

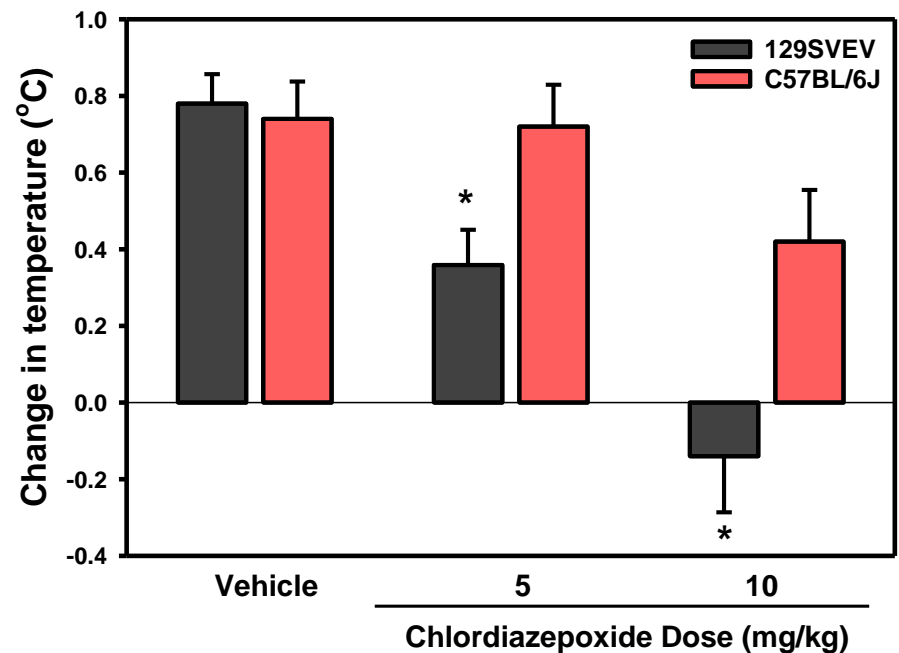
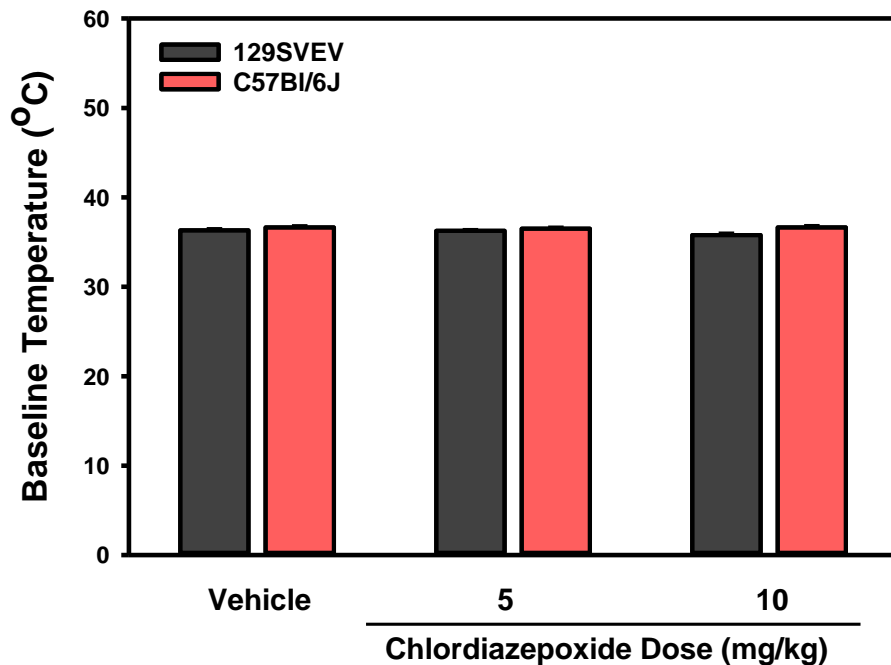


