2021

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Introduction

Alcohol Use Disorder (AUD) alone effects nearly 6% of the adult population within the United States. Few treatments for AUD exist, with no new FDA-approved therapeutic treatments within the last 15 years. Additionally, the limited treatments we do have are estimated to produce sustained abstinence in less than 20% of individuals.

Psychedelics, such as lysergic acid diethylamide (LSD), psilocybin and 2,5-dimethoxy-4-iodoamphetamine (DOI) affect processes related to cognition, perception and sensory processing. These compounds are serotonergic agonists and act primarily through the 5-HT_{2A} receptor in the frontal cortex.

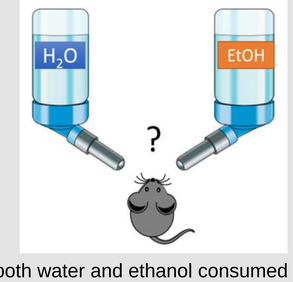
It has been demonstrated that serotonin has modulatory effects on the mesolimbic pathway, which is implicated in the neurobiology of addiction.

Clinical findings have demonstrated the ability of psilocybin to decrease alcohol consumption in heavy drinkers and studies with rodent models have suggested DOI and LSD have the ability to decrease ethanol preference and consumption.

The present study aims to evaluate the effects of psychedelic, 2,5-dimethoxy-4-iodoamphetamine (DOI), on ethanol drinking behavior in adult male C57BL/6 mice.

Methodology

Subjects 15 adult male C57BL/6 mice were kept on a reverse light cycle and had food and water *ad libitum.*
Training Mice were trained on the two-bottle choice paradigm by being given access to one bottle of 20% ethanol and one bottle of water every other day (off days mice had two bottles of water) for four weeks to obtain a baseline reading of drinking behavior. Following these four weeks, mice were assigned to either the treatment group or vehicle group based on weight and baseline drinking behavior from the week prior to testing.
Testing On the first day of the fifth and sixth weeks, mice were injected intraperitoneally with a dose of DOI (2 or 5 mg/kg) or saline vehicle 30-minutes prior to access to 20% ethanol. These DOI doses were chosen based on previous behavioral studies and dose response curves. Ethanol was given using 15 ml glass bottles with rubber stoppers. Liquid volumes were recorded prior to putting bottles in the cages.



Measurements The amount of both water and ethanol consumed on drinking days was measured at 2- and 24-hours and analyzed to calculate consumption and preference. Empty cages containing bottles of both ethanol and water were used as a measure of bottle leaks or evaporation. Raw consumption values were corrected and converted into preference percentages. Total fluid consumption was also calculated.
Data analysis All statistical analysis was done using GraphPad Prism version 9.0.

Results

Figure 1. Effects of a moderate and high dose of DOI on ethanol preference and consumption. Dotted lines represent injection of 2 mg/kg DOI on drinking Day 14 (start of week 5) and 5 mg/kg DOI on Day 17 (start of week 6).

