SCN1A epilepsy: new treatments

Cleveland Clinic Genetics of Epilepsy Conference
September 13th, 2020

Andrew Escayg, Ph.D.
Dept. of Human Genetics
Emory University

SCN1A mutations cause GEFS+ and Dravet

Genetic epilepsy with febrile seizure plus (GEFS+)	Dravet Syndrome
Inherited	De novo
• Febrile seizures >6 years • Adult afebrile epilepsy • Clinically variable within a family	• Complex, prolonged febrile seizures • Afebrile severe seizures • Moderate-severe ID • Ataxia • 15-20% mortality
Amino acid substitutions	All types
Altered channel properties	Loss-of-function
Treatment responsive	Treatment resistant

Recent treatments for *SCN1A*-derived epilepsy

- **Stiripentol**

Myers et al., 2018, *Developmental Medicine and Child Neurology*
Stiripentol efficacy and Safety in Dravet syndrome: a 12-year observational study

- **Low dose fenfluramine**

Lagae et al., 2019, *Lancet*
Fenfluramine hydrochloride for the treatment of seizure in Dravet syndrome: a randomized, double-blind, placebo-controlled trial

- **Cannabidiol**

Miller et al., 2020, *JAMA Neurology*
Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo
on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial

Exploring alternative treatments for *SCN1A* epilepsy

- Nanoparticle-encapsulated oxytocin

- Modulation of the cannabinoid 2 receptor (CB2R)

Escayg Laboratory

Escayg Laboratory
Jennifer Wong, Ph.D.
Lindsey Shapiro
Kari Mattison
Thomas Shiu
Samantha Reed
Jordan Owyoung

George Inglis, Ph.D.
Noor Badshah

Collaborators
Kevin Murnane, Ph.D,
Martin D'Souza, Ph.D.
Clementina Manera, PhD

Funding
NIH-NINDS

Exploring the use of neuropeptides for the treatment for *SCN1A* epilepsy

Oxytocin (OT)

- Increases neuronal inhibition
- OTRs are expressed in discrete brain regions and circuits
- Pro-social behavior
- Neuroprotective and anti-inflammatory properties

Barriers to clinical use of neuropeptides

- Poor blood-brain-barrier penetrance

- Rapidly metabolized

Nanoparticle encapsulation of oxytocin

Oppong-Damoah et al., 2019, *Horm. Behav.*

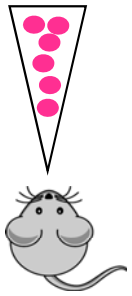
- Nanoparticle encapsulation increases the brain penetrance and duration of action of intranasal oxytocin

Zaman et al., 2018, *Int. J. Pharm.*

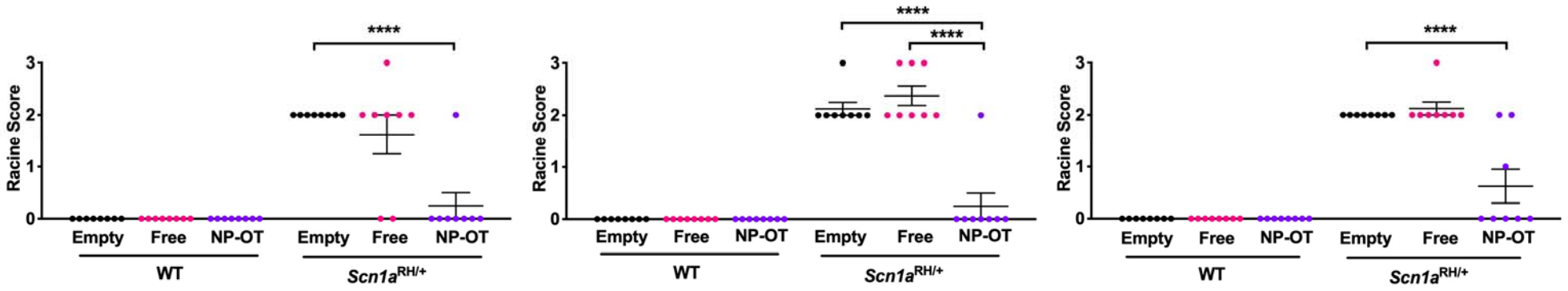
- Nanoparticle formulations that allow for sustained delivery and brain targeting of the neuropeptide oxytocin

Rabies virus glycoprotein (RVG)-conjugated BSA nanoparticles

Kevin Murnane, Ph.D.
Martin D'Souza, Ph.D.



