UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

GRADUATE PROGRAM IN LIFE SCIENCES

SUR1-TRPM4 Upregulation is a Target for Chronic Seizure Management

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Introduction:

- Despite best medical management, 30% of epilepsy patients have refractory seizures and significant side effects to current antiepileptics[1].
- In an *in* vitro model of epilepsy, our lab recently showed that upregulation of glycolysis and LDHA were mediated by the AMPK/HIF1α pathway
- In other CNS pathologies, HIF1α 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 and contribution to seizures in a chronic epilepsy model.

Methods:

- Mice were injected with an IP sub-convulsive dose (35mg/kg) of GABA antagonist pentylenetetrazole (PTZ) or PBS control every second day for 20 days.
- For mRNA and protein analysis, *in situ* hybridization and immunohistochemistry (ISH+IHC) were performed for SUR1 and TRPM4 on PTZ vs PBS kindled mice. Imaging and quantification were then performed.
- Separately, mice were given daily SUR1 inhibitor glyburide (GLY) (30ug) during PTZ kindling. Furthermore, after kindling, mice were given 10 days of GLY followed by PTZ challenge dose.

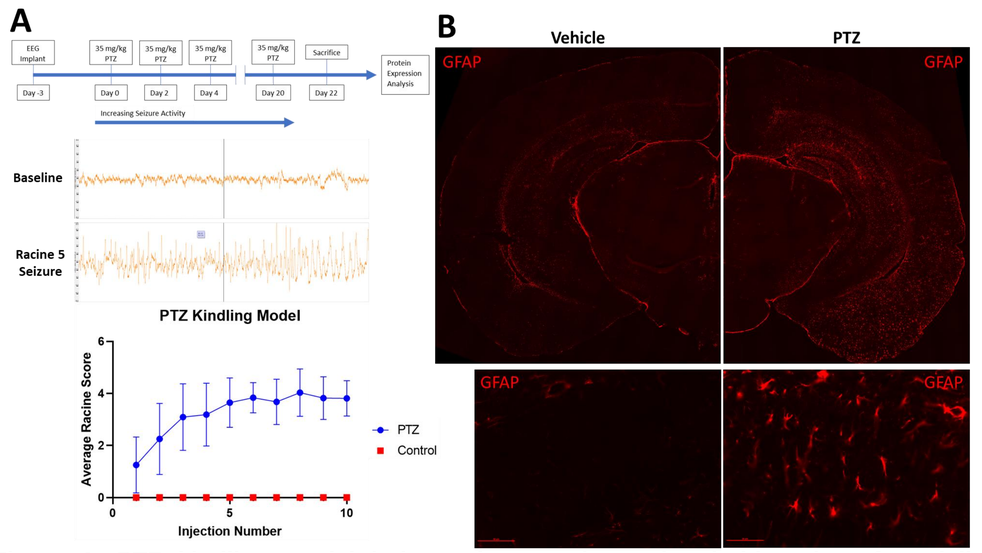

Figure 1. PTZ kindling model induces lower seizure threshold and preferentially impacts the hippocampus and temporal cortex.

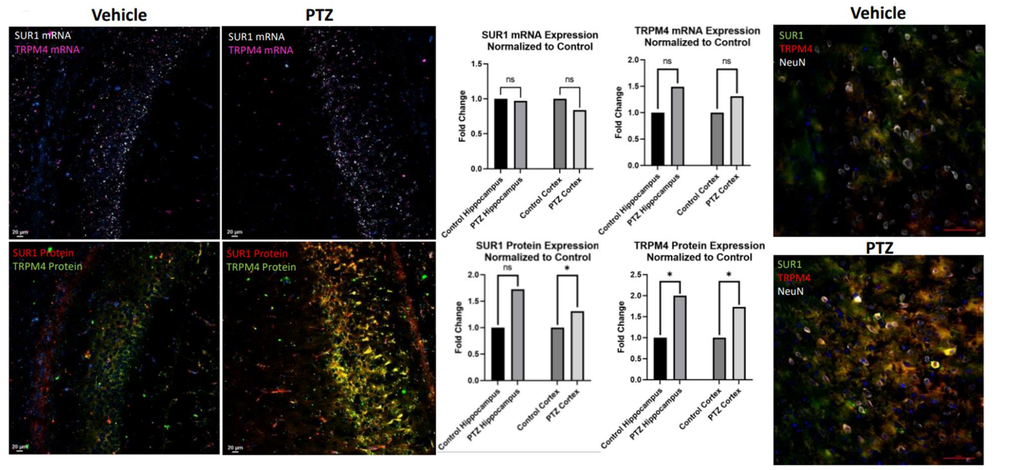

Figure 2. SUR1-TRPM4 protein expression is upregulated in neurons after PTZ kindling.

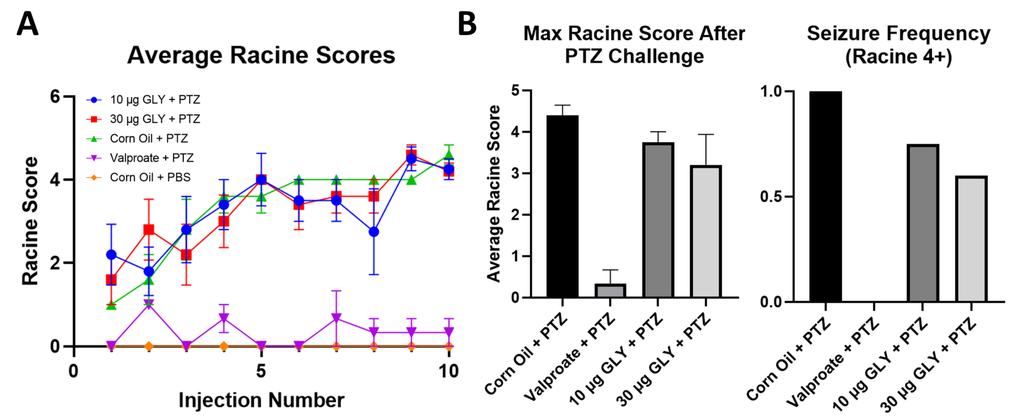

Figure 3. SUR1-TRPM4 inhibitor GLY does not affect PTZ kindling induction but partially attenuates seizure formation after long-term treatment.

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.
- In PTZ susceptible brain regions (hippocampus and cortex), neurons of PTZ kindled mice demonstrated increased SUR1-TRPM4 expression compared to vehicle controls. This result was statistically significant at $p<0.05$ using two-tailed Student's T-Test.
- PTZ kindling induction was not affected by daily GLY administration. However, PTZ-kindled mice receiving long term GLY treatment demonstrate reduced seizure phenotype after PTZ challenge.

Conclusions:

- Similar to acute seizures, SUR1-TRPM4 channel expression is elevated in chronic epilepsy.
- SUR1-TRPM4 inhibition was demonstrated to reduce seizures in a mouse model of chronic epilepsy.
- Ultimately, our work aims to identify epilepsy-specific mechanisms that can be therapeutically targeted for chronic epilepsy management.

References:

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