Neurosteroidogenesis and Individual Differences in Vulnerability to Developing Escalated Alcohol Intake Following Chronic Social Defeat Stress

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INTRODUCTION and GOALS

Translational research on PTSD present a paradox: although men are more likely to experience a traumatic event, women are twice as likely to develop PTSD, however, most studies are male focused which broadens gender disparities.

Alcohol Use Disorder (AUD) is highly comorbid with PTSD, where self medicating tends to cause binge drinking[1]

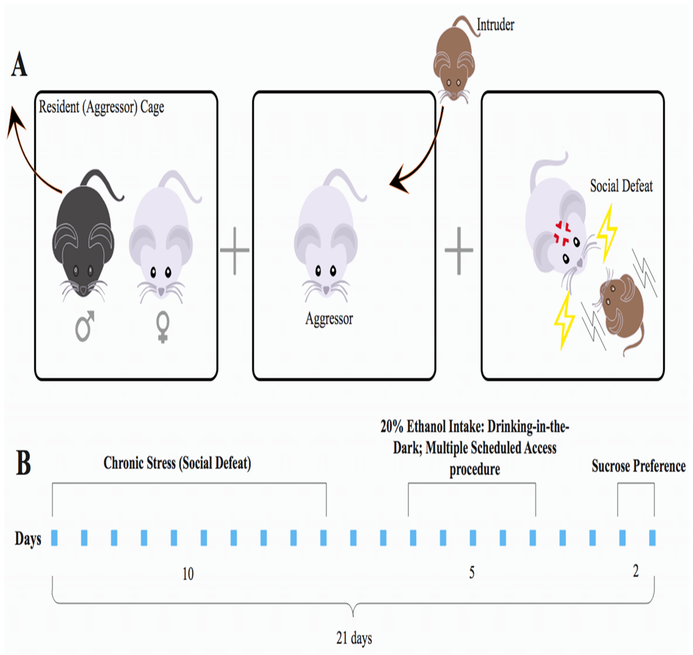
There are no approved compounds that have demonstrated efficacy to treat AUD comorbid with PTSD.

Our goal was to establish an animal model to explore the role of neurosteroid levels in predicting drinking in individuals exposed to social defeat, while investigating potential sex differences in the physiological conditions and changes to stress reactivity that follows trauma.

We previously used a genetically outbred, diverse population of mice(HAP1) and found individual differences in the effects that chronic social defeat stress has on alcohol drinking in both males and females.

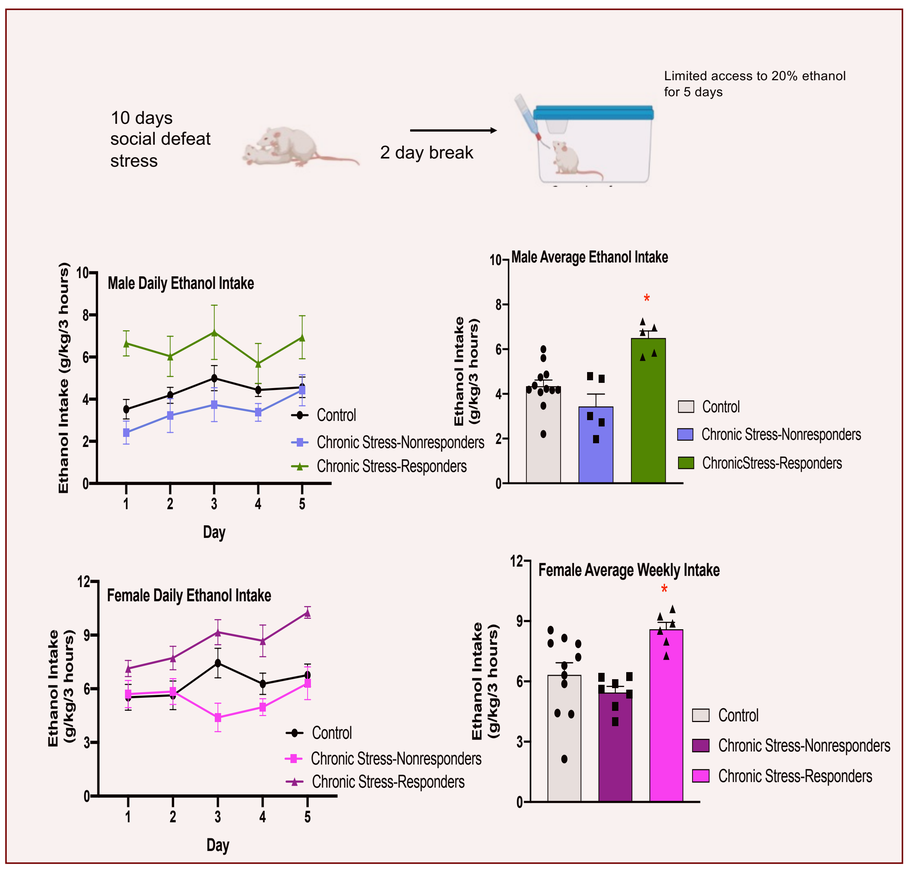
Genetically **inbred female** C57Bl/6J mice still show **individual differences** in vulnerability to **chronic social defeat stress** and may be a great model to investigate role n**eurosteroidogenesis** plays in **comorbid Alcohol Use Disorder/PTSD.**