NP-OT significantly increases and sustains resistance to 6 Hz-induced seizures in RH/+ mutants



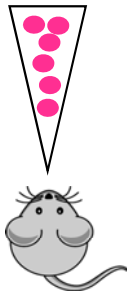
20 minutes | 2 Hours | 6 Hours

- Nanoparticle encapsulation improves BBB penetrance
- Provides sustained release and seizure protection

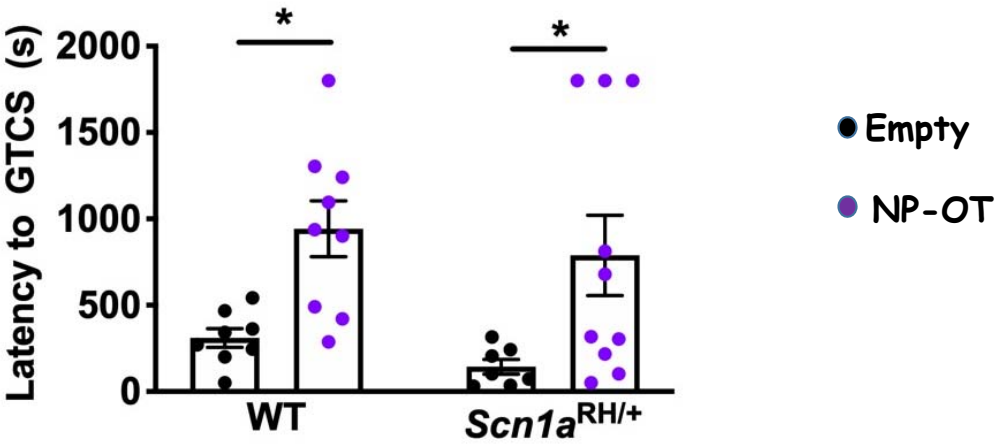
N = 8/group

100 μg OT

Wong et al. Under review



NP-OT significantly increases resistance to PTZ-induced seizures



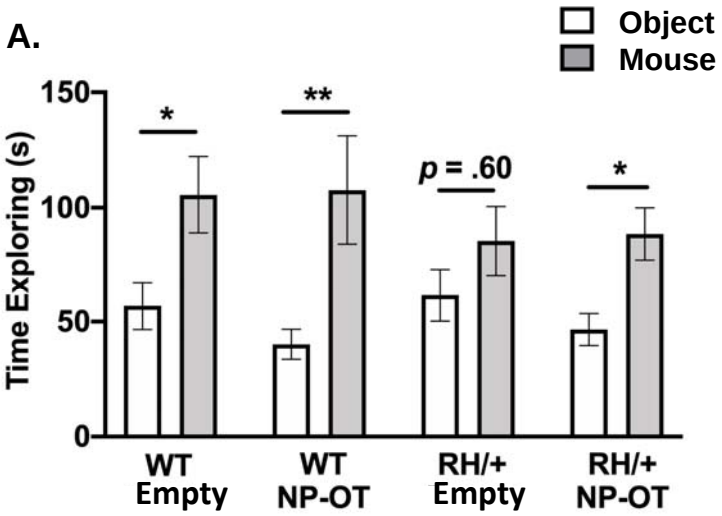
Mutant and WT mice were protected

100 μg OT

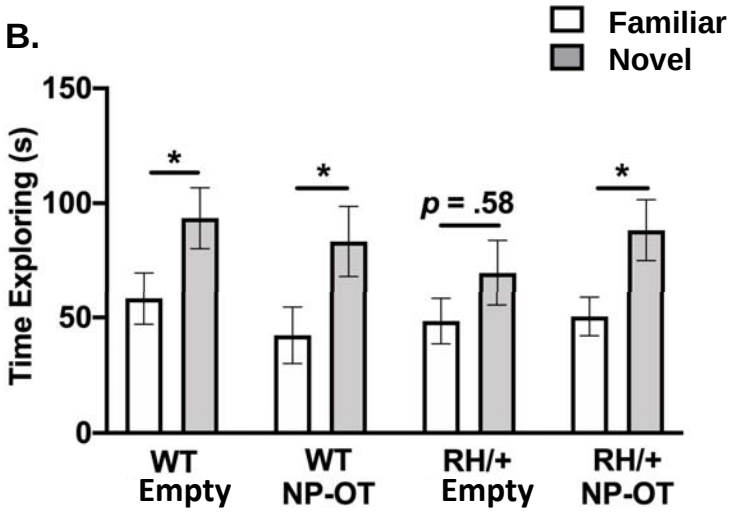
WT	*Scn1a*$^{RH/+}$
Empty: *N* = 8	Empty: *N* = 7
NP-OT: *N* = 9	NP-OT: *N* = 10

