

Relationship Between Sex and MK-801's Effects in Rats

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Background

- Existing research on effects of MK-801 on rats has indicated that there are differing effects of NMDA receptor antagonists based on sex.
- Existing research also shows different foraging behaviors between the sexes which indicates behavioral differences in decision-making among male and female rats.
- Therefore, we are investigating whether sex affects decision-making in a foraging context under the effects of MK-801.
- This research will help us understand the biological effects of sex on decision-making and the sex-dependent sensitivities to MK-801.

Hypotheses

- We hypothesize there will be a significant effect of sex on lever choice behavior in the Diminishing Returns task.
- We hypothesize there will be a significant dose-dependent effect of MK-801 on the lever choice behavior of female rats compared to male rats.
- We hypothesize there will be a significantly stronger dose-dependent behavioral effect of MK-801 on female rats.

Methodology

Subjects

- 8 Female and 8 Male Sprague Dawley Rats from Envigo Labs were pair-housed in a humidity and temperature controlled room on a reverse 12-hour light-dark cycle. Rats were maintained at 85% body weight after 5 days of acclimation and had ad libitum access to water.

Measures

- Rats were first lever-trained in operant chambers to associate lever presses with sugar pellet rewards. They had to make 20 accurate lever presses within 10 minutes, which took approximately 1 week before they moved onto the Diminishing Returns task.
- The Diminishing Returns task was used to measure the decision-making skills in an operant chamber with two levers, a sugar pellet dispenser, and a response light above each lever.
- The Diminishing Returns task uses two conditions for measuring decision-making:
 - No Reset: one lever has a fixed delay (FD) of 10 seconds before receiving a reward and the second lever has a progressive delay (PD) that increases by 1 second each time it is chosen.
 - Reset: Same as No Reset except each FD lever press resets the delay back to 0.
- The task ran for 1 hour, in which rats made decisions for the FD or PD lever to obtain the most rewards. This task involves an optimal method of obtaining the most rewards by the end of each session, which is to respond on the PD lever 80% of the time during the Reset condition and to respond on the FD lever the majority of the time in the No Reset condition.
- After a period of approximately 1 week of training in each condition, rats received injections of MK-801 and saline on a Latin square counterbalanced schedule with 24 hours between each dose. The doses of MK-801 were 0.06 mg/kg, 0.1 mg/kg, and 0.2 mg/kg.
- The lever choices rats made in the task were collected using Ablet II Software (22.03.22.0) for analysis.

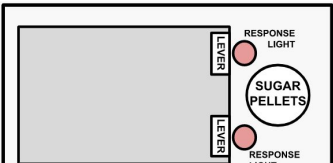
Analysis

- Only data from sessions where rats received injections of MK-801 and saline were analyzed.
- R (V.4.2.3) was used for statistical analyses and the design of figures.

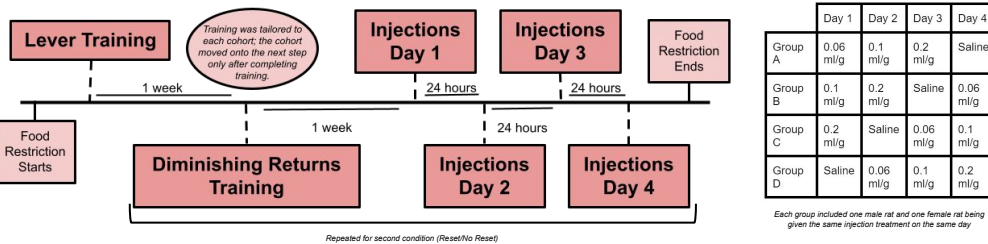
Diminishing Returns Task

Lever Training - Rats received a reward every time a lever was pushed

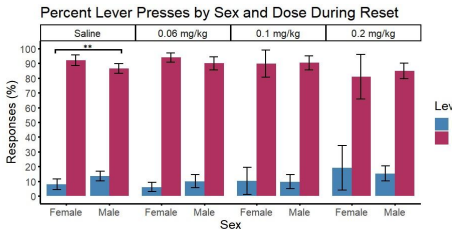
Diminishing Returns Task - Rats chose between a Fixed-Delay (FD) (ten-second intervals) and a Progressive-Delay (PD) lever (one second progressive increase) to receive rewards



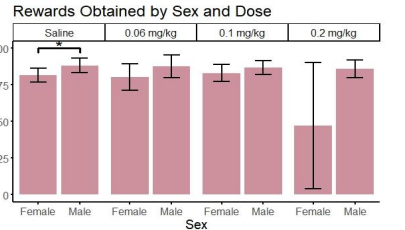
Experiment Timeline and Injection Schedule



Sex Affects Decision-Making During Reset Condition

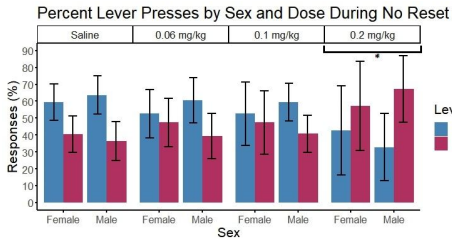


- During the Reset condition of the Diminishing Returns task, there was a significant difference in percent of lever choices between the PD and FD levers made by male and female rats after receiving the saline (control) treatment.
- This indicates an effect of sex on the decision-making process in this task.
- There was not a significant difference in the effect of the doses of MK-801 on the proportion of PD to FD levers by sex in this condition.

