive dose (35mg/kg) of pentylenetetrazole (PTZ) every second day for 20 days to kindle seizures. Six control mice were injected with a PBS vehicle.
- Seizures were monitored behaviorally and electrographically with intracranial EEG.
- Immunohistochemistry labeling was performed on PTZ vs control brains for SUR1 and TRPM4.
- Cortical and hippocampal regions were imaged at 20X magnification, and cells meeting a 1.5X peak intensity threshold for both SUR1 and TRPM4 were quantified.

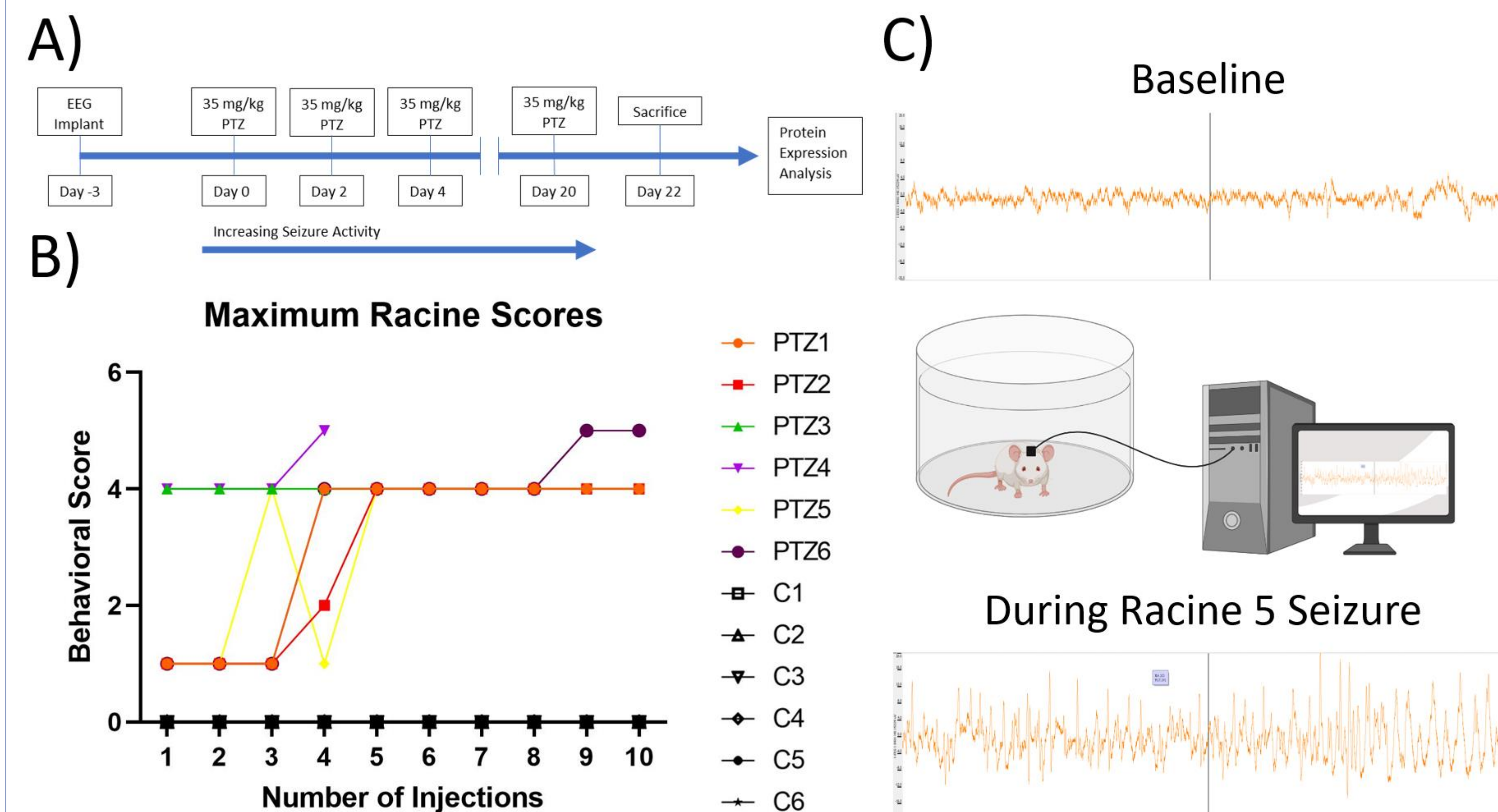


Figure 1. PTZ progressively lowers seizure threshold. A) Overview of experimental design B) Behavioral scoring of seizure phenotype over 10 PTZ injections shows progressively increased seizure scores with PTZ injections C) Representative EEG baseline vs seizure activity during a racine 5 seizure

