Establishment of a choice procedure to study alcohol self-administration: Relevance to alcohol use disorder

M. Windram[1], D. Lovelock[1], J. Besheer[1,2]

[1]Bowles Center for Alcohol Studies, [2]Department of Psychiatry, University of North Carolina at Chapel Hill

Introduction

Alcohol use disorder (AUD) affects 10.6% of Americans ages 12 and older, as of 2021.[1] Operant self-administration (SA) with rats has provided an effective model for studying alcohol use, but it has some limitations. Traditional SA designs involve placing an animal in an operant chamber with the ability to self-administer a single substance, which may not be fully representative of typical human drinking experience. Additionally, it is often necessary to conduct parallel experiments where subjects are offered a non-drug reward (typically a sweetened solution) in order to test for specificity. As only one substance is offered at a time, choice cannot be assessed with current models despite decision-making playing an important role in alcohol use disorder.[2,3]

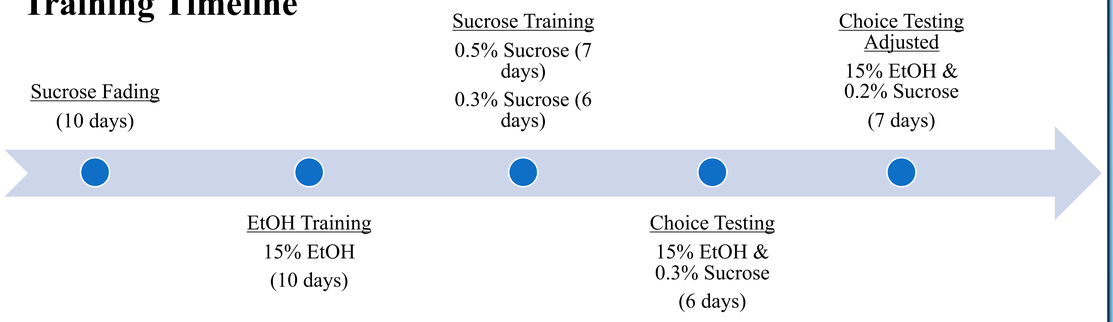
This project aimed to implement a testing procedure in which rats were given the choice between sucrose and alcohol, evaluating desire for alcohol even when presented with another attractive self-administration option. Other past projects have used similar two-choice methods; however, these projects have primarily focused on discrimination between saccharin and alcohol[4,] and choice procedures have not yet been used towards finding new pharmacological treatments for AUD. Use of sucrose as an alternative reward models decision-making between alcohol and non-alcohol rewards. Drinking behaviors in humans are impacted by many external factors, and single-choice operant self-administration is not completely representative of real-world situations. Choice self-administration with another attractive reward improves face validity for more realistic drinking behavior.

Thus, in the current experiment we trained rats to self-administer alcohol and sucrose simultaneously. Naltrexone is an FDA approved drug that reduces drinking in humans and reduces alcohol intake in SA, so we chose this drug to test our choice model and compare it with expected results.[5]

Methods

Apparatus

Training Timeline



Choice Procedure Training

Single Lever Training

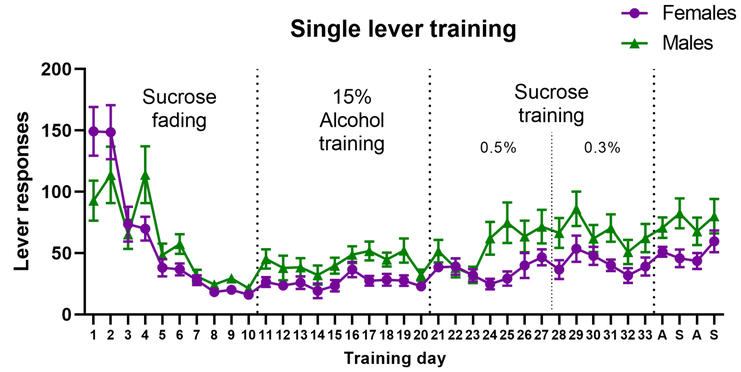


Figure 1. Lever responses for single-lever training. Training began with a sucrose fade, then EtOH SA. Sucrose SA was adjusted until single lever responses were similar to prior EtOH lever responses. The last four days are training days of alternating alcohol and sucrose sessions.

