Sigma-1 Receptor Antagonist PD144418 Selectively Reduces Female Motivation for Sucrose During Negative Energy Balance

Kelsey Mason[1,2], Leticia Rivera[2], Mikala Cessac[4], Jeffrey Bodeen[1,2], Emily L Bathe[2], Melissa Tapia[1], Jenna Lee[3], Matthew Will[1]

Introduction

Sigma-1 receptor ligands have been examined in previous studies for their role in rewarding processes, especially in cases of substance abuse. PD144418 (PD) is a potent and selective sigma-1 receptor antagonist that has been used to investigate these processes. Previous experiments using PD indicate that it produced a dose-dependent reduction in locomotor activity induced by cocaine and methamphetamine, while not altering basal locomotor activity in mice. Also, PD has been shown to lower the motivational effort of a food-reinforced behavior in male rats without changing food palatability or appetite. Research has yet to investigate whether PD can change motivational effort of food-reinforced behavior when energy homeostasis is changed, which takes place under depriving the subject of food for 24 hours. Moreover, there is no research indicating whether the effects observed in males is also seen in females. As such, this study examined the effects of PD on food motivation in male and female rats using an operant task under either an ad libitum or food-deprived condition.

Materials/ Methods

Progressive Ratio

- Male (n = 8) and female (n = 8) rats were trained on a fixed ratio schedule to press levers for a sucrose pellet in operant chambers.
- Rats progressed through fixed ratio schedules ((FR1/ TO-20 → FR3/TO-20 → FR5/TO-20) before moving to progressive ratio schedule (PR/TO-20).
- A single intraperitoneal injection of either saline, 3.16 µmol/kg, or 10 µmol/kg of PD144418 was administered and rats were placed back in their home cage for 15 mins before testing began.
- Each rat was tested within each treatment group once (saline + no food deprivation, 3.16 µmol PD144418 + no food deprivation, 10 µmol PD144418 + no food deprivation, saline + 24h food deprivation, 3.16µmol PD144418+24h food deprivation, and 10 µmol PD144418 + 24 h food deprivation).

Locomotor Activity

- Male (n = 4) and female (n = 4) rats were given two days to acclimate to locomotor chambers (50 cm x 50 cm x 38 cm).
- Following acclimation, baseline activity was recorded over 60 minutes using a program called ANYmaze.
- Rats were injected with either saline, a low dose (3.16 µmol/kg), or a high dose (10 µmol/kg) of PD144418, fifteen minutes prior to testing.
- After injections, animals were placed in the locomotor chambers
- Locomotor activity was examined over the 60-minute testing period.

Progressive Ratio

Ad Libitum

Figure 1

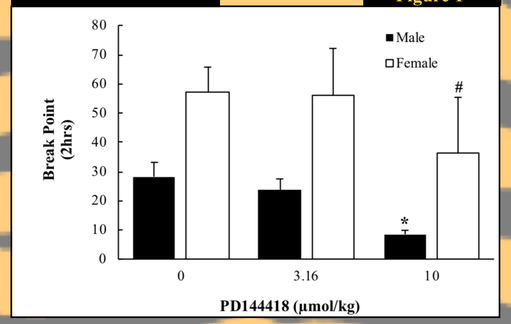
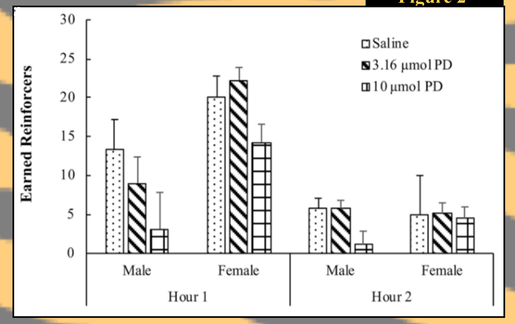