Wong et al. Under review

NP-OT restores normal social behavior in RH/+ mutants

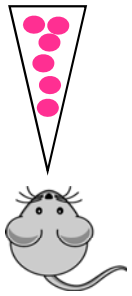


Sociability

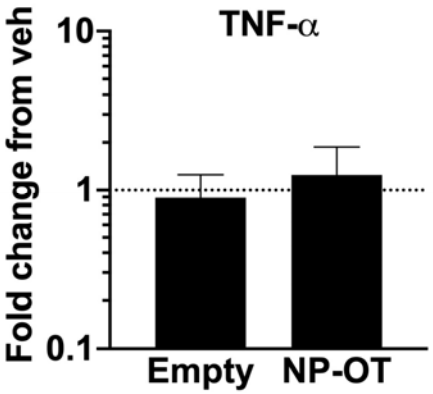


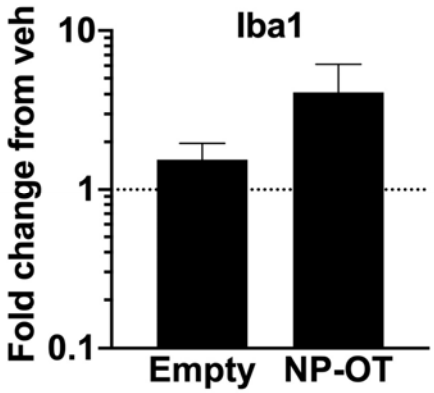
Social discrimination

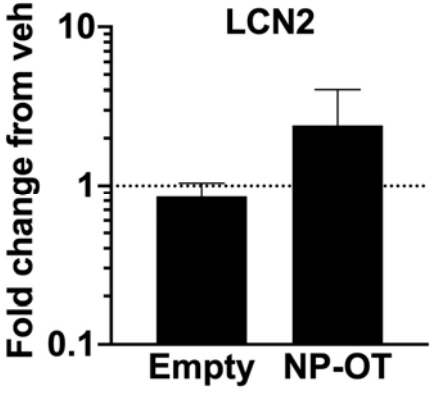
Wong et al. Under review

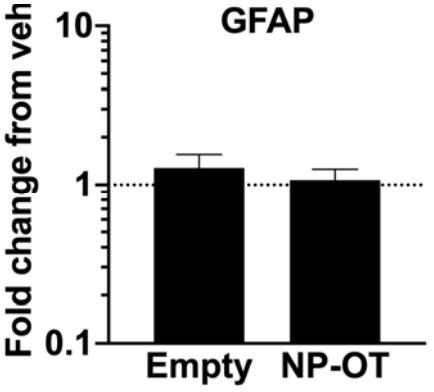


