



Redefining Drug Discovery Through Innovation

Preclinical Models of Seizure and Tremor in Mice

Preclinical Models

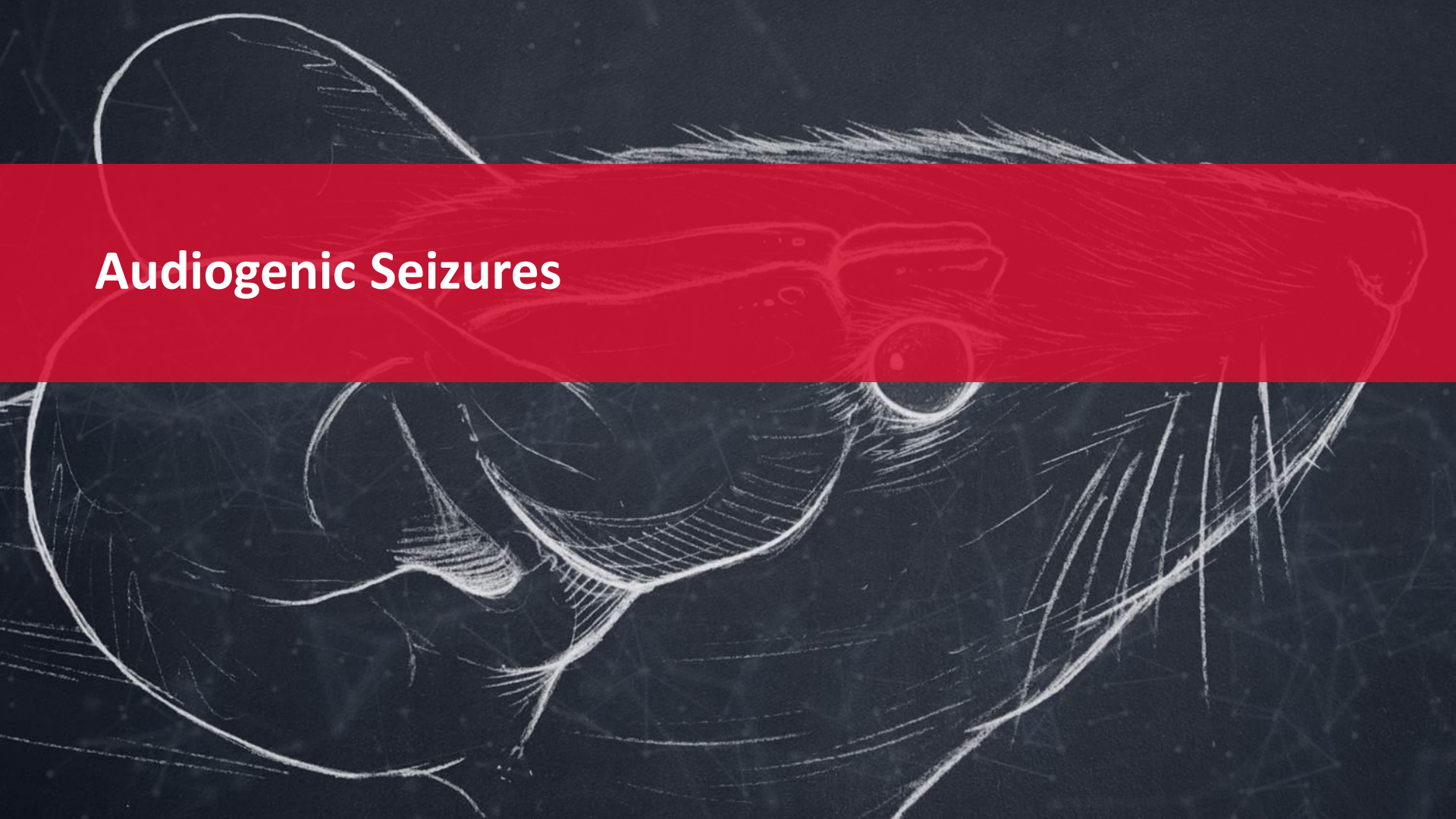
- Audiogenic seizures
- Chemical Induced Seizure
- Electroshock – induced seizure
 - Maximal Electroshock
 - 6Hz
- Harmaline-induced tremors





Redefining Drug Discovery Through Innovation

Audiogenic Seizures



Audiogenic seizures

- Fragile X (FMR1) KO mice are tested at 3 weeks of age
- Mice are individually placed in a Plexiglas chamber and allowed to explore for 15 sec. They are then exposed to a 125 dB tone for 2 minutes, followed by 1 minute of no sound, and then a repeat 2 minute tone. The mice are scored based on their response, latency, and seizure intensity:

0: no response

1: wild running and jumping

2: clonic seizures

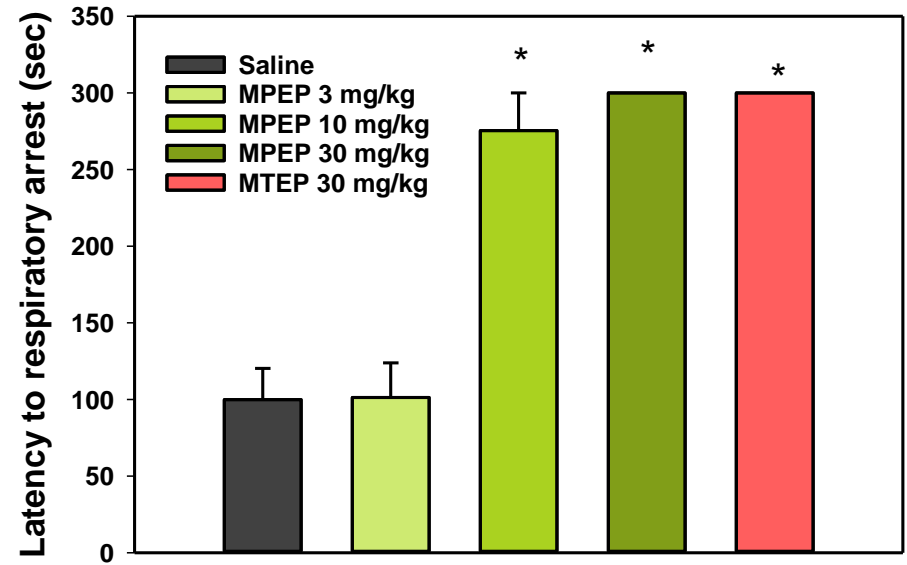
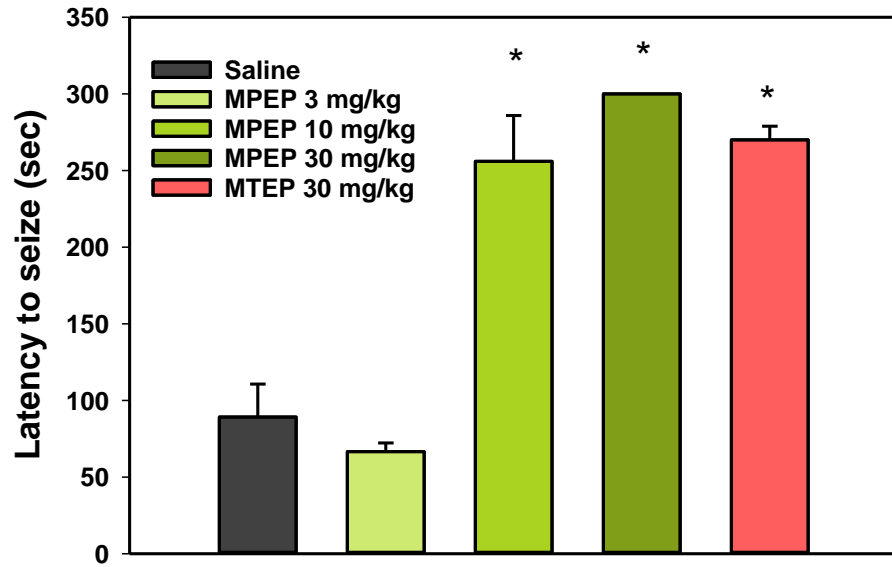
3: clonic/tonic seizures