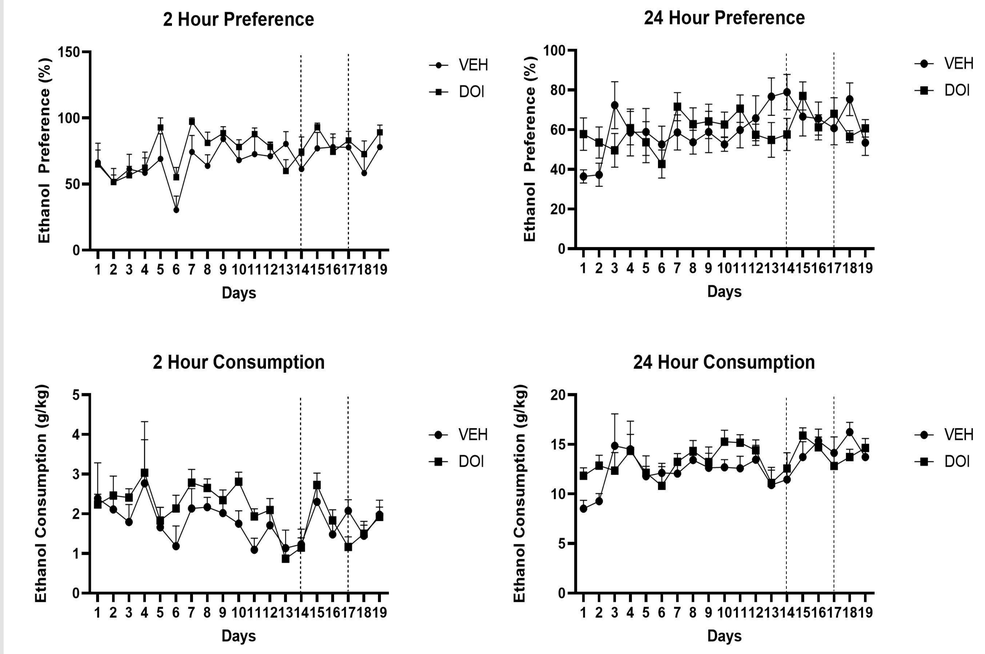
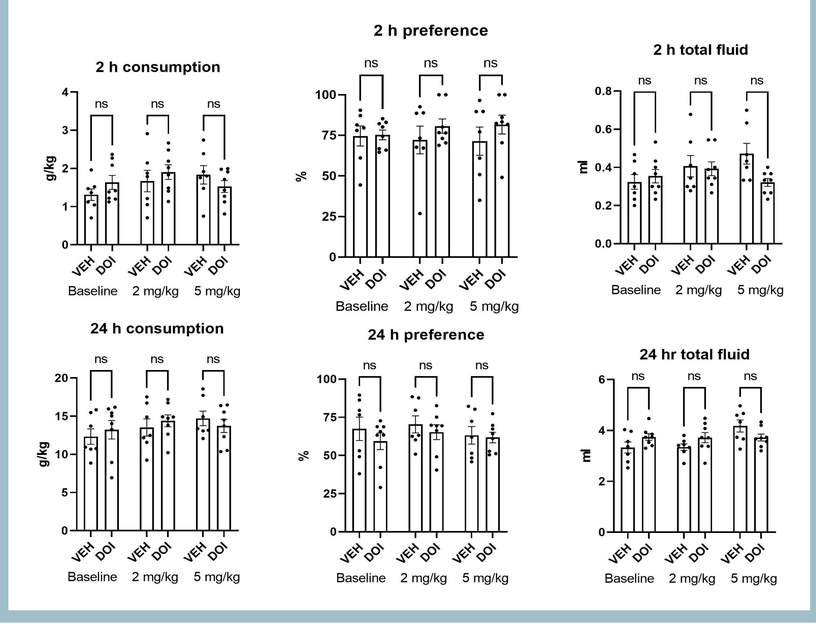


Figure 3. Comparison of average consumption, preference and total fluid consumption for baseline, 2 mg/kg and 5 mg/kg DOI. (Two-way ANOVA with multiple comparisons; α<0.05).



Conclusion

We hypothesized that a moderate dose of DOI would decrease ethanol preference and consumption.

- DOI did not affect ethanol consumption or preference at the 2- or 24-hour measures compared to baseline (week prior to DOI injection).
- The DOI-treated group showed no difference from the vehicle-treated group after receiving an either moderate (2 mg/kg) or high (5 mg/kg) dose of DOI.
- There was an overall interaction of time and treatment in both 2- and 24-hour fluid consumption in the groups (2-way ANOVA; 2-h total fluid [p=0.0343] and 24-h total fluid [p=0.0112]).

- Our results are most likely due to:
  - Issues with group randomization - Mice were assigned a group based on weights and average drinking values from the last drinking day prior to the first DOI treatment week.
  - Not allocating the mice into low and high drinking groups as seen is other experimental designs

- Further statistical analysis to determine the relationship of the baseline behavior to the behavior seen following DOI needs to be completed for further interpretation of results.

- More experiments are warranted before fully understanding how psychedelics can alter behavioral phenotypes associated with substance use disorder and alcoholism.

Acknowledgements

Department of Pharmacology and Toxicology; Department of Physiology and Biophysics; VCU Alcohol Research Center.

Miles Laboratory; González-Maeso Laboratory

Funding:
NIHR01 MH084894(J. G.-M.) and NIH R01 MH111940(J. G.-M.)
NIAAA: U01AA016667, P20AA017828 (MFM)

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