Repeated NP-OT administration does not elicit an inflammatory response









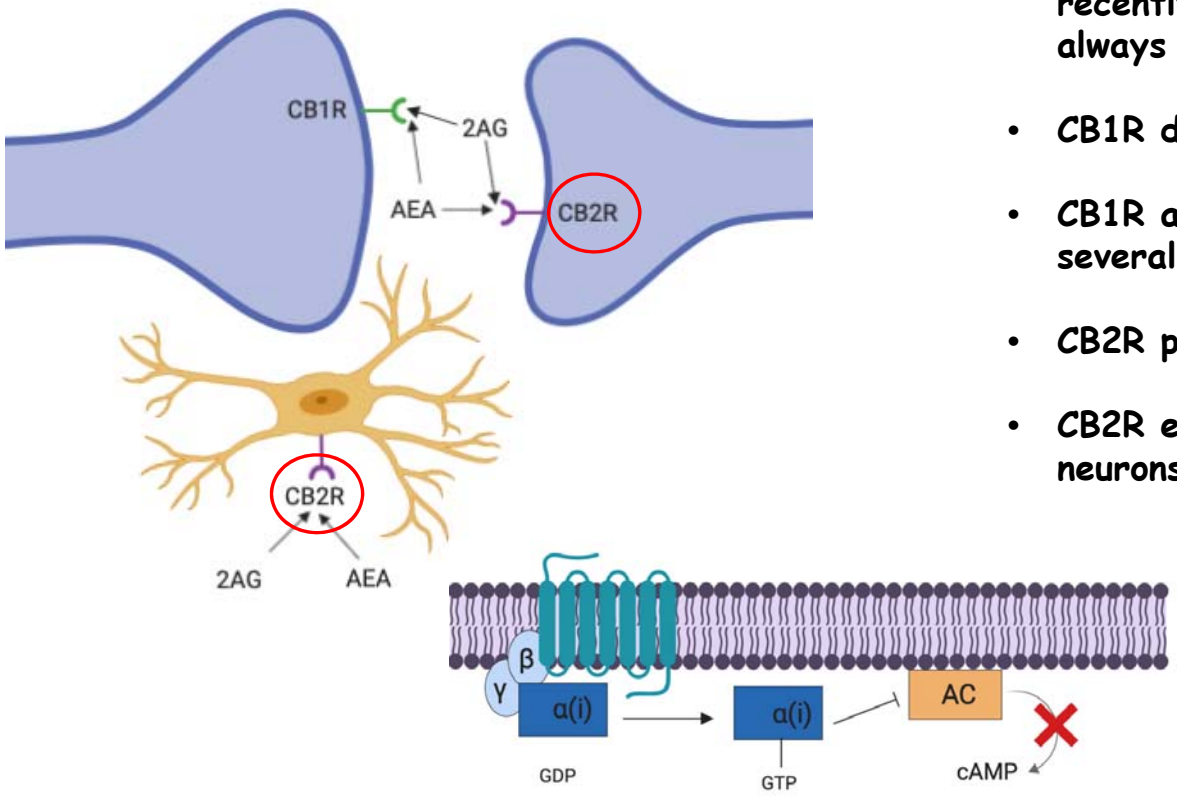
NP-OT (100 μg OT) was administered for 5 days in CF1 WT mice and sacrificed 24H after the last administration

N = 4-5/group

Wong et al. Under review

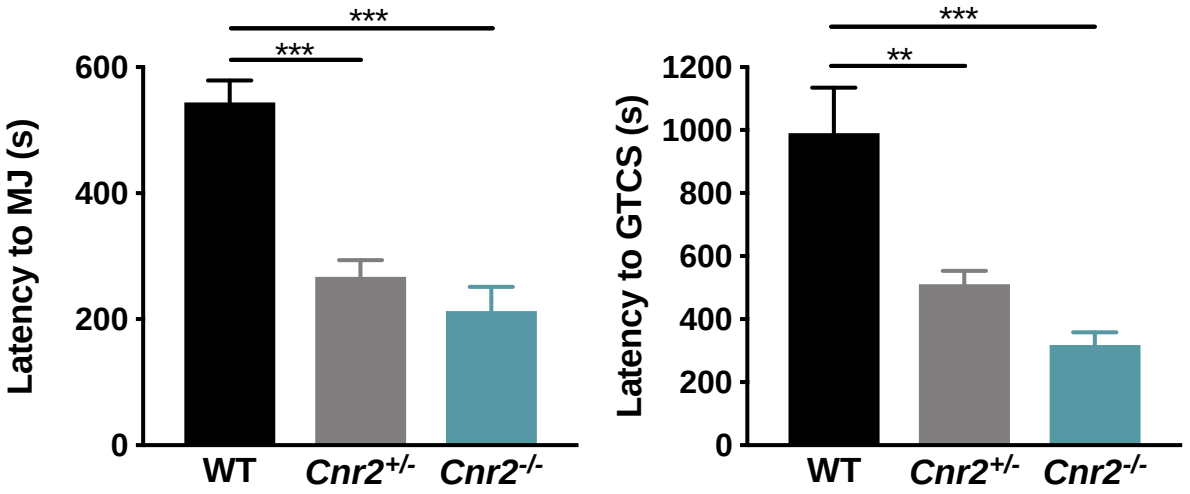
Modulation of CB2 cannabinoid receptors in *SCN1A*-derived epilepsy