Figure 2



Food Deprivation

Figure 3

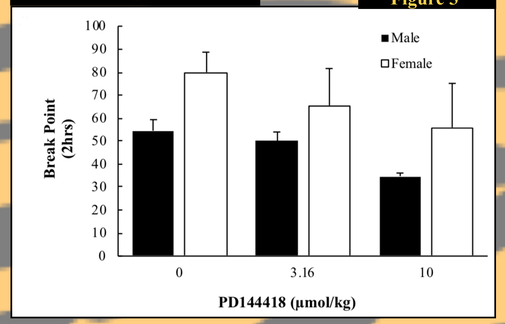
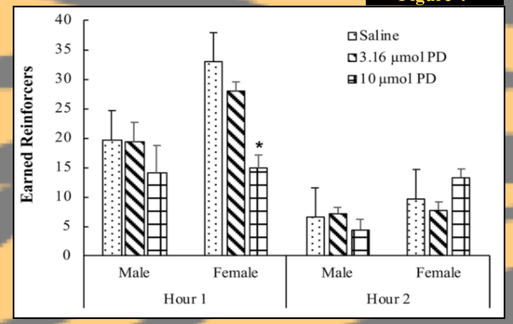


Figure 4



Locomotor Activity

Figure 5

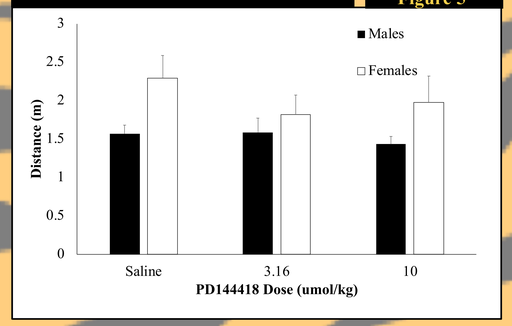
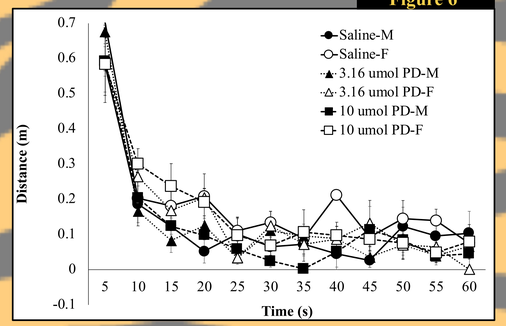


Figure 6



Results

Progressive Ratio

- Male and female rats showed no difference in baseline breakpoints after 2 days of training.
- Animals displayed a significant decrease in both breakpoint and earned reinforcers when given the highest dose of PD144418 (10 µmol/kg) under both ad libitum and food deprived conditions, as shown in Figures 1 and 3
- Females had higher breakpoint and earned more sucrose pellets than males on average in the ad libitum condition, as shown in Figure 1.
- Animals earned more sucrose pellets in the first hour than in the second hour in both conditions, as shown in Figures 2 and 4.
- PD144418 reduces female responding during negative energy balance under food deprived conditions, as shown in Figure 4.
- (*) $p < 0.05$ compared to saline-M; (#) $p < 0.05$ compared to saline-F

Locomotor Activity

- Both male and female baseline locomotor activity did not significantly increase or decrease between day 1 and day 2.
- PD144418 (3.6 µmol/kg and 10 µmol/kg) did not significantly affect the locomotor activity in males or females, as shown in Figure 5.
- Rats in all cases had more locomotor activity within the first 5 minutes of runtime compared to the rest of the 60-minute period, where activity was constant, as shown in Figure 6.

Conclusion

This study indicates that when sated, as in ad libitum conditions, PD144418 decreased breakpoint and number of active lever presses in order to obtain sucrose pellets. When under energy deficit, as in food deprived conditions, PD144418 does not alter breakpoint in males nor females. However, the drug decreases the number of active lever responses and earned reinforcers in females in a time-dependent manner. Thus, the motivation of female rats to press a lever to obtain sucrose pellets is decreased by PD144418. Additionally, this study suggests that PD144418 does not have an affect on locomotor activity in both male and female rats. This finding demonstrates that there was no confound on operant responding due to changes in locomotor properties of PD144418, suggesting that the drug only altered the rewarding properties of the pellet.

REFERENCES

1 | Lever, J.R., et al., (2014) Relationship between cerebral sigma-1 receptor occupancy and attenuation of cocaine's motor stimulatory effects in mice by PD144418. *J Pharmacol.*

2 | Tapia et al. (2019). Sigma-1 receptor antagonist PD144418 suppresses food reinforced operant responding in rats. *Behav Brain Res.*

ACKNOWLEDGEMENTS

This study was funded, in part, by the Psychological Sciences Undergraduate Research Fund.

1 | Psychological Sciences
2 | Biological Sciences
3 | Interdisciplinary Neuroscience Program
4 | Nutrition and Exercise Physiology