Redefining Drug Discovery Through Innovation

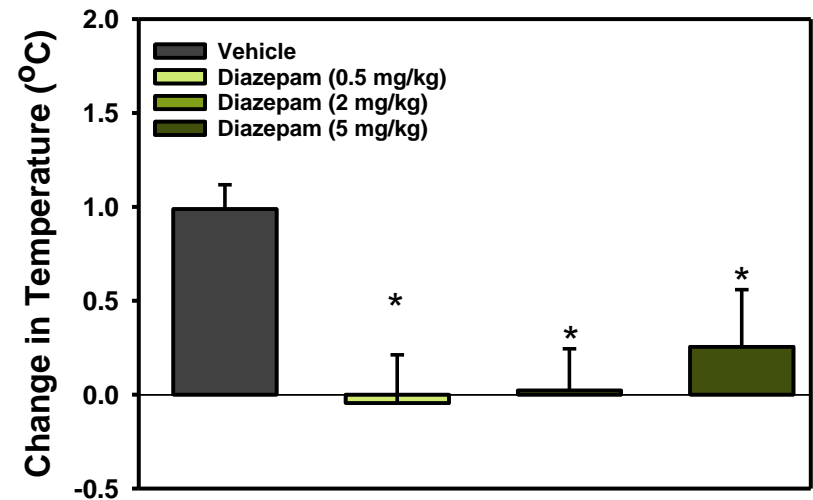
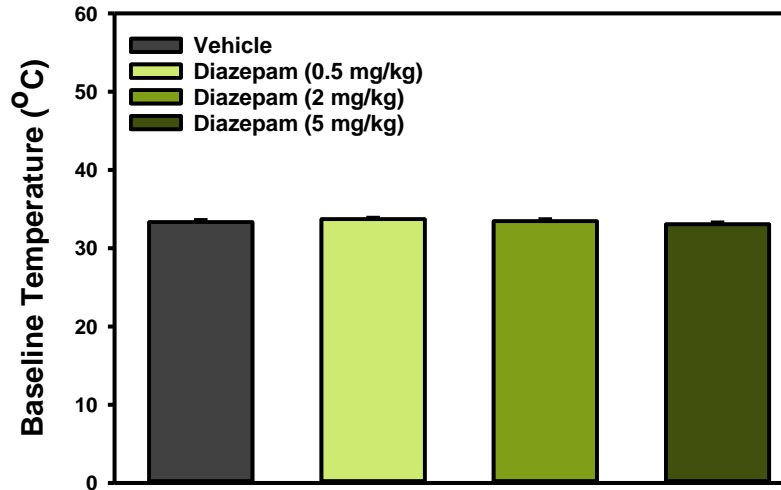
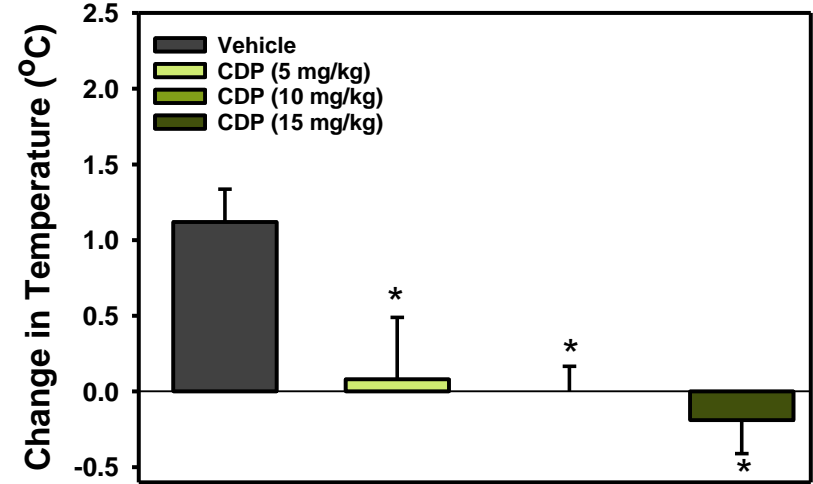
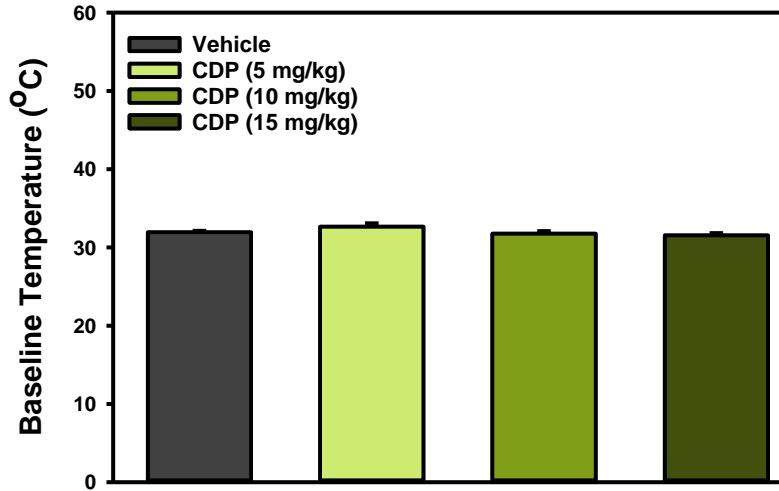
Preclinical Models of Anxiety

Stress-Induced Hyperthermia (SIH)

- SIH will demonstrate that a stressor will increase body temperature. This effect is attenuated with anxiolytics.
- Temperature is measured twice within a 10 minutes period. Change in temperature (T2-T1) is SIH
- 129SVEV has higher sensitivity to CDP compared to C57 mice in this test

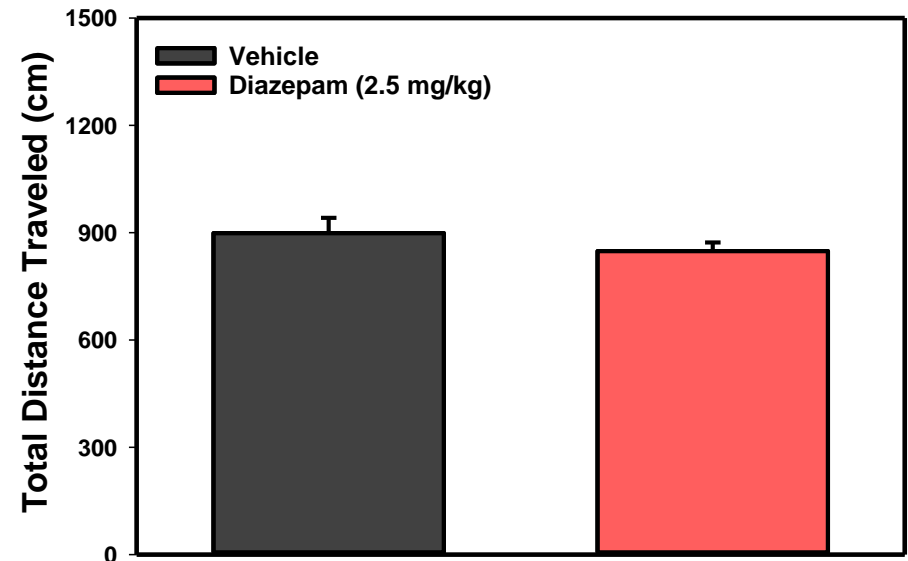
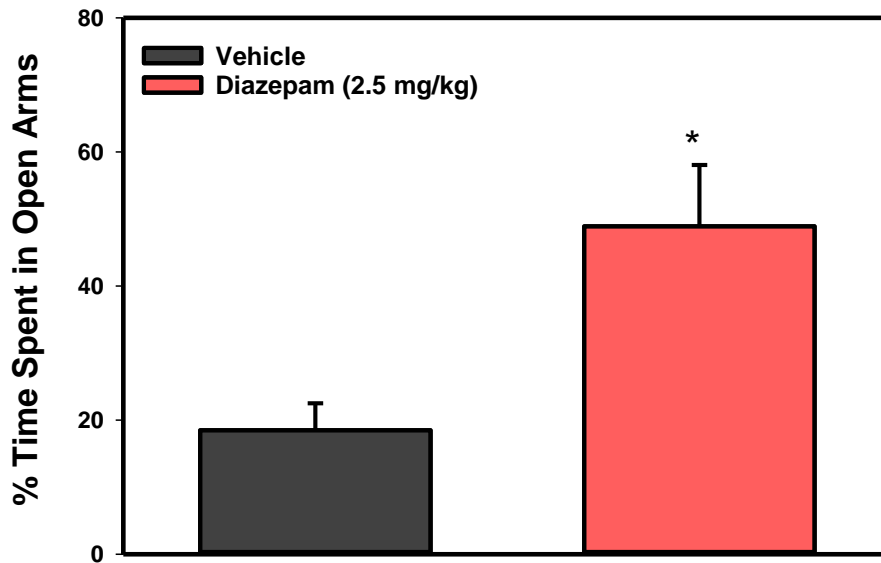