The Endocannabinoid System (ECS)



- System in the brain on which marijuana acts
- Cannabidiol, an exogenous ligand, recently FDA approved but not always effective
- CB1R densely expressed on neurons
- CB1R activation accompanied by several psychotropic side effects
- CB2R predominantly on microglia
- CB2R expressed at low levels in neurons but highly inducible

CB2R knockout mice are more susceptible to PTZ-induced seizures

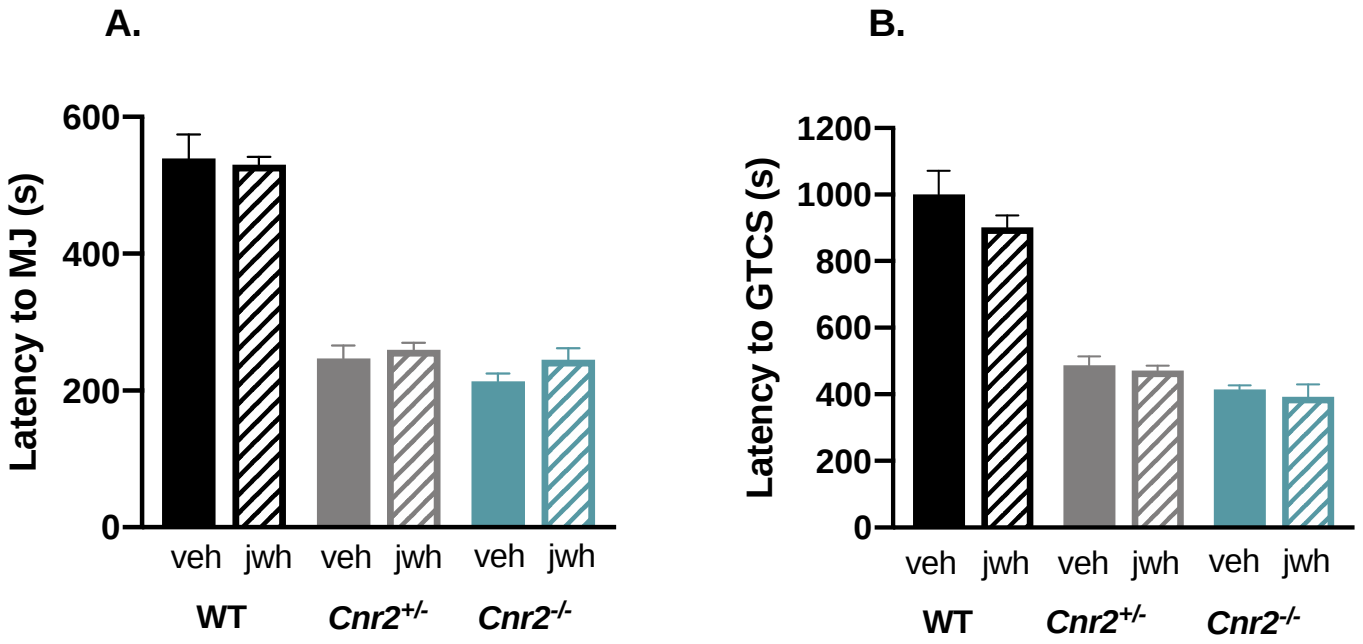


N= 8/group

Shapiro et al., 2019, *Epilepsia*