4: tonic seizures

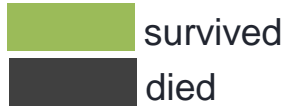
5: respiratory arrest



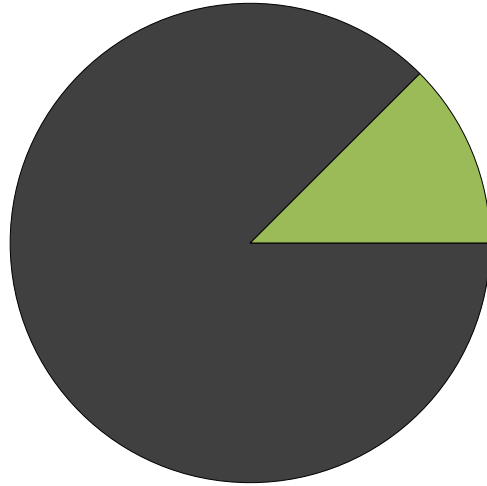
Effects of MPEP and MTEP on audiogenic seizures



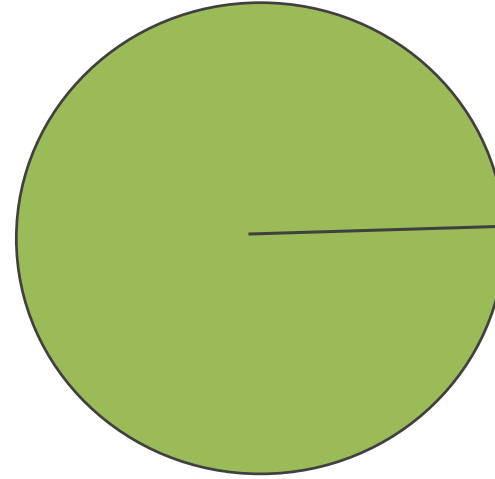
Effects of MPEP and MTEP on survival



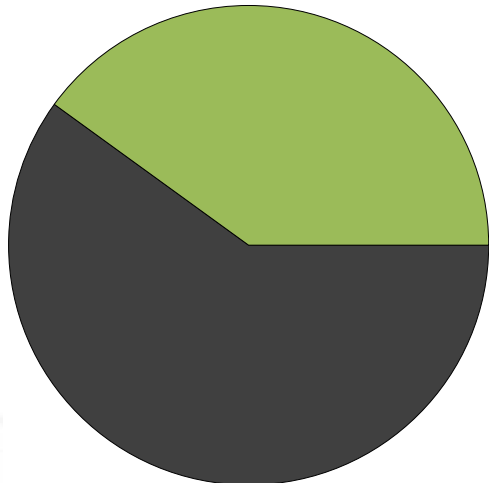
Vehicle



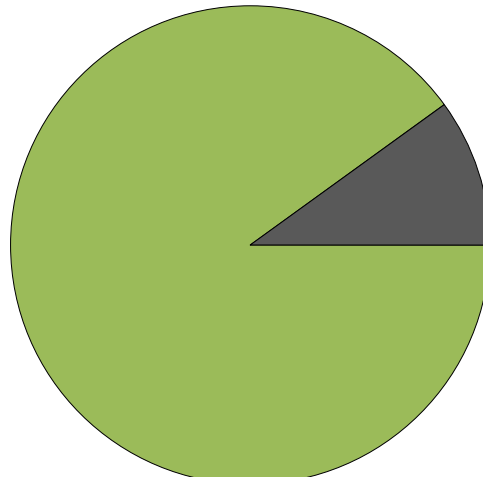
MTEP (30 mg/kg)



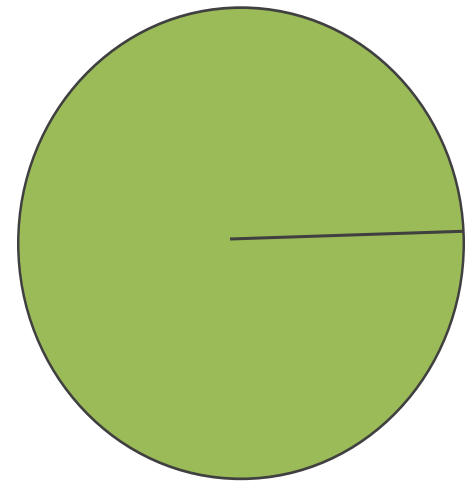
MPEP 1 mg/kg



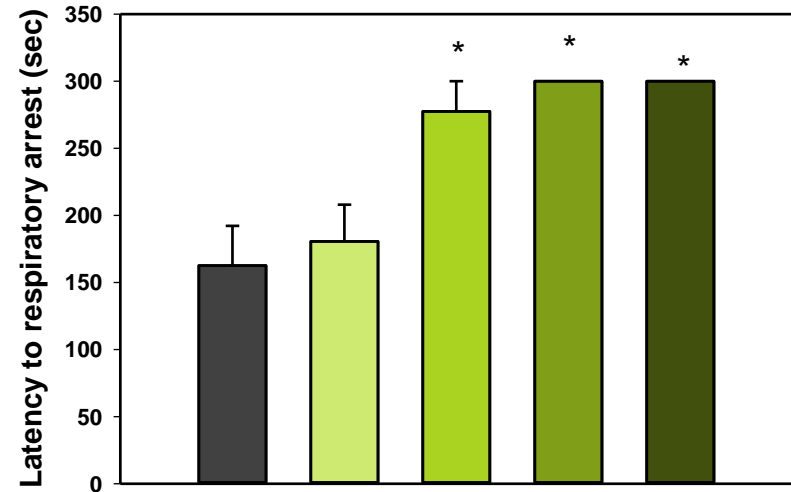
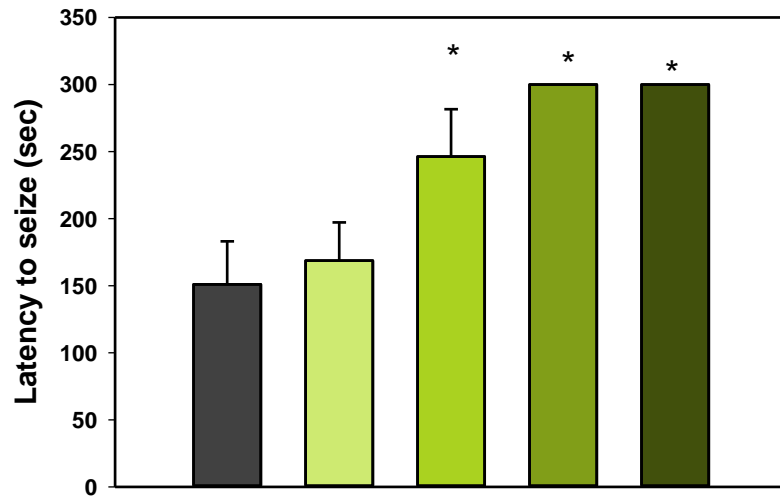
3 mg/kg