Effects of CDP and Diazepam on SIH in SD rats

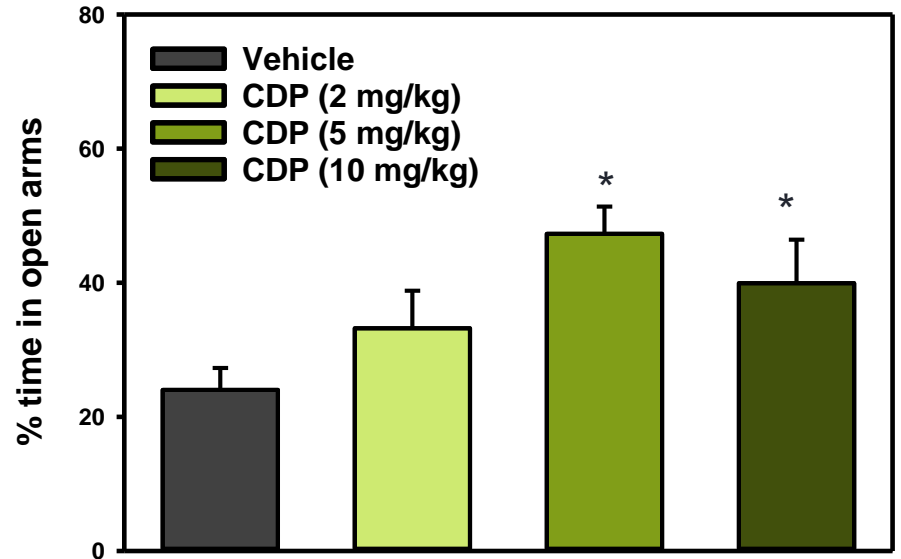
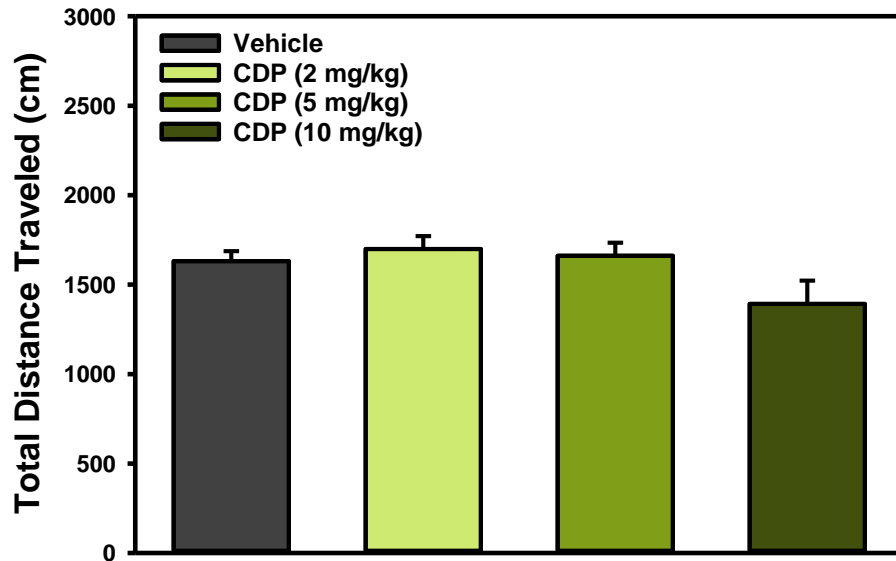


Elevated Plus Maze (EPM)

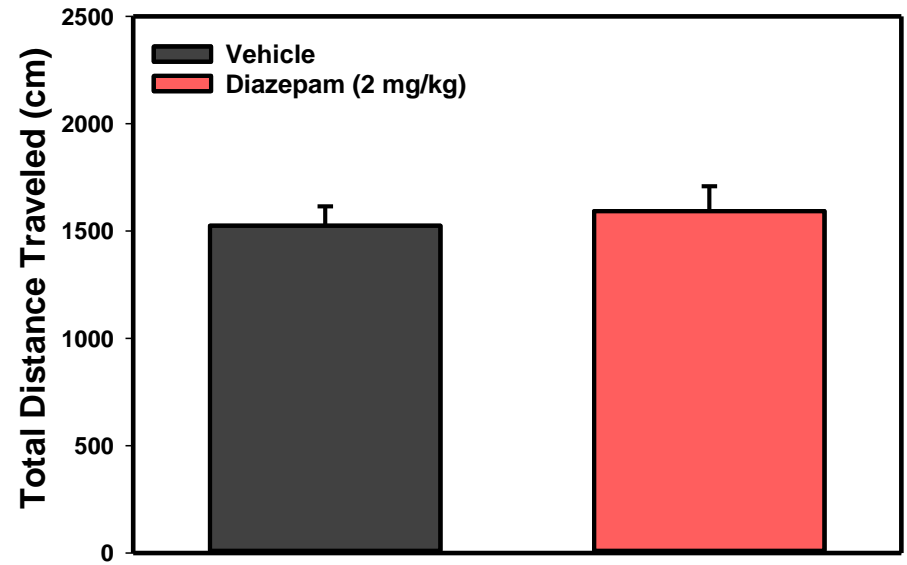
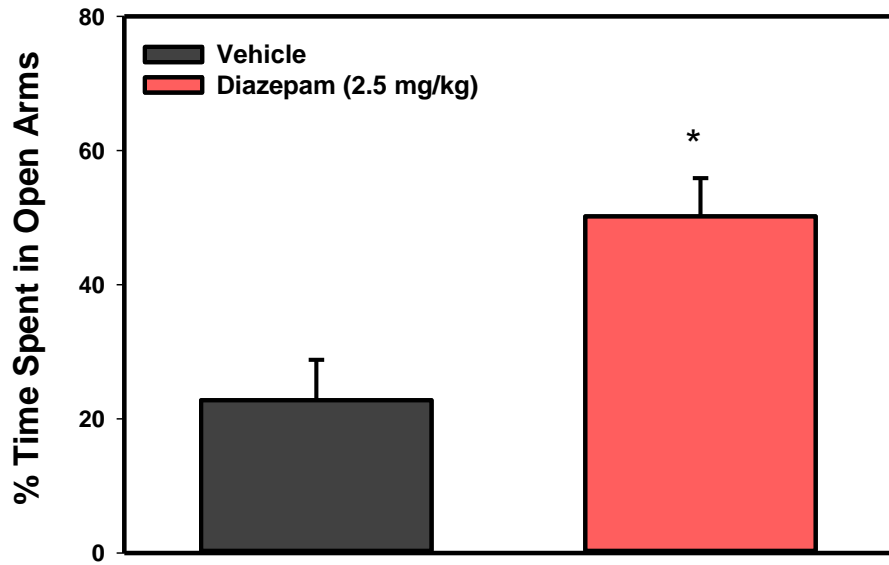
- EPM is widely used as an anxiety paradigm and is based on unconditioned responses of rodents to a potentially dangerous environment. A combination of maze height, luminosity and open space is assumed to induce fear or anxiety, the degree of which is assessed by measuring the amount of time the subject spends in the open arms of the maze.
- Anxiolytics like diazepam increases the time spent in the open arm without affecting the locomotor activity of the mice