Choice Training

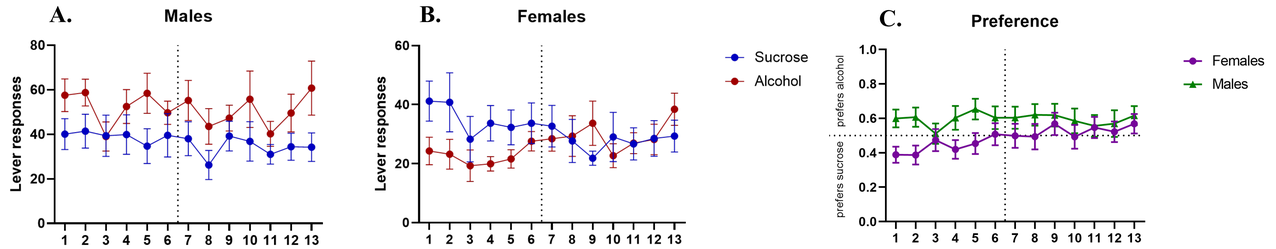


Figure 2. Lever responses for choice procedure with alcohol and sucrose. On session 1, rats were first introduced to the choice procedure in which both alcohol and sucrose self-administration options were present. On session 7, the sucrose solution was adjusted from 0.3% sucrose to 0.2% sucrose. **(A)** Male rats consistently demonstrated higher lever responses for alcohol. **(B)** Female rats did not respond significantly differently after the sucrose solution was adjusted. **(C)** Preference of alcohol vs sucrose. The preference was calculated by dividing the amount of alcohol lever responses by the total lever responses.

Naltrexone Administration

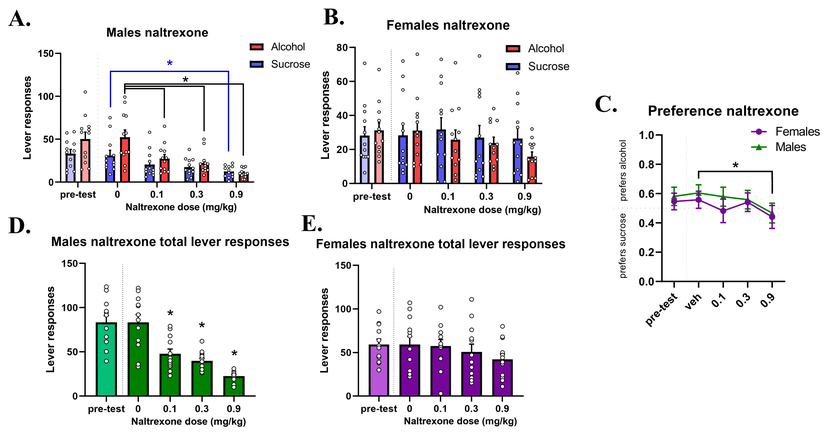


Figure 3. Lever responses after Naltrexone administration using average of pre-testing sessions and lever responses on test days. **(A)** Males demonstrated significantly fewer lever responses to alcohol at all doses while responding for sucrose was only reduced at the highest dose. **(B)** Females demonstrated no significant change in lever responses after Naltrexone administration. **(C)** Preference of alcohol vs sucrose after Naltrexone administration. Preference shifted toward sucrose at the highest dose. **(D,E)** Males and females total lever responses before and after Naltrexone administration. Males total lever responses decreased significantly at all doses. *p<0.05

References

1. SAMHSA, Center for Behavioral Health Statistics and Quality. 2021 National Survey on Drug Use and Health. Table 5.6B—Alcohol use disorder in past year: among people aged 12 or older; by age group and demographic characteristics, percentages, 2021. [cited 2023 Apr 15]. Available from: https://www.samhsa.gov/data/sites/default/files/reports/rpt39441/NSDUHDetailedTabs2021/NSDUHDetailedTabs2021/NSDUHDetTabsSect5pe2021.htm#tab5.6b
2. Heilig, M., Augier, E., Pfarr, S. et al. 2019. Developing neuroscience-based treatments for alcohol addiction: A matter of choice?. *Transl Psychiatry.* 9(255). Available From: https://doi.org/10.1038/s41398-019-0591-6
3. Acuff, S.F., MacKillop, J. & Murphy, J.G. 2023. A contextualized reinforcer pathology approach to addiction. *Nat Rev Psychol*. Available From: https://doi.org/10.1038/s44159-023-00167-y
4. Eric Augier, et al., 2018. A molecular mechanism for choosing alcohol over an alternative reward. *Science.* 360(6395): 1321-1326. DOI:10.1126/science.aao1157

Acknowledgements

Thanks to NIAAA grant AA028255 and the Bowles Center for Alcohol Studies for making this work possible.

Conclusions

- The use of two-choice self-administration allows for representation of drinking behaviors in rats when multiple competing rewards are present.
- Naltrexone decreased alcohol intake in male rats at all doses while sucrose intake was decreased only at the highest dose.
  - Naltrexone did not significantly change alcohol or sucrose intake in female rats.
- This two-choice self-administration system has potential to streamline pharmacological testing of novel treatments for AUD.