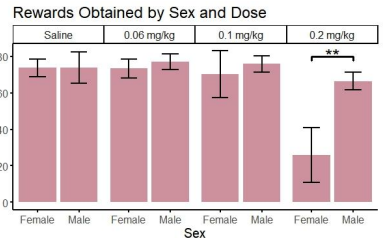


- In this condition, there was a significant difference in the number of rewards obtained between male and female rats.
- By having a lower proportion of PD to FD lever presses than females, males obtained more rewards, demonstrating they were not only making different lever choices, but the choices were more rewarding.
- There was not a significant difference between sexes after receiving the doses of MK-801, with 0.2 mg/kg producing a high amount of error in females.

High Dose of MK-801 Alters Decision-Making During No Reset



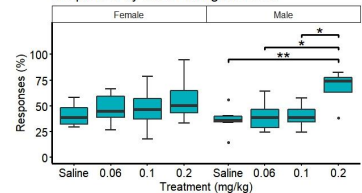
- During the No Reset condition, there was a significant difference in the percent of lever choices made by both male and female rats after receiving the 0.2 mg/kg dose of MK-801 compared to the other injections.
- This indicates an effect of the high dose of MK-801 on the decision-making process in this task.
- The lower doses of MK-801 and the saline treatment did not show significant differences on the proportion of PD to FD levers between sexes.



- Injections of the 0.2 mg/kg dose of MK-801 resulted in male rats obtaining significantly more rewards than females during this condition.
- This demonstrates a stronger effect of the drug on female rats and their decision-making ability to obtain the most rewards during the task.
- The lower doses of MK-801 and the saline treatment did not significantly affect the number of rewards rats obtained.

High Dose of MK-801 Affected Decisions of Male Rats

Responses by Dose During No Reset



- Though there was not an overall difference between sexes and the proportion of PD to FD lever presses during the No Reset condition, males were significantly affected by the 0.2 mg/kg dose compared to the other injections, resulting in a significantly higher proportion of PD to FD lever presses during this condition.

Discussion, Limitations, and Future Research

- The results of this study are mixed. There was a significant effect of sex alone on decision-making in the Reset condition but not the No Reset condition after receiving saline. After receiving saline in the Reset condition, male rats made less rewards on the PD lever than females, so their overall percent on the PD lever was closer to the optimal 80% resulting in more rewards. This decision-making behavior was not reflected in the No Reset condition, however. This could be due to how the rats conceptualize the foraging behavior involved in the different conditions of the task to obtain the most rewards, which could be affected by sex.
- MK-801 did not tend to have a significantly stronger effect on female rats except at the high dose of 0.2 mg/kg, but this was also shown by the number of rewards they obtained based on their lever choices during the No Reset condition. Males were also significantly affected by the 0.2 mg/kg dose during this condition since they had a higher proportion of PD to FD lever presses compared to other doses, though they still responded more successfully than females, demonstrating their decision-making was not as impaired.
- Our hypothesis that sex would have a significant effect on lever choice behavior in the Diminishing Returns Task was mostly supported. During the Reset condition, there was a significant difference in the percent lever choice and the number of rewards obtained between the male and female rats during the saline treatment.
- Our hypothesis that there will be a significant dose-dependent effect of MK-801 on the lever choice behavior of female rats compared to male rats was partially supported. At the 0.2 mg/kg dose, in both the Reset and No Reset condition, females obtained fewer rewards than males. The percent lever presses showed no significant difference. This shows that, while females were still pressing the levers, males were making choices that were more rewarding.
- This study had a limitation of a small sample size, which can contribute to higher error in statistical analyses. This was also combined with the addition of the 0.2 mg/kg dose being added to the injection schedule after the other doses, so the number of rats that received the high dose was less than the number that received the other doses. This could have contributed to a higher chance of Type II error in the analyses of this dose's effects. There was also a limitation in the design of the operant chamber. The levers in these chambers do not retract after they are selected, which could have caused rats to incorrectly associate repeated presses or switching to a different lever to result in a reward. The chambers do have response lights above each lever that light up when a lever is chosen to help associate lever selections with rewards.
- For future research, other drugs like ketamine could be used to test the effects of different NMDA receptor agonists. Alternatively, adding an NMDA receptor agonist like D-cycloserine would also be beneficial to compare the effect of an agonist on decision-making. Larger sample sizes can also be implemented in order to further test statistical significance of findings. Additionally, starting the rats on higher doses (0.2) earlier would reduce error in significant findings, allowing for the same amount of rats to receive the high dose.

References

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