30 mg/kg

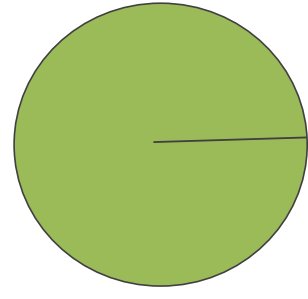
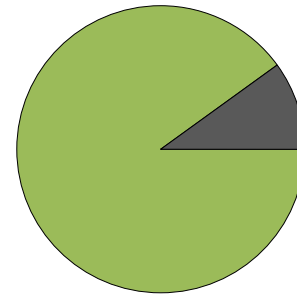
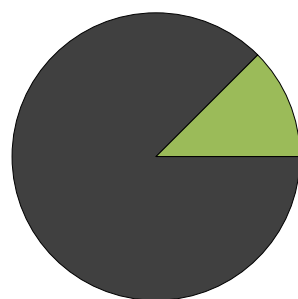
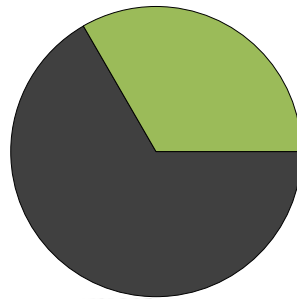
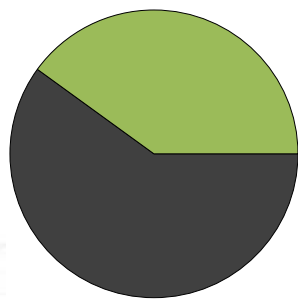


Effects of diazepam on audiogenic seizures



Vehicle
 Diazepam 0.03 mg/kg
 Diazepam 0.1 mg/kg
 Diazepam 0.3 mg/kg
 Diazepam 1 mg/kg

survived
 died



Diazepam 0

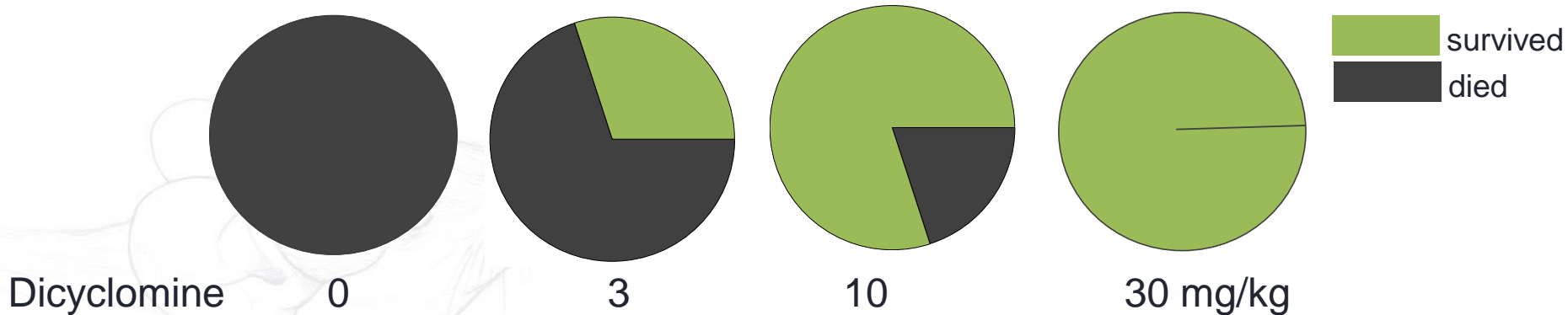
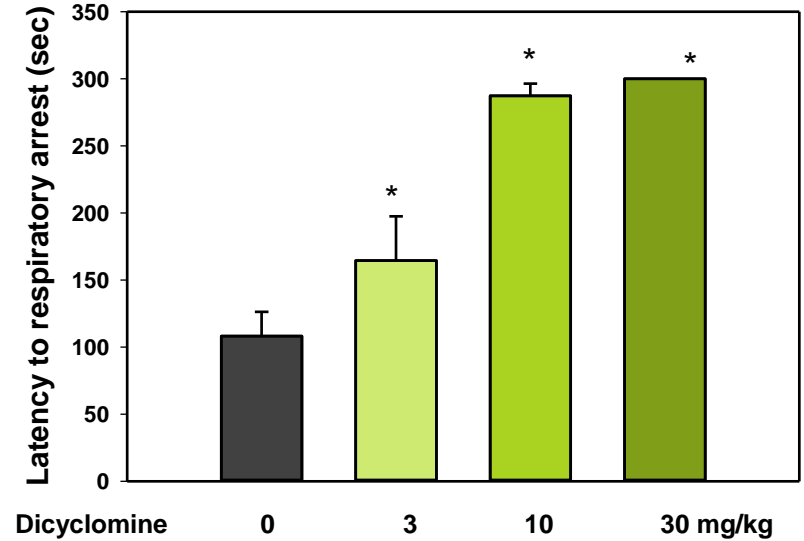
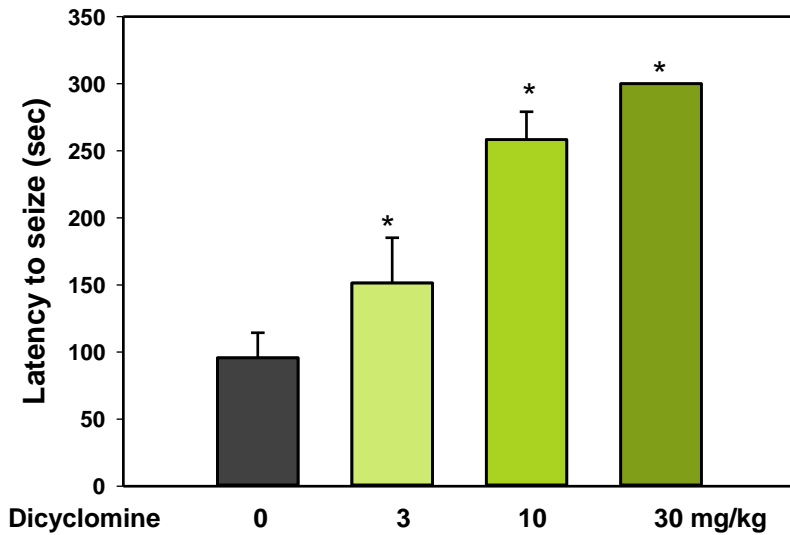
0.03