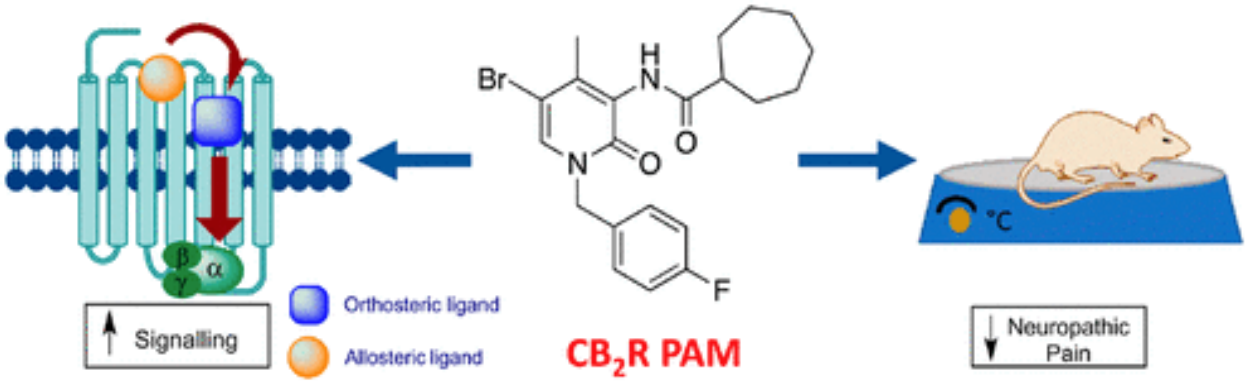
Reduced cannabinoid 2 receptor activity increases susceptibility to induced seizures in mice

The CB2R agonist JWH-133 did not increase resistance to PTZ-induced seizures



Shapiro et al. , 2019), *Epilepsia*

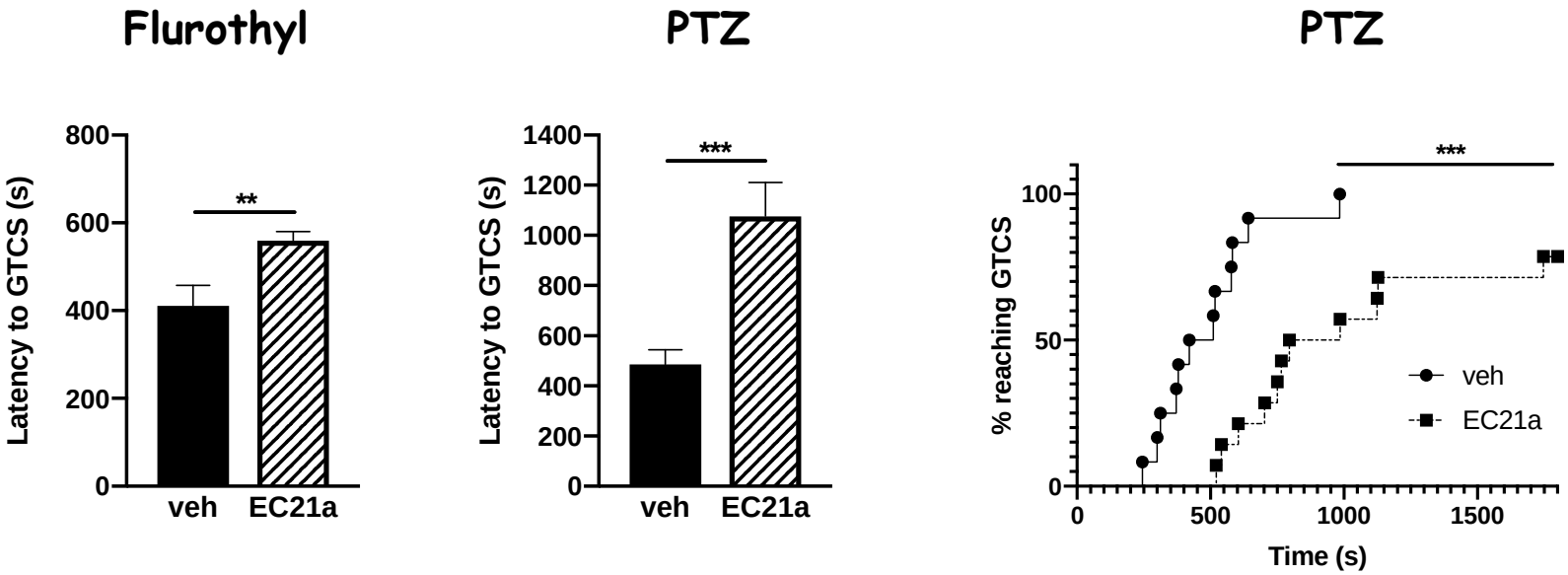
Ec21a: a CB2R positive allosteric modulator (PAM)



- Ec21a *only* has effect in the presence of orthosteric ligand
- More agonist binds in presence of Ec21a
- Agonist stays bound longer in presence of Ec21a

Gado, et al., 2019, J Med Chem (Clementina Manera)