Effects of Chlordiazepoxide in the EPM in SD rats

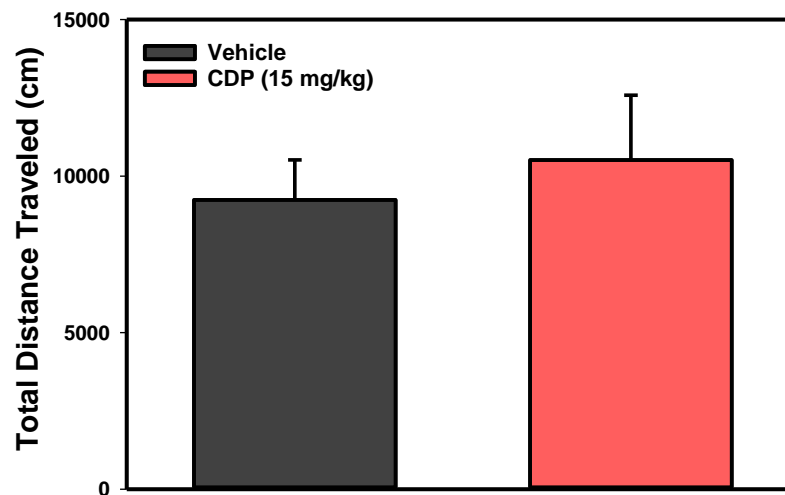
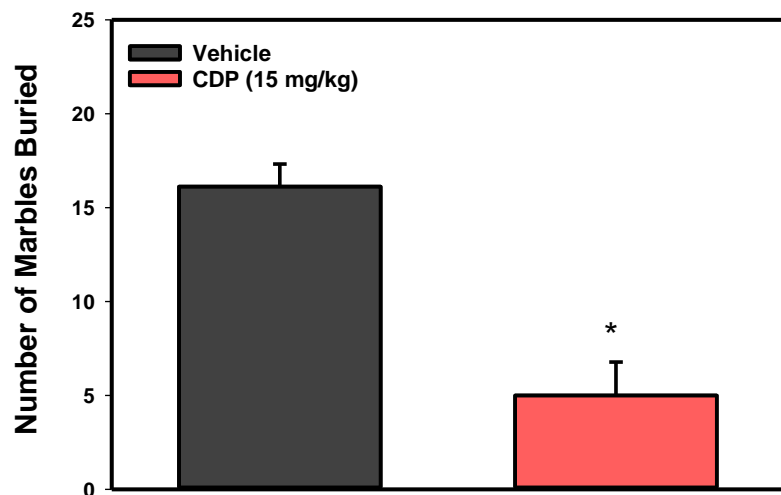