0.1

0.3

1 mg/kg

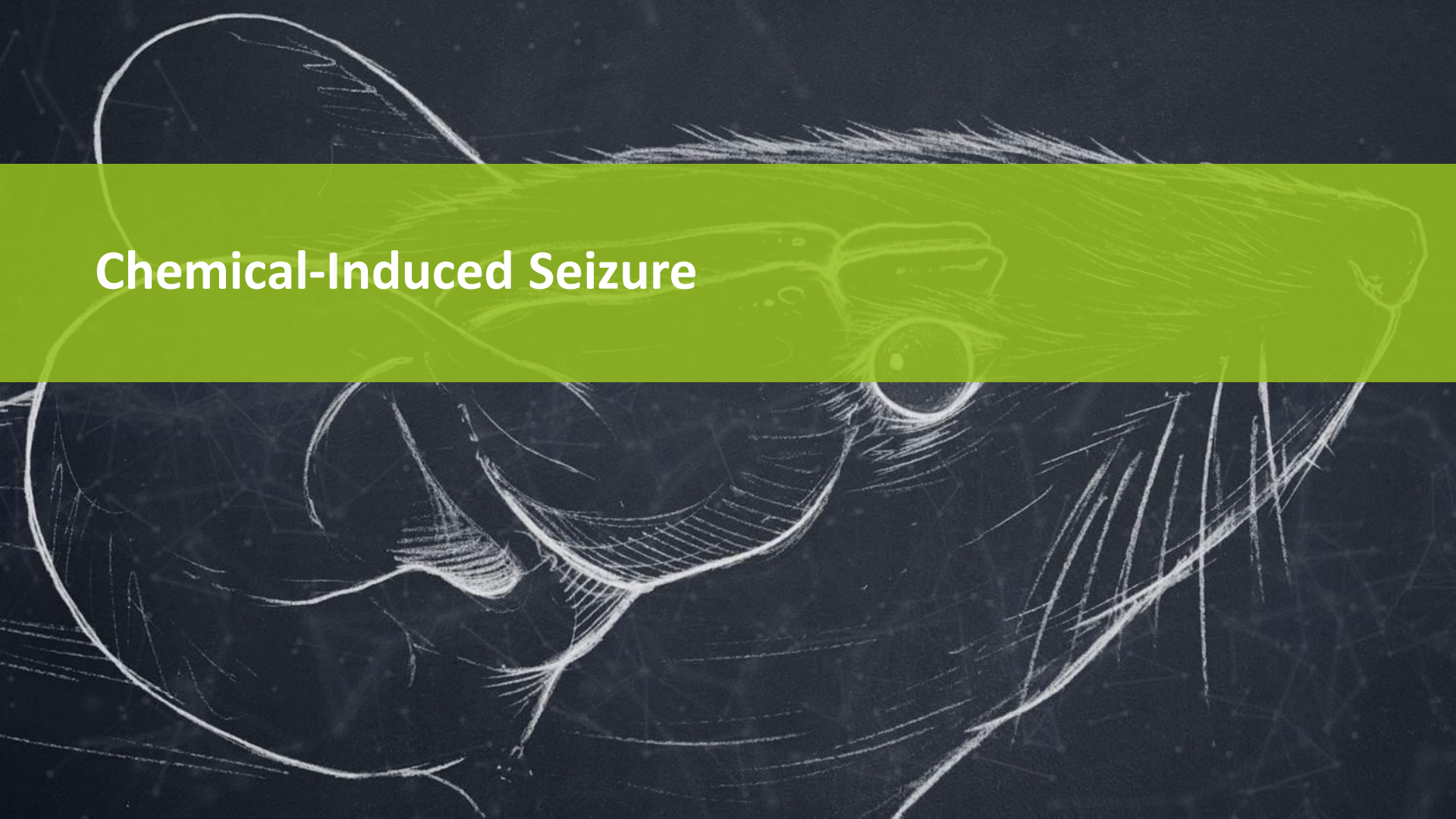
Effects of dicyclomine on audiogenic seizures





