

Effects of Sex on Resistance to Punished Alcohol-Seeking

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Introduction

- The neural pathways through which alcohol exerts effects on behavior can be studied using rodent models. Punished alcohol drinking is used to model the tendency of addicts to consume drug despite negative outcomes.¹
- Previously, we have found that there is a sex difference in binge-like, but not aversion-resistant, alcohol consumption.²
- To further study the relationship between sex differences in relation to alcohol consumption and resistance to punishment, an operant conditioning paradigm was used.

Methods

Subjects: C57BL/6J male and female mice were generated from breeding pairs purchased from The Jackson Laboratory, Bar Harbor, ME.

- Mice were food restricted to 85% of their free feeding weight
- Alcohol Quinine/Foot Shock Operant Paradigm and Criteria**
- Operant Paradigm lasted for 30 minute sessions
- Mice were put on the program *Food 1*, which consisted of nose poking for a grain of pellet for three consecutive days
- Drink 1* consisted of mice nose poking for 10% sucrose solution for 3 consecutive days (receiving sucrose after each poke)
- Drink 3* consisted of mice nose poking for 10% sucrose solution for 3 consecutive days (receiving sucrose after every 3 pokes)

Sucrose Fading Procedure

- Mice were put on *Drink 3*, where mice nose poked for 10% sucrose and 10% EtOH for at least three days, but no more than 5
- Mice were put on *Drink 3*, where mice nose poked for 5% sucrose and 10% EtOH for at least three days, but no more than 5
- After a maximum of five days, mice were put on *Drink 3*, where mice nose poked for 10% EtOH, only moving on until there is <20% variation for consecutive days

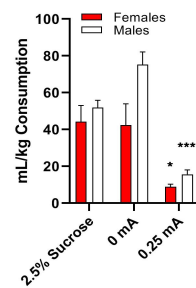
Foot Shock Procedure

- Pre-Shock days:** mice receive 10% EtOH for every nose poke
- Punishment Protocol:** 1st poke: light cue; 2nd poke: shock; 3rd poke: reward
- Mice were given a 0.25 mA shock

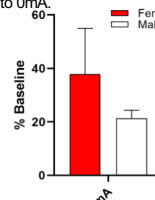
Data Analysis:

- The number of nose pokes during training and punishment sessions were averaged for the male and female groups.
- Consumption data were expressed as g of EtOH consumed per kg of body weight for each individual mouse and averaged across groups (male and female).
- Percent of baseline were calculated as $\frac{\text{Consumption on 0.25 mA Day}}{\text{Consumption on 0 mA Day}}$

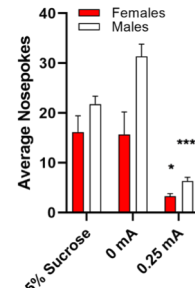
Experimental Timelines



Males and females significantly reduced consumption of sucrose when punishment was introduced. There was a significant main effect of amplitude. Follow-up Holm-Sidak's test revealed that 0.25 mA shock significant reduced seeking in both males and females ($p = 0.0007$ and 0.0362 , respectively) when compared to 0mA.

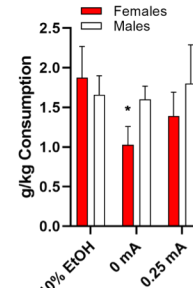


Shock amplitude affects responses.

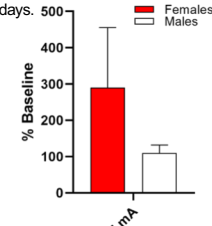


Males and females significantly reduced number of nosepokes when punishment was introduced. There was a significant main effect of amplitude for both males and females ($p = 0.0005$ and 0.0419 , respectively). Follow-up Holm-Sidak's test revealed that there was a suppression of nosepokes at the 0.25mA day when compared to the 0 mA day.

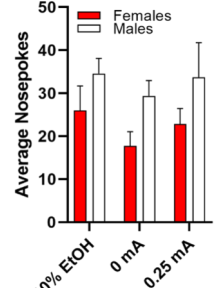
Results



Males and females maintain stable EtOH consumption when punishment was introduced. There was a significant main effect of amplitude for females ($p = 0.0349$) Follow-up Holm-Sidak's test revealed that 0 mA shock significant reduced seeking in females when compared to 10% EtOH days.



Shock amplitude affects responses.



Males and females appear aversion-resistant when punishment was introduced. Both males and females maintained constant levels of nosepokes. ($p = 0.7127$ and 0.7016 , respectively) Follow-up Holm-Sidak's test revealed that the introduction of punishment did not reduce the number of nosepokes when compared to the 0 mA day.

Conclusions

- Both males and females were shown to be aversion resistant with a 0.25 mA footshock.

Future Directions

- Further, we cannot conclude that these results are not due to a difference in pain sensitivity between males and females. Thus, we will measure pain sensitivity in a flinch, jump, vocalize test.
- Testing with a higher shock amplitude may reveal sex differences in aversion-resistant alcohol seeking.

References

- Radke, AK., et al. (2017). Chronic EtOH Effects on Putative Measures of Compulsive Behavior in Mice. *Addiction Biology* 22 (2): 423-34.
- Sneddon, EA, White, RD, Radke, AK. (2018). Sex differences in binge-like and aversion-resistant alcohol drinking in C57BL/6J mice. *Alcoholism: Clinical and Experimental Research*.

Acknowledgements

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