SOCIAL DEFEAT PROTOCOL



- Blood samples of the C57BL/6J mice were taken 30 minutes after their first defeat.
- Following chronic social defeat, mice were isolated and given limited access to alcohol (20%, v/v) 3 hours a day for 14 days to assess changes in the escalation of binge drinking for intruder mice and non-stressed controls.

GENETICALLY OUTBRED BINGE DRINKING MODEL

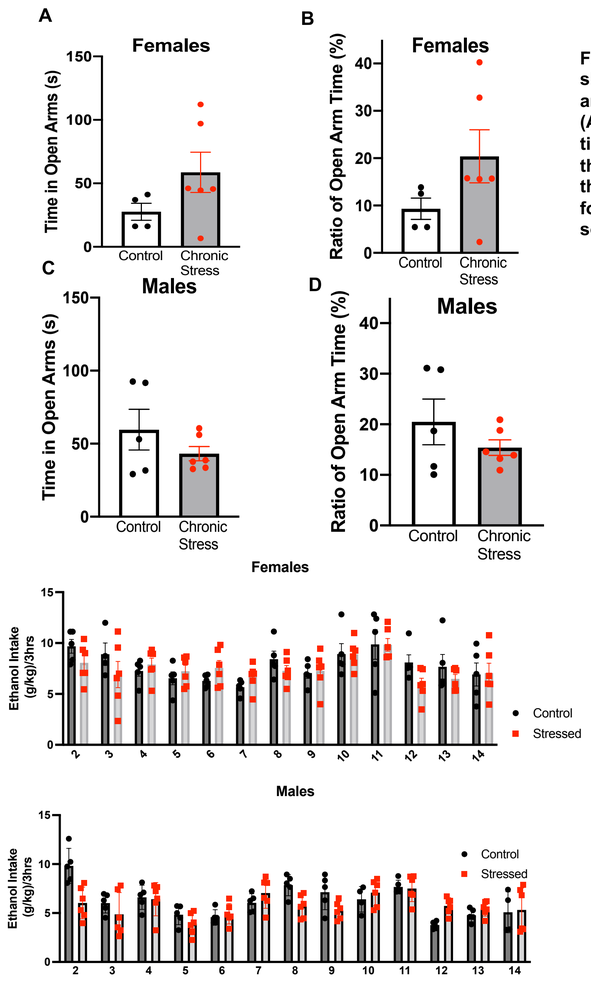


Among HAP1 male and female mice with limited access to alcohol after 10 days social defeat; Responders show significant increase in intake (*p's>0.05).

- **Our present aim was to replicate this effect with an inbred, genetically homogenous population of mice.**

We hypothesized that C57BL/6J inbred mice will show similar variability in vulnerability to social defeat stress, with some mice consuming more alcohol following stress and others showing resilience.

RESULTS



Female mice show spread in amount of time (A) and ratio of time (B) spent in the open arms of the maze following chronic social defeat.