Redefining Drug Discovery Through Innovation

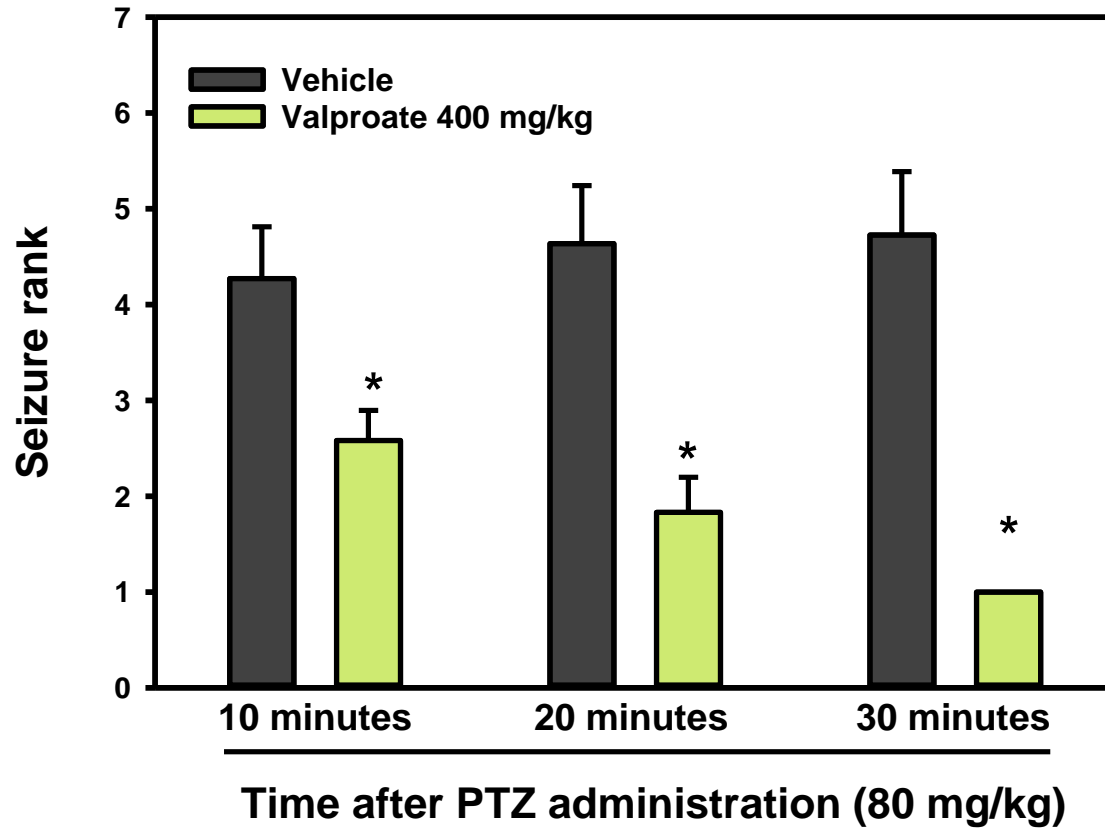
Chemical-Induced Seizure



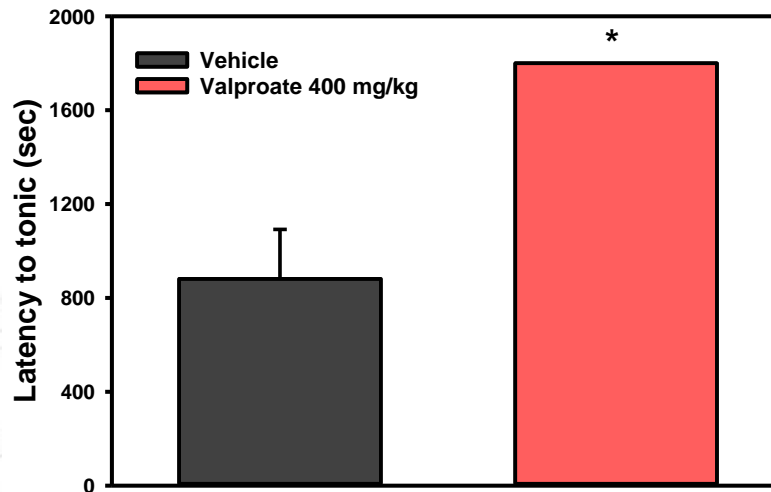
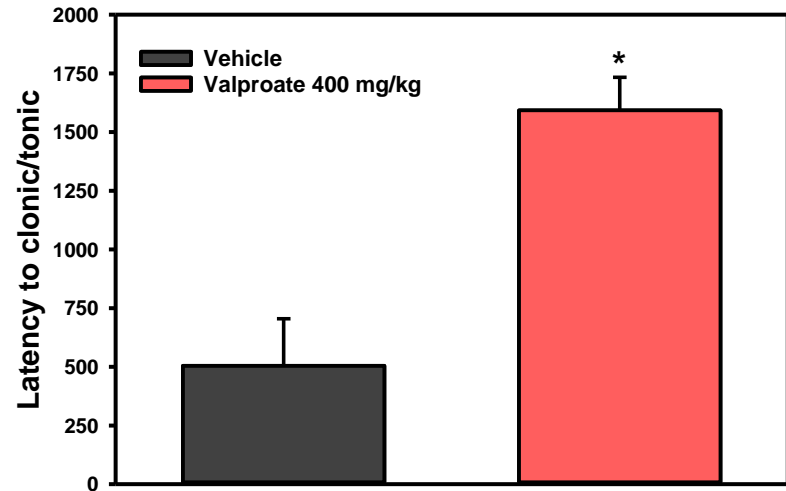
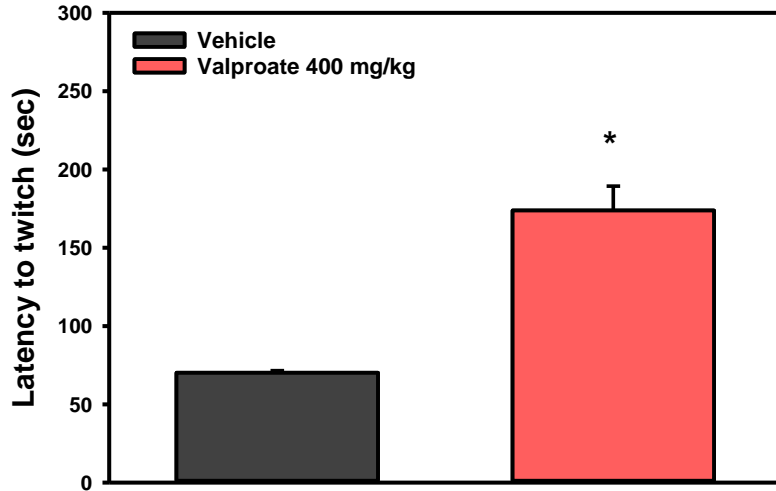
Methods

- Mice are injected PTZ and observed for 30 minutes
- Seizures are ranked as follow
 - Rank 0 = No motor seizure
 - Rank 1 = Staring, move into prone posture, ears flattened, mouth or facial movement, slight tremor, small movements, slight intermittent twitch, tail elevated, increased respiration, ataxia
 - Rank 2 = Prone, immobility, hindlimb splay, increased tremor intensity, absence seizure, ataxia, head nod/bow, isolated body twitches, straub or elevated tail, tail wag
 - Rank 3 = Slight clonic/tonic seizures less than 5 sec duration, muscle fasciculation, straub tail, tonic praying seizure; salivation
 - Rank 4 = Rearing, pawing, chomping, head bow, head arch, salivation, absence seizure, praying seizure, trumpet seizure, pop seizure, clonic/tonic seizure with increased frequency and duration
 - Rank 5 = clonic/tonic seizure greater than 5 sec duration with loss of righting reflex
 - Rank 6 = crazy seizure, tonic seizure with extension of hindlimbs; death