Ec21a confers seizure resistance in CF1 WT mice



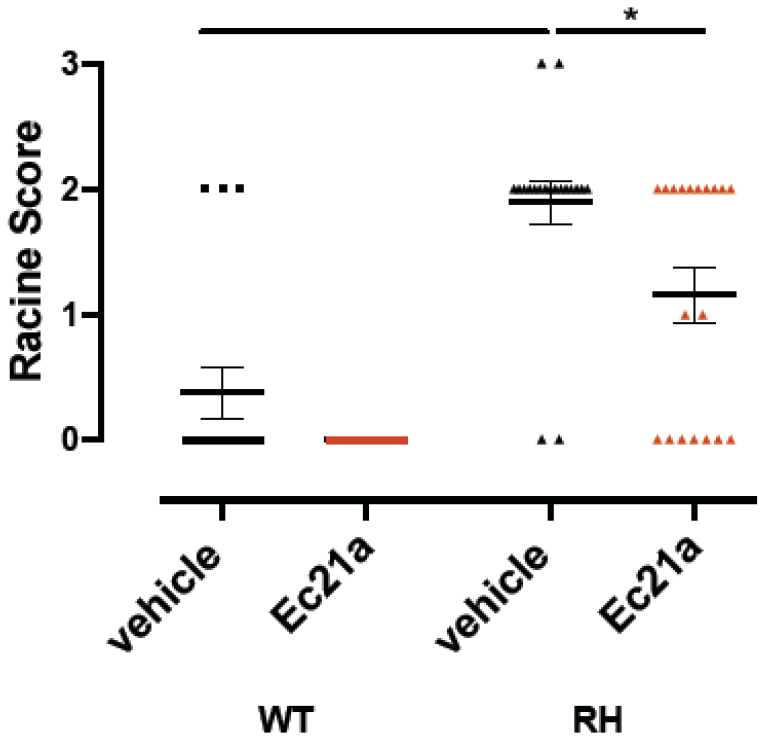
Ec21a – 10 mg/kg

N=9-12/group

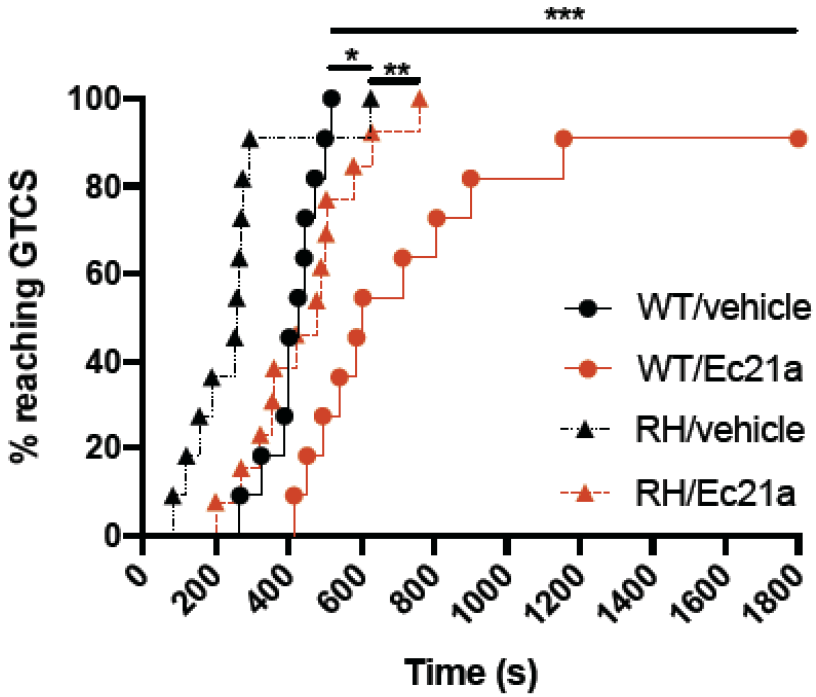
Shapiro et al. Under review

Ec21a is seizure protective in *Scn1a* RH/+ mutant mice

6 Hz



PTZ



Ec21a - 10 mg/kg

N=11-13/group

Shapiro et al. Under review

SUMMARY

- NP-OT provides robust and sustained protection against induced seizures
- Actively applying to other neuropeptides
- CB2R modulation confers seizure protection
- CB2R modulation might provide greater efficacy in chronic models