Effects of Diazepam in the EPM in SD rats



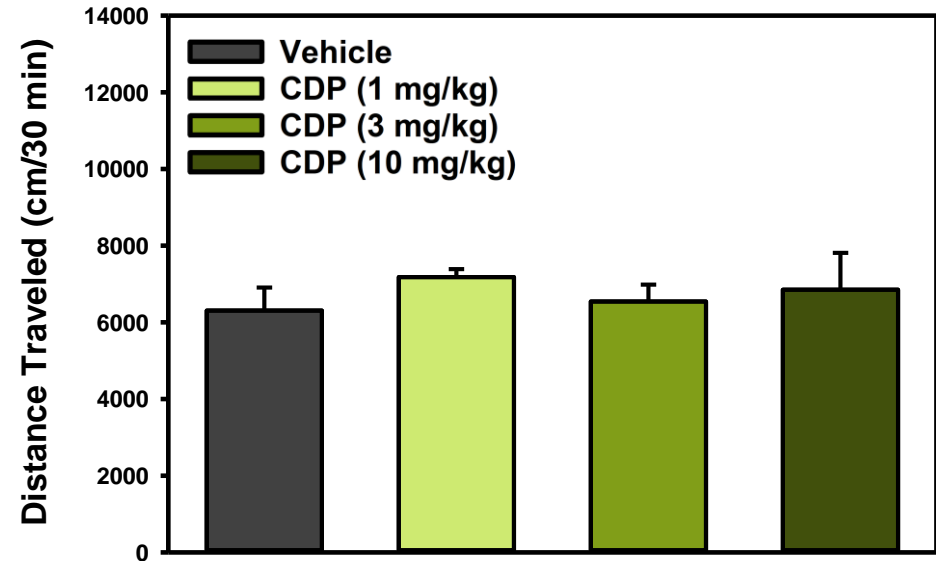
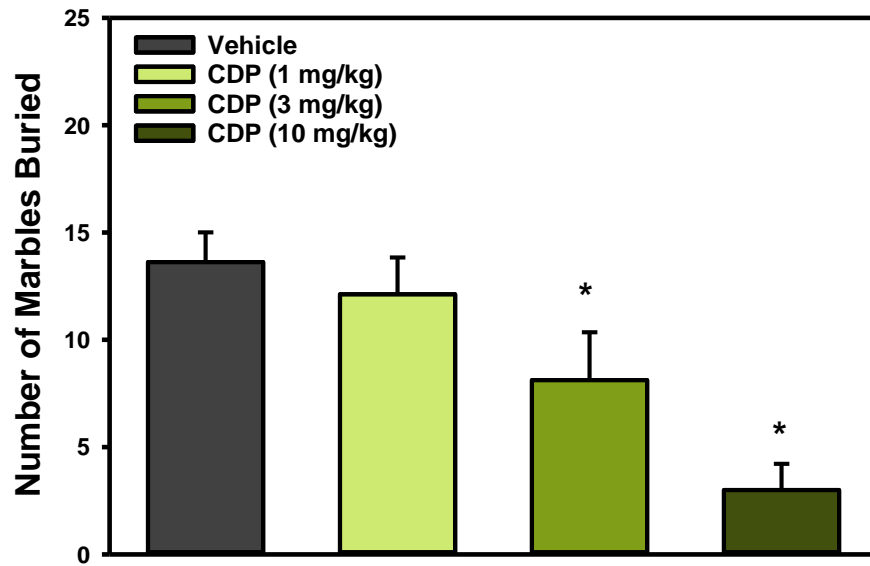
Marble Burying

- Marble burying is used as a model for both anxiety and obsessive compulsive disorder.
- Mice pretreated with anxiolytic agents show less marble burying ability compared to the control.
- C57Bl/6J mice are used in this test. Number of marbles buried and distance traveled are measured in a 30 minute test period

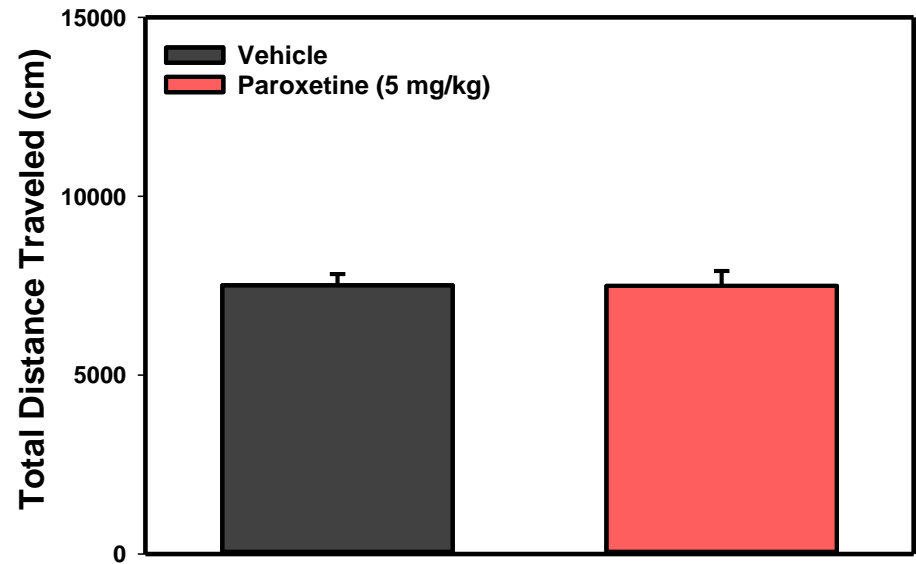
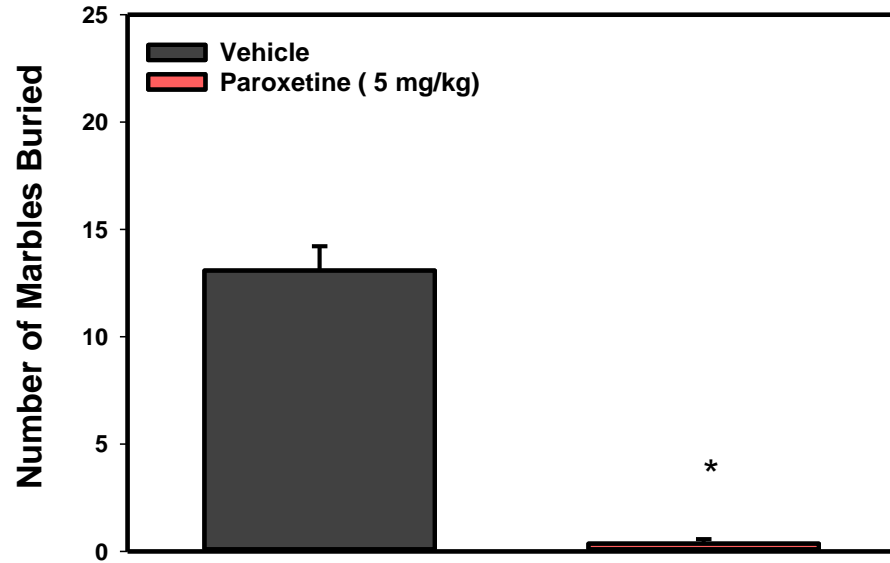


Chlordiazepoxide (CDP) decreased the number of marbles buried without affecting locomotor activity of the mice