Valproate Attenuates PTZ-Induced Seizures

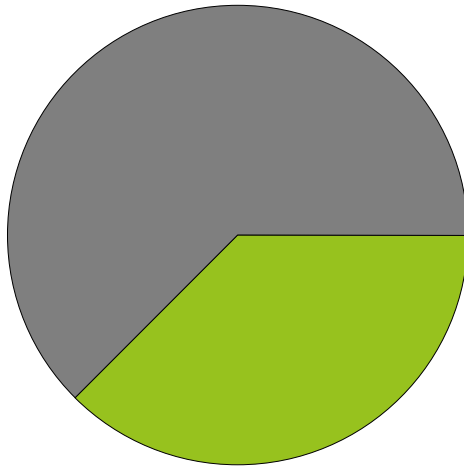


Valproate Increases the Latency to Seizure

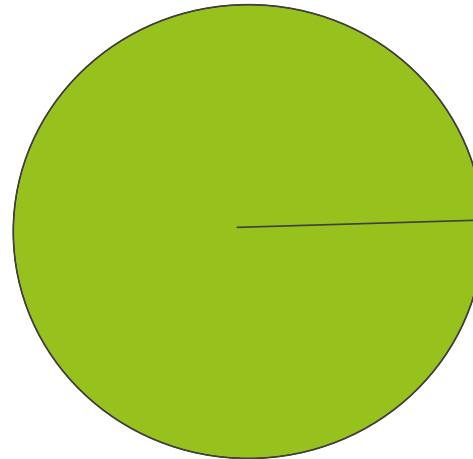


Valproate Increases Survival

Vehicle



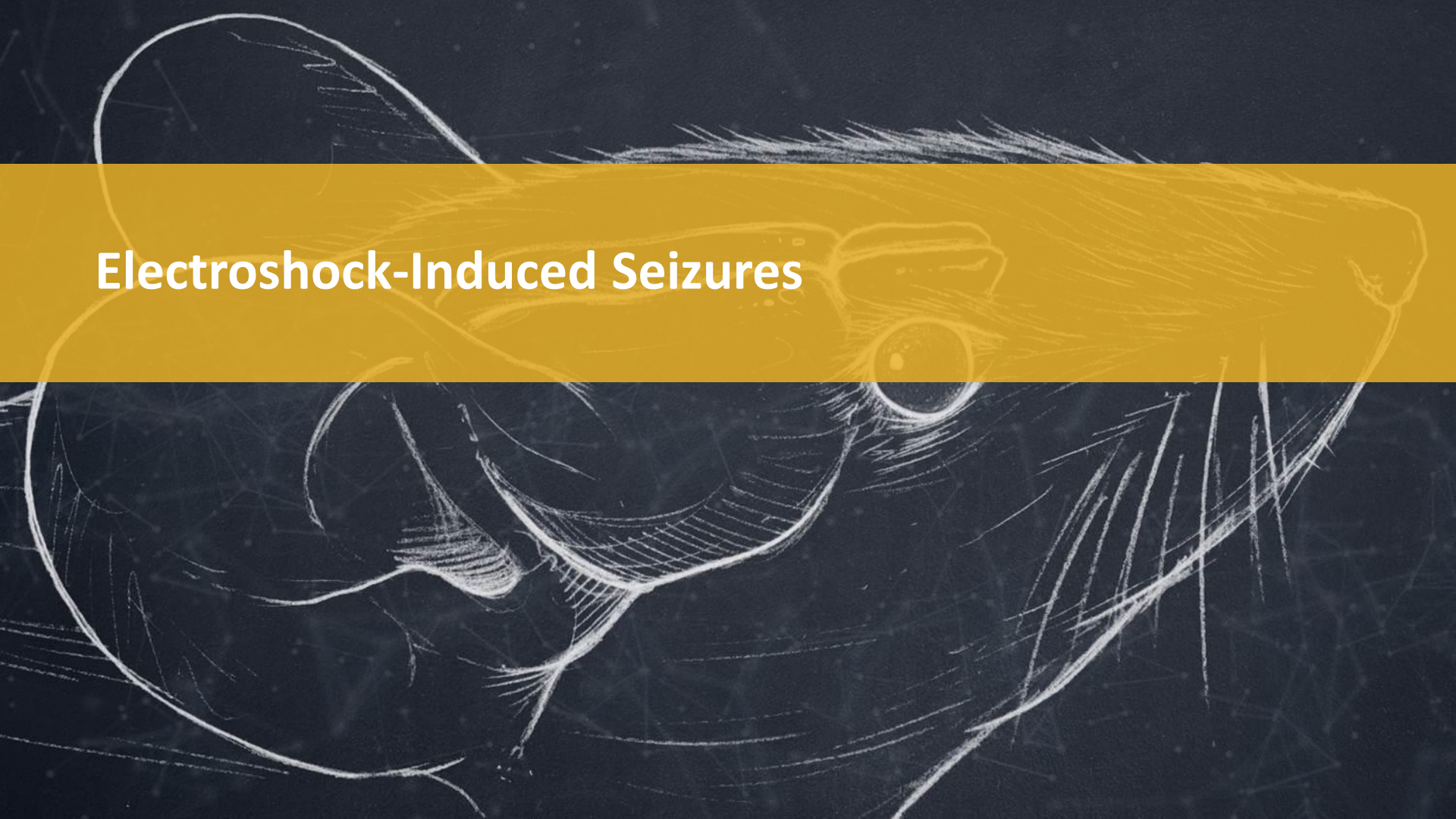
VPA 400 mg/kg





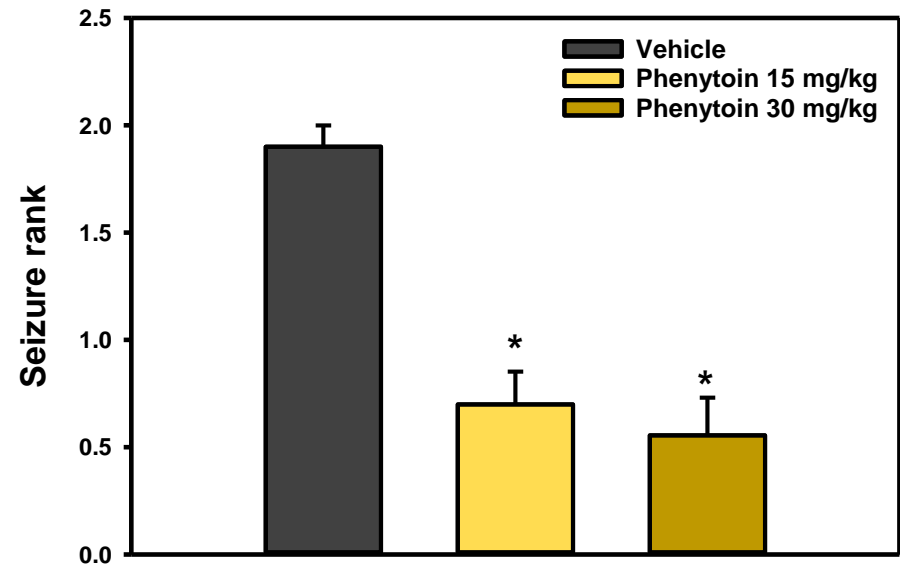
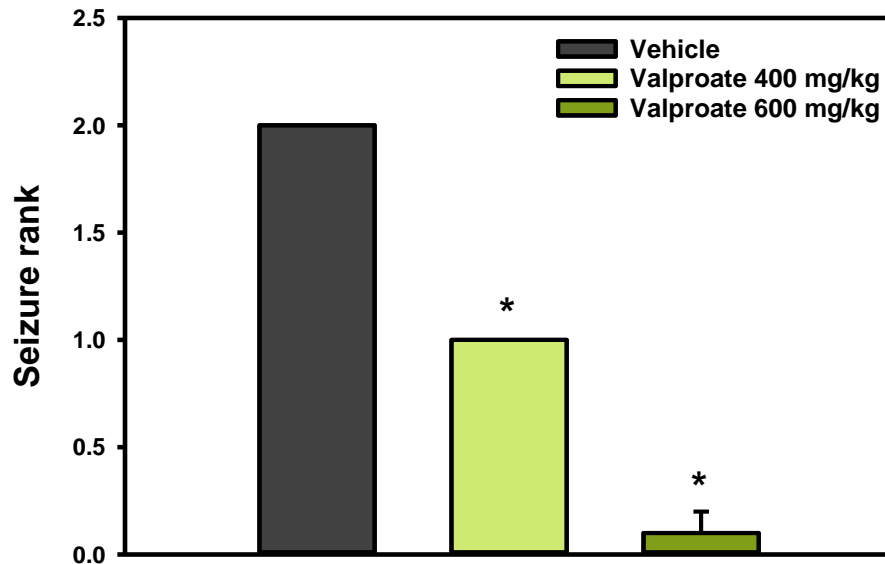
Redefining Drug Discovery Through Innovation

Electroshock-Induced Seizures



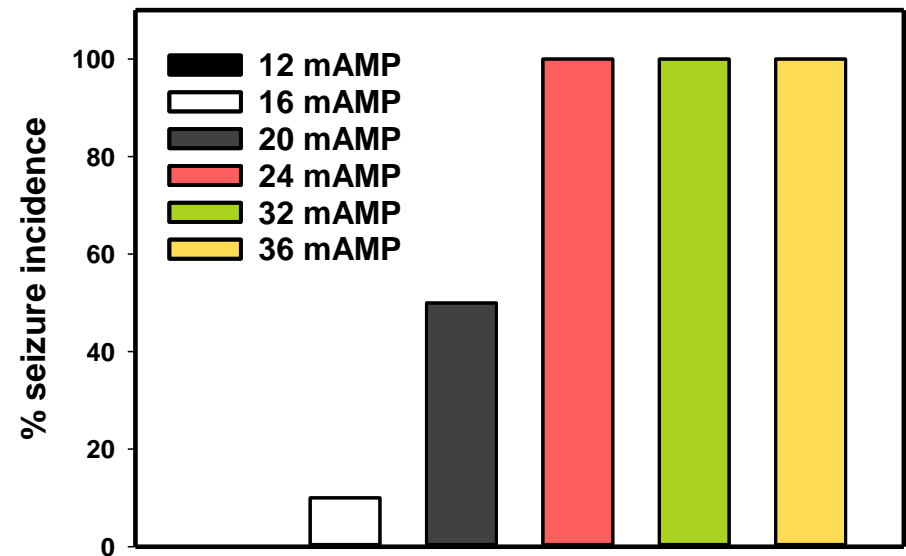
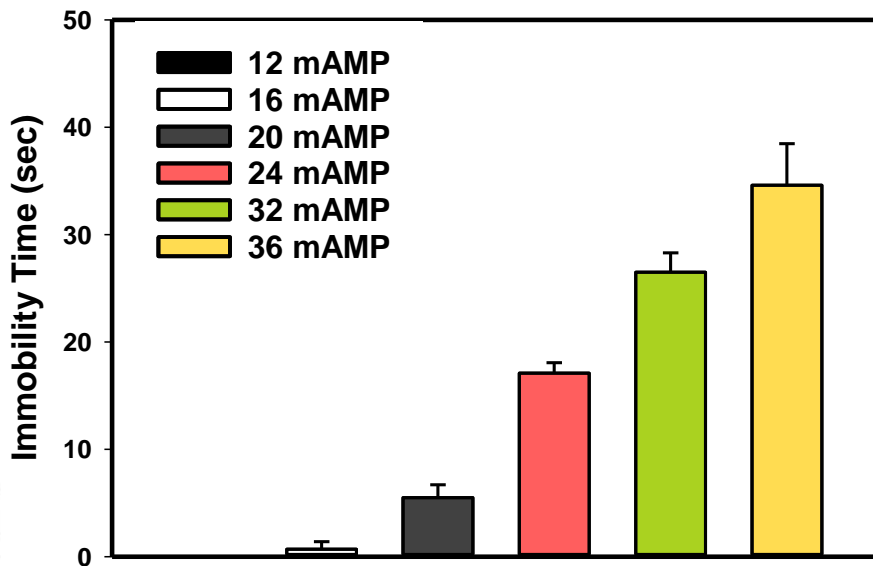
Valproate and Phenytoin Decrease Shock-Induced Seizures