Male mice show uniform reduction in time (C) and Percent of time (D) spent in the open arm of the plus maze following chronic social defeat.

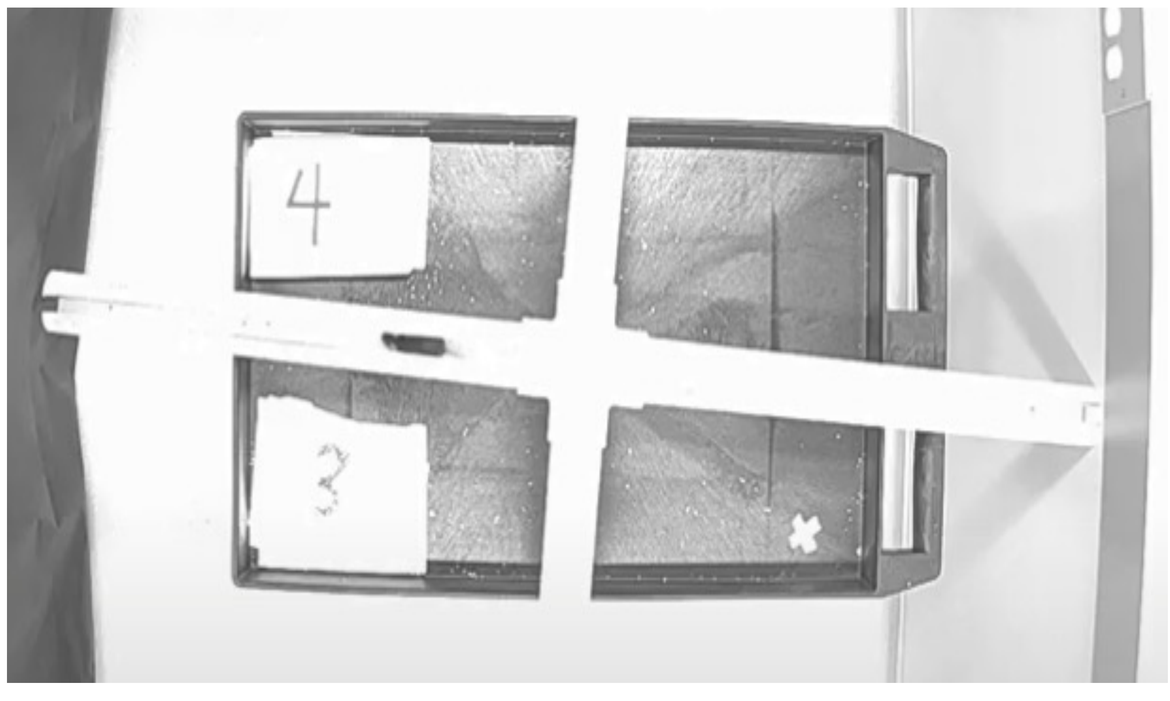
When compared to the controls, the chronically stressed animals did not significantly escalate their drinking.

CONCLUSION

- My experiment supports the correlation between individual differences and sex differences in binge drinking in relation to chronic stress.
- This establishes a useful model to explore the rationale for targeting allopregnanolone signaling as a novel therapeutic approach for individuals with comorbid AUD and PTSD.
- Our framework contributes to the understanding of stress-related sex differences in the field of preclinical neuroscience.
- This work is ongoing, but data assessed thus far support successful initiation of chronic stress for both male and female mice from this inbred strain.
- Future work will determine if these mice show variability in the effect that chronic stress has on binge drinking behavior and whether this variability may be predicted by changes in circulating neurosteroid levels in both males and females experiencing chronic stress and expand more information on female stress.

ELEVATED PLUS MAZE

- The anxiety-like behavior of chronically stressed C57BL/6J mice and non-stressed controls was evaluated using the Elevated Plus Maze (EPM) before drinking and 2 weeks following forced abstinence. Videos of behaviors were quantified using the software, BORIS.
- After a withdrawal period, another blood sample was taken and tissue was harvested to assess neuronal response to stress or acute alcohol, using c-Fos immunoreactivity.
- Behaviors and images were coded by experimenters blinded to treatment groups.



CITATIONS

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