Dose Response for CDP in Marble Burying Test

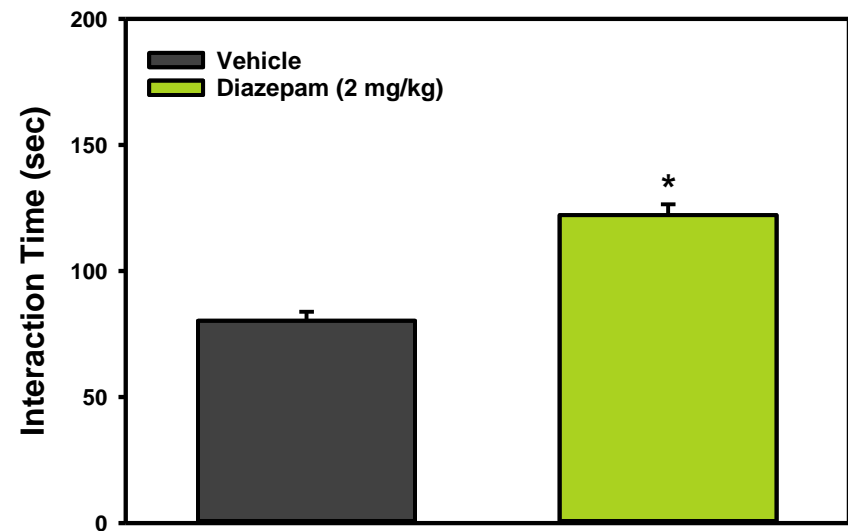
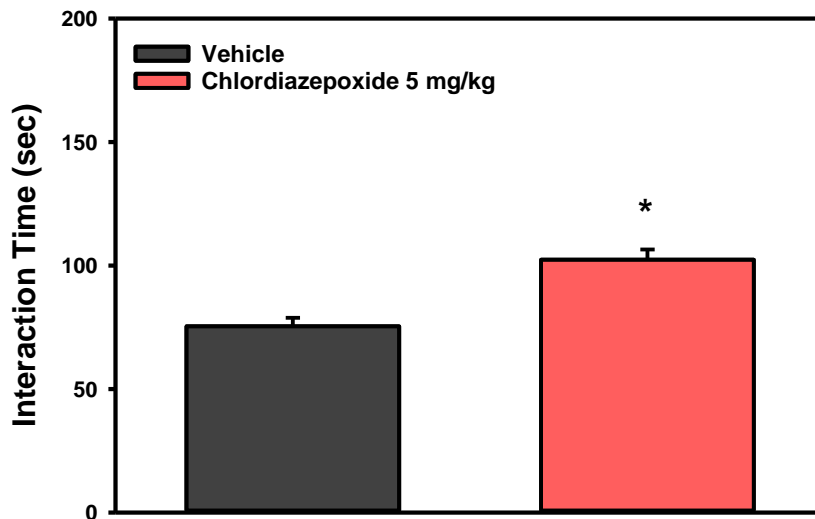


Effects of Paroxetine on Marble Burying



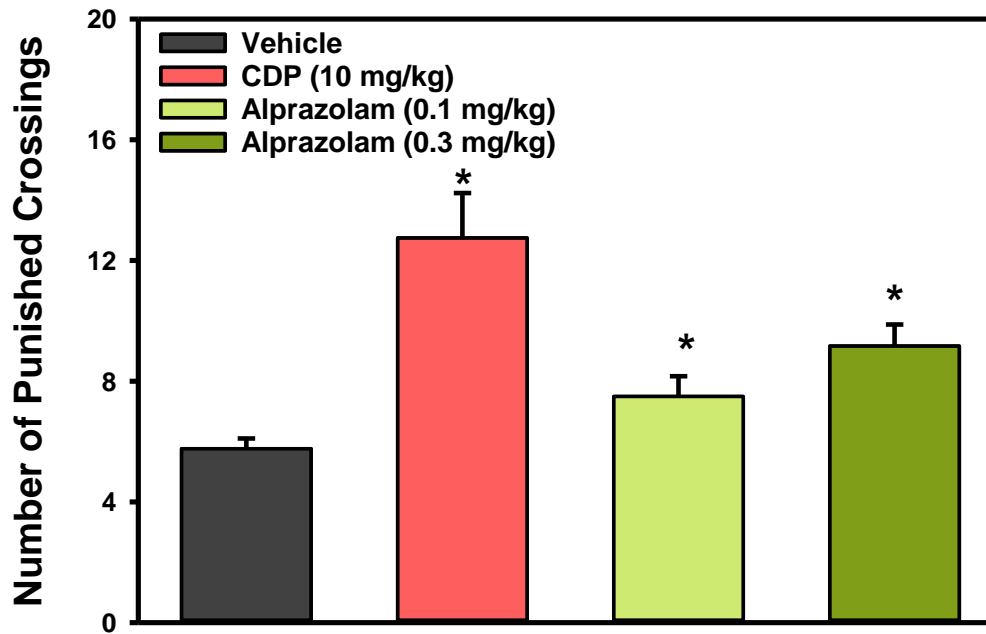
Social Interaction

- The social interaction test is used to assess anxiety-related behavior in rodents by using natural behaviors as the dependent measures. When two unfamiliar rodents are placed together, the animals will spend a certain amount of time interacting with each other, measured as sniffing, grooming and following. Anxiolytic drugs will increase interaction time.
- A pair of rats from the same treatment group is placed in a novel open field environment and the number of interactions (following, sniffing, grooming, and climbing) are measured for 6 minutes



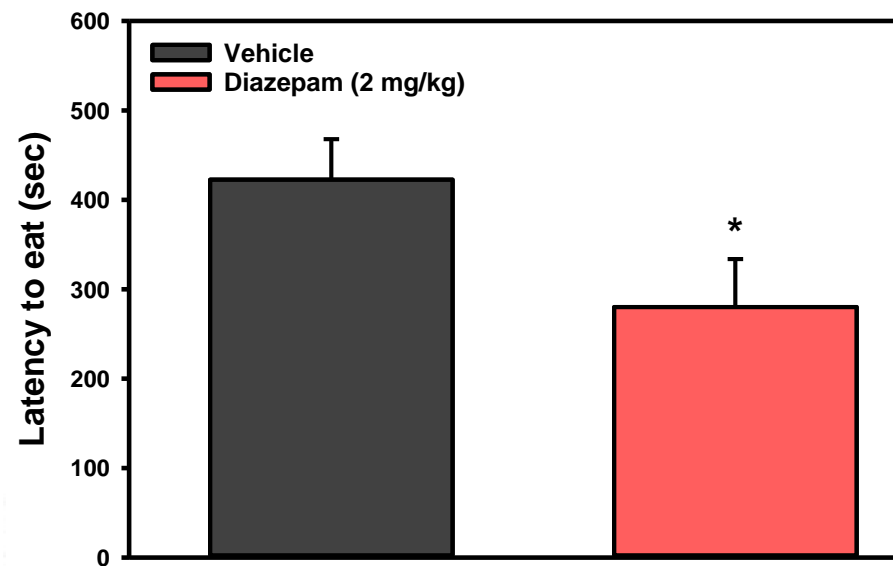
Four Plate Test

- The four–plate test is an unconditioned fear model of anxiety. Mice (Swiss Webster strain) receive a mild foot shock which suppresses exploratory behavior of the new environment.
- Known anxiolytic compounds such as benzodiazepines induce anti-punishment effects by increasing the number of plate crossings.