- 129SVEV mice are used. Seizures are scored following corneal stimulation:
 - Rank 1: Clonic/tonic seizures
 - Rank 2: Full tonic hindlimb seizures

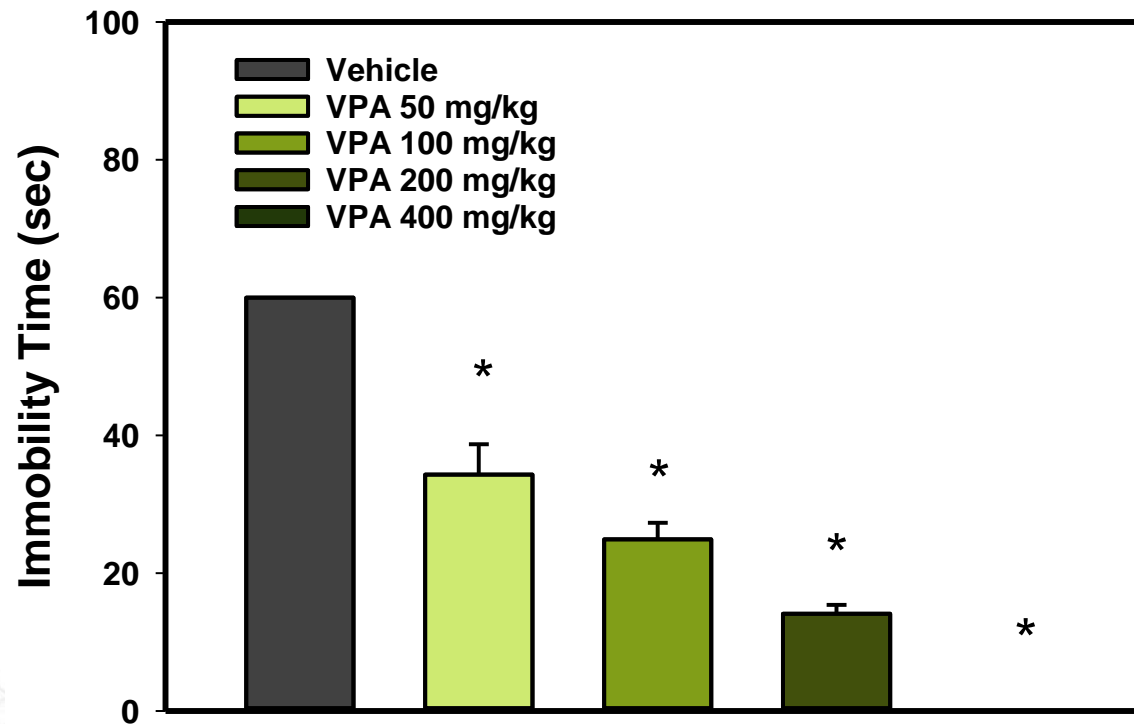


6 Hz

- CF1 mice Mice stimulated via the cornea using a corneal probe. A drop of Tetracaine HCl 0.5% in saline is administered in each eye prior to stimulation.
- Animals are observed for 1 minute post-stimulation
- The main seizure end point is the duration of immobility.
 - Mice resuming normal behavior within 7 s after the end of the stimulation are considered as not displaying seizure behavior.
 - Additional measures such as seizure scoring and related behaviors were recorded.



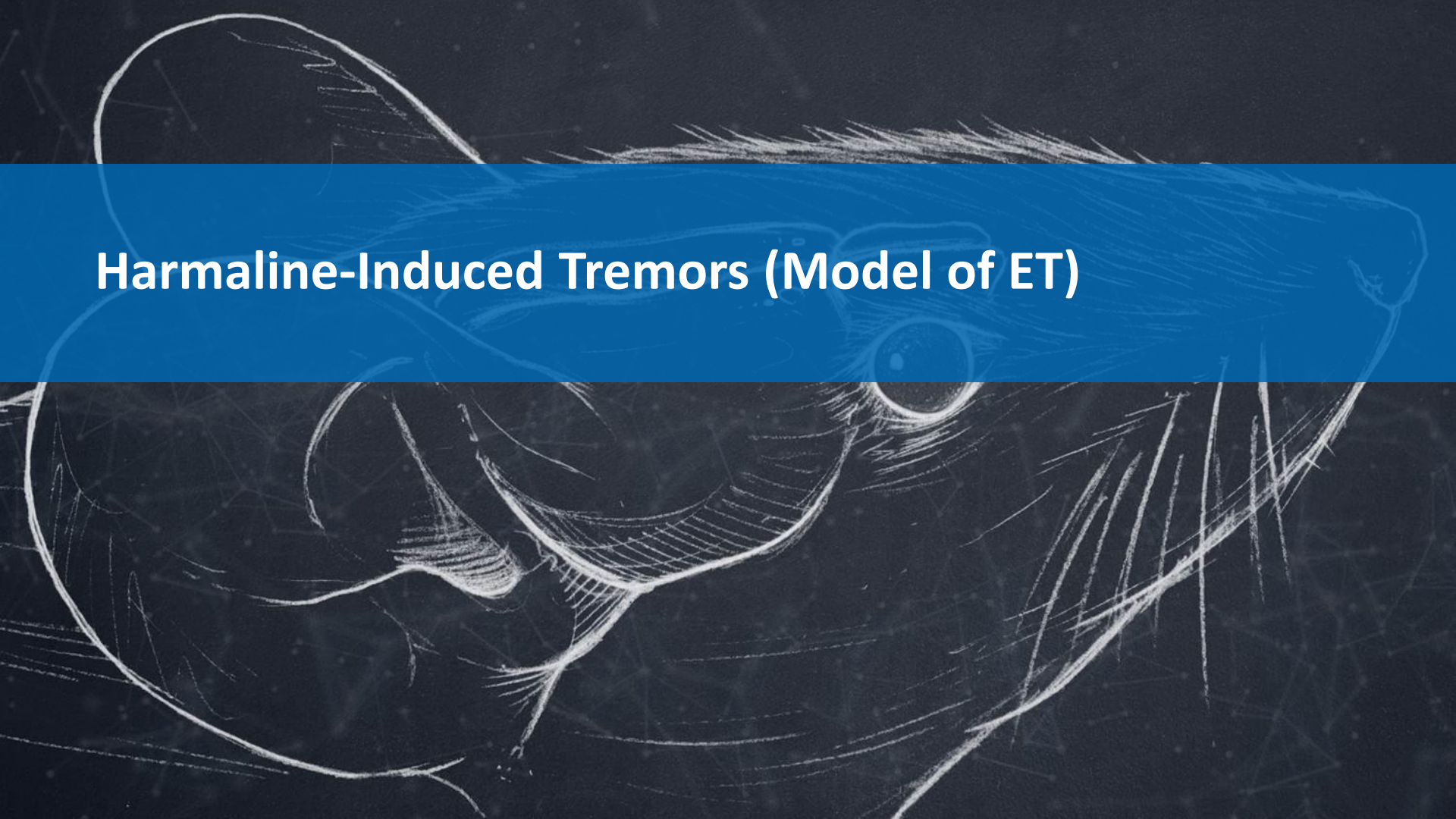
Valproate Decreases Seizure Intensity at 32 mAMP