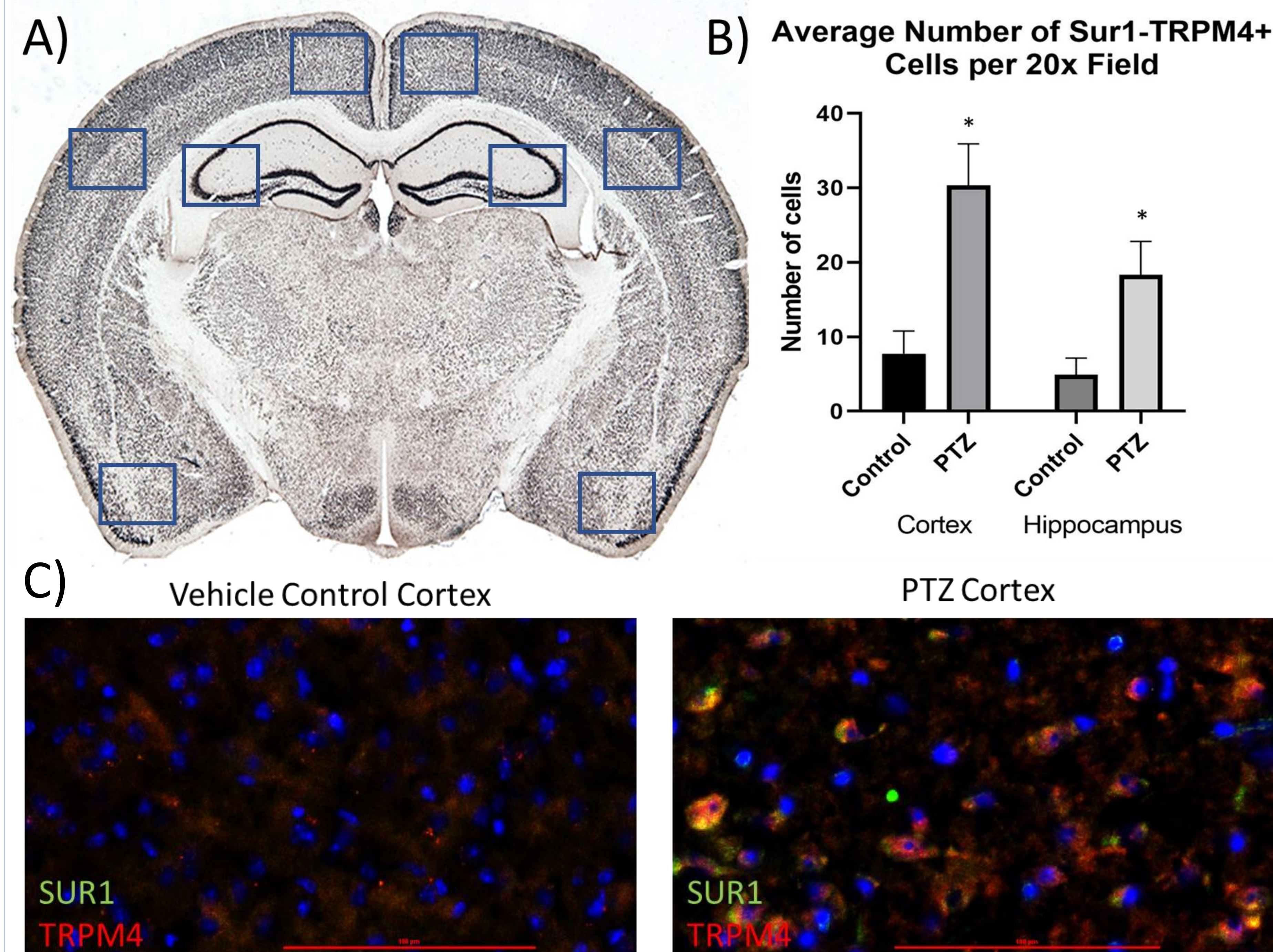


Figure 2. Immunohistochemical analysis of SUR1-TRPM4 expression after PTZ kindling. (A) Eight 675 μ M x 675 μ M regions of interest were analyzed for SUR1 and TRPM4 expression. (B) Cells meeting a 1.5X significance threshold were quantified. (B,C) In both the cortex and hippocampus, significantly more cells co-labeled for SUR1 and TRPM4 are present in PTZ mice compared to control.

Results:

- PTZ kindling causes a gradual increase in seizure response over the course of induction, as indicated by increase in Racine Score and presence of more frequent epileptic activity on EEG recordings.
- No control mice demonstrated behavioral or EEG evidence of seizure activity.
- PTZ-kindled mice demonstrated increased SUR1-TRPM4+ cell counts compared to vehicle controls. This result was statistically significant at $p < 0.05$ using two-tailed Student's T-Test in both the cortex ($p = 0.012$) and hippocampus ($p = 0.038$)

Conclusions:

- Similar to acute seizures, SUR1-TRPM4 channel expression is elevated in chronic epilepsy.
- Next, we aim to characterize the functional implications of SUR1-TRPM4 upregulation by determining whether this causes neuronal hyperexcitation and subsequently further seizures.
- Ultimately, our work aims to identify epilepsy-specific mechanisms that can be therapeutically targeted for chronic epilepsy management.

References:

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