Novelty Suppressed Feeding

- Novelty-suppressed feeding (NSF) measures a rodent's aversion to eating in a novel environment.
- This test assesses stress-induced anxiety by measuring the latency of an animal that has been food deprived overnight to approach and eat a familiar food in an aversive environment.
- The test is sensitive to acute anxiolytics and chronic antidepressants.



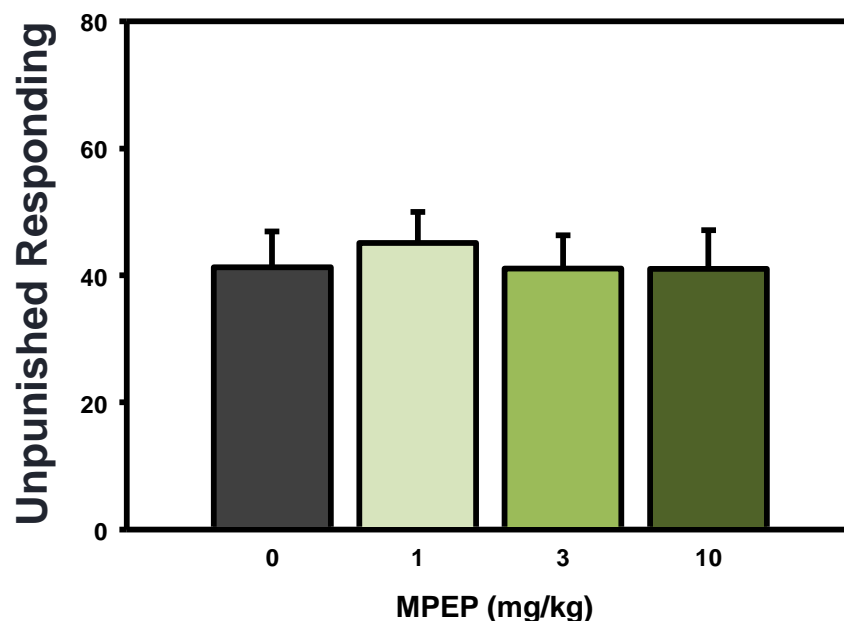
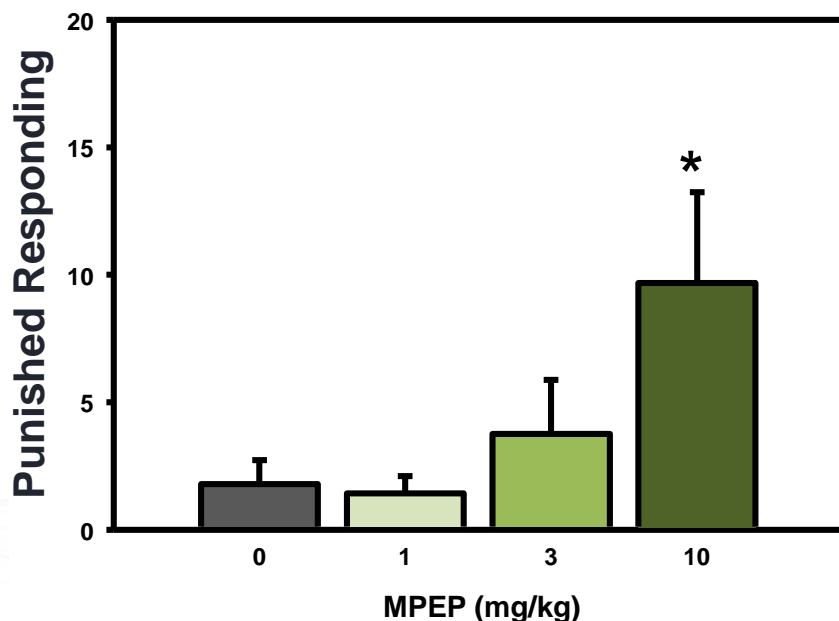
Vehicle