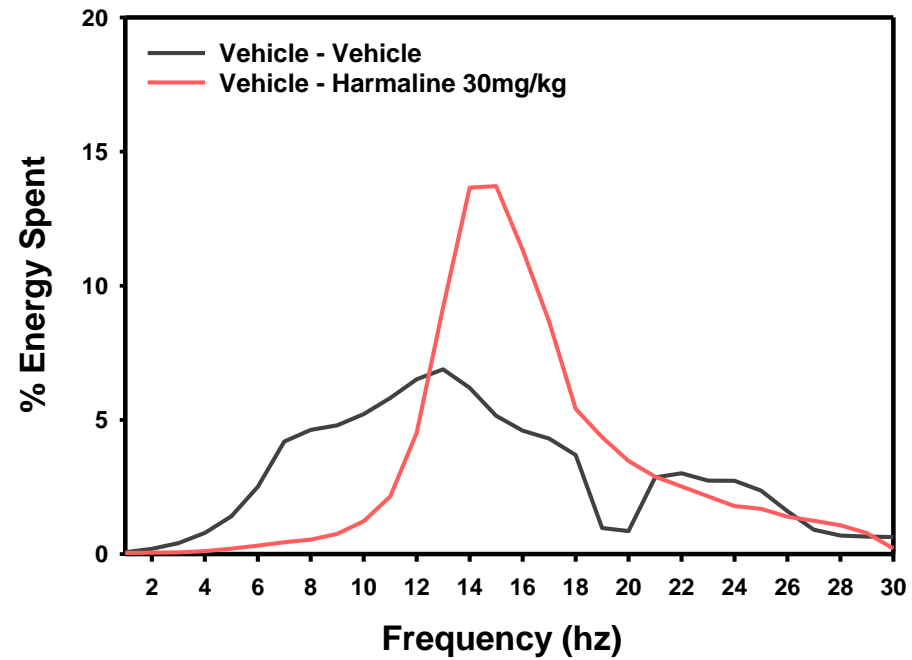
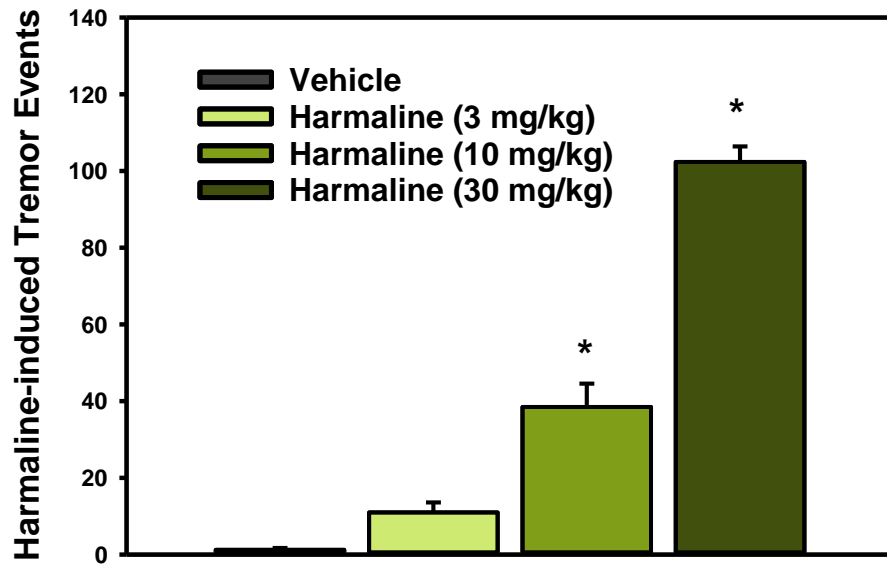


Redefining Drug Discovery Through Innovation

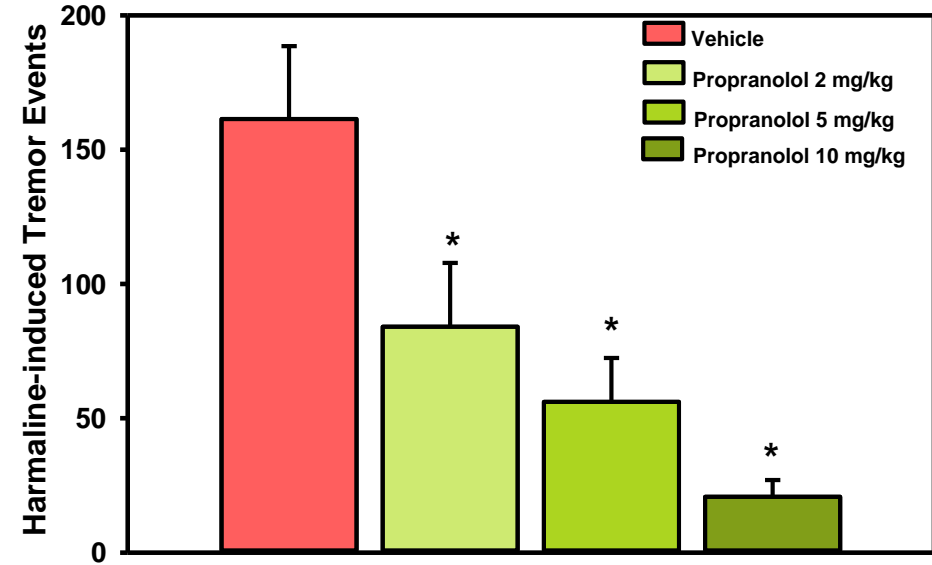
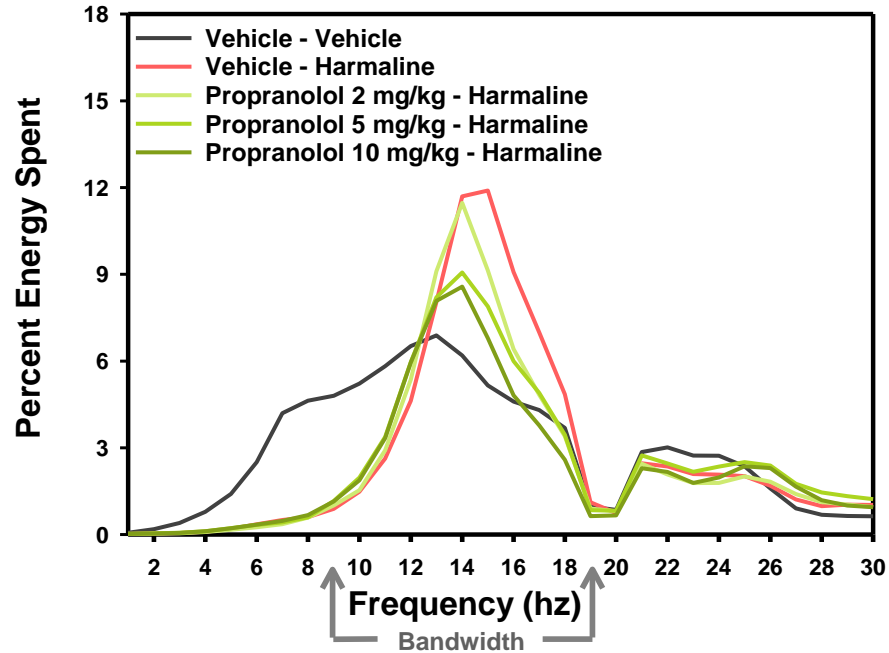
Harmaline-Induced Tremors (Model of ET)



Harmaline Dose Response



Propranolol Attenuates Harmaline-Induced Tremors



Primidone decreases Harmaline induced tremors