Diazepam

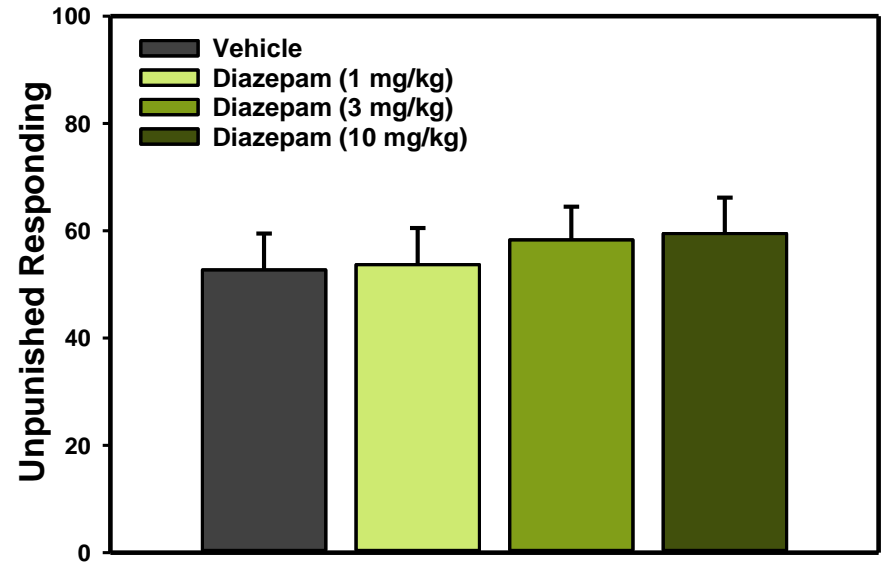
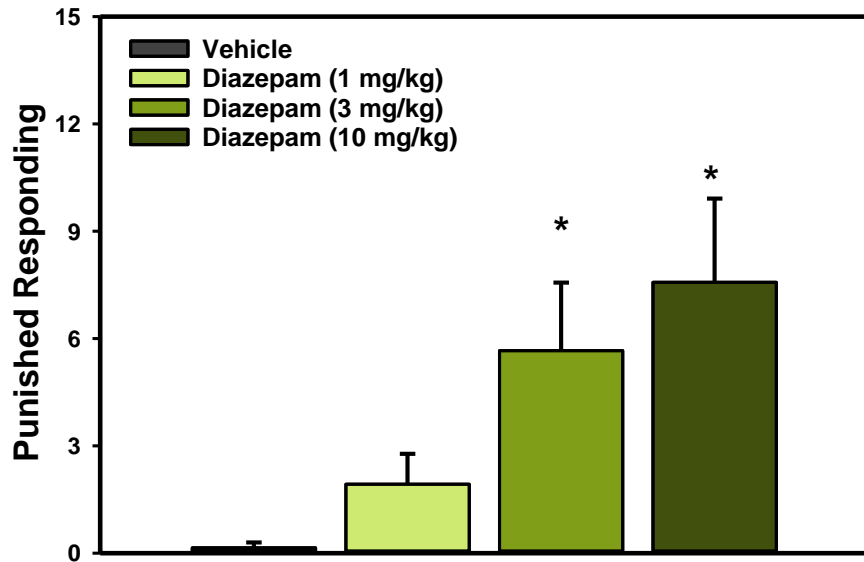
Modified Geller Seifter Conflict Test

This test serves as a putative animal model of anxiety. Rats learn to press a lever for a food reinforcement. Noxious stimuli (such as mild foot shock) suppress the responding in rodents.

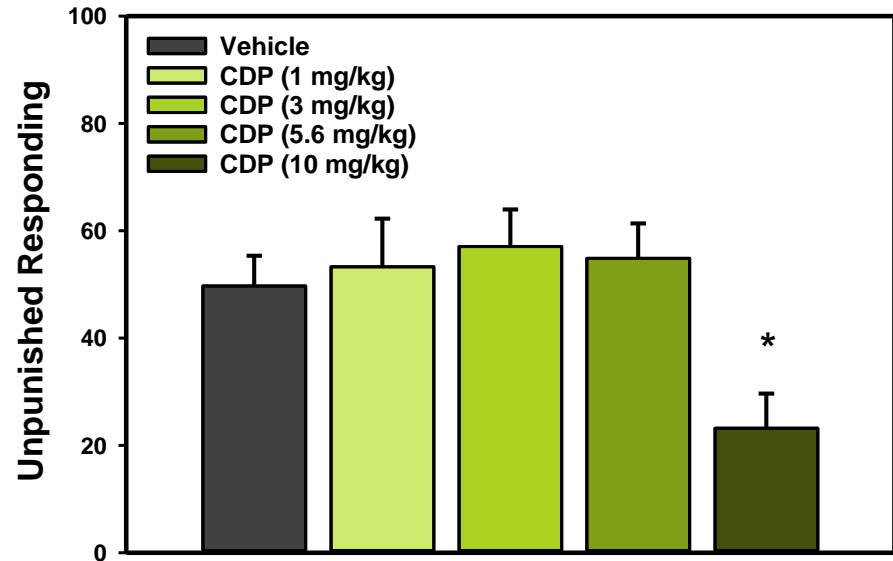
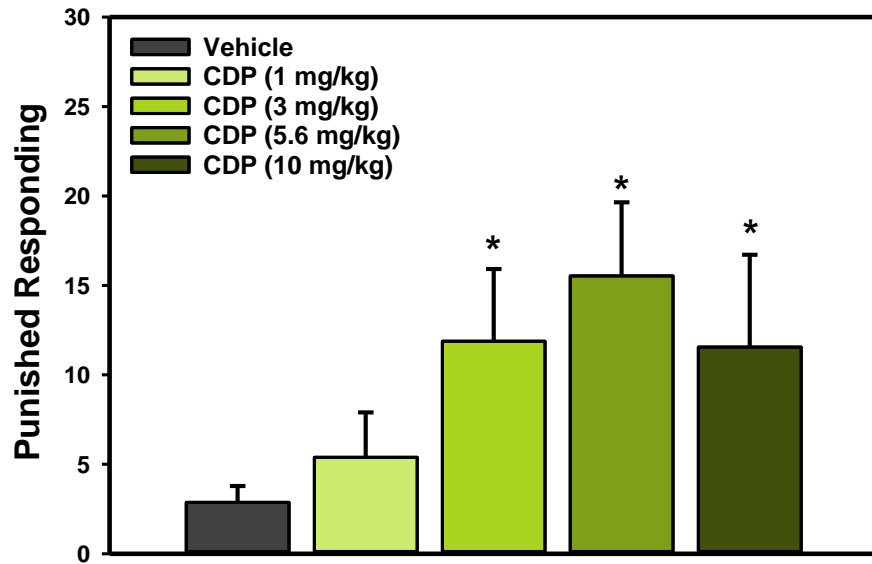
Anxiolytic drugs increase the number of shocks accepted in the punished condition without affecting unpunished responding (number of food reinforcements without a footshock). This task has the advantage of selectivity for anxiolytic drugs showing no effects of other classes of psychotropic drugs



Effects of Diazepam on Punished Responses



Effects of Chlordiazepoxide on Punished Responses



- Administration of the chlordiazepoxide (CDP) significantly increased punishing responding.
- At the highest dose tested (10 mg/kg), CDP significantly decreased unpunished responding. These data indicate that the anxiolytic properties of CDP (10 mg/kg) were associated with locomotor sedative side effects