Kappa Opioid Receptors in the Bed Nucleus of the Stria Terminalis (BNST) and Social Stress-Escalated Alcohol Consumption

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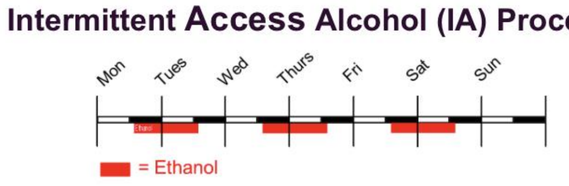
Introduction

Aversive stress experiences can lead to escalated drug consumption and increase the risk of relapse to drug seeking. Individuals who consume alcohol in negative social contexts or to alleviate the effects of social stress show a higher likelihood of developing alcohol use disorder. Social stress has been most effectively modeled in animals through social defeat paradigms. Repeated social defeat stress (SDS) enhances the rewarding and reinforcing effects of several drugs of abuse, including alcohol. However, the neural mechanisms by which SDS leads to increased alcohol consumption are not well understood.

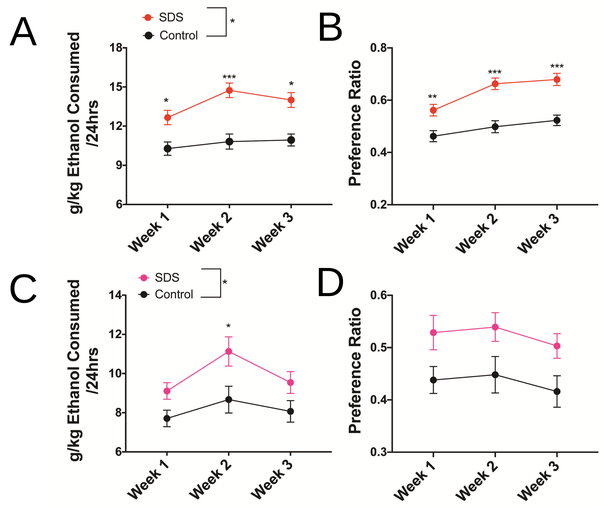
We cannulated mice with cannulae aimed at the BNST. We allow these mice to recover for two weeks, following which half the mice were subjected to social stress for ten days. The other half were control mice that were handled similar to the stressed mice but did not undergo social stress. Following ten sessions of social stress, the mice were housed undisturbed in their home cages for ten days after which, they were subjected to the intermittent access (IA) two-bottle choice alcohol consumption procedure.

Methods

Mice were stereotaxically implanted with canulae aimed at the BNST and allowed to recover for two weeks before being subjected to social defeat stress

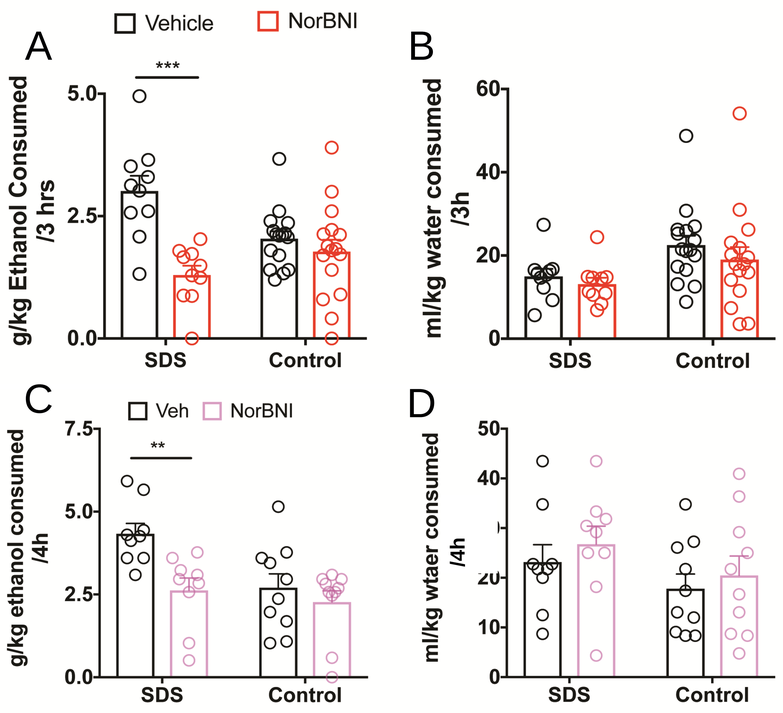


SDS increases alcohol consumption and preference in both male and female B6 mice



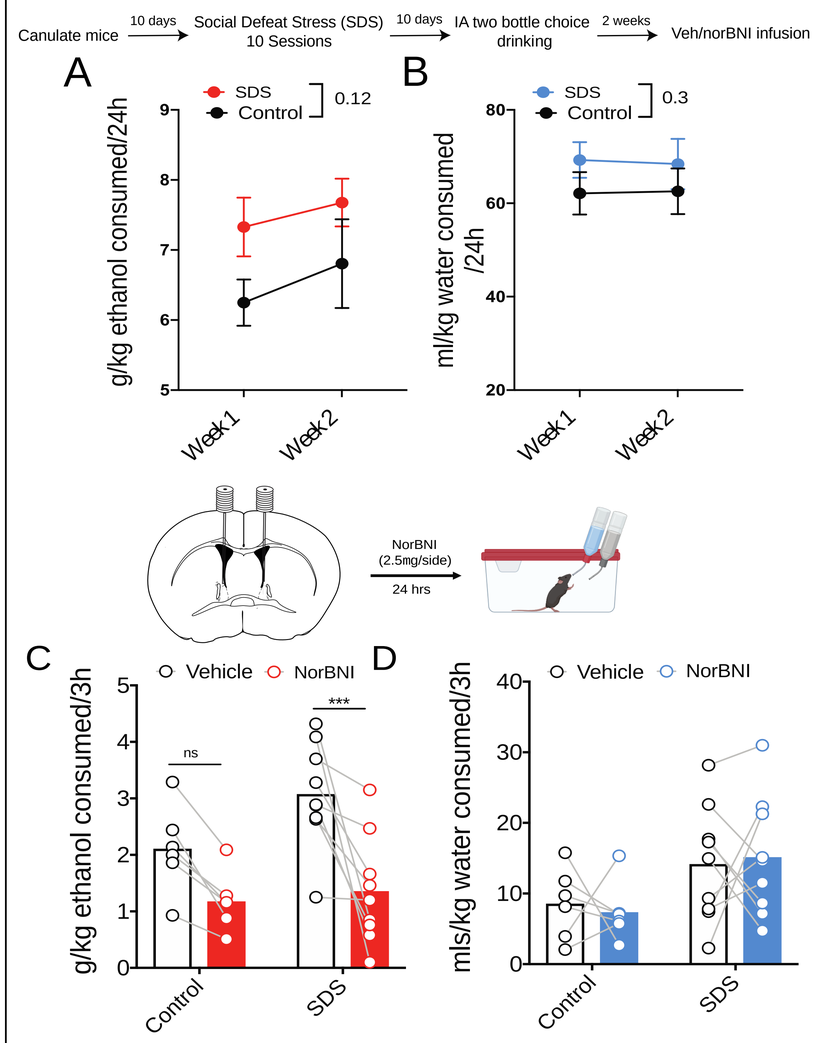
Previous studies in the Maiya lab showed that SDS significantly enhanced (A) alcohol consumption [F_{Stress} (1, 62) = 22.09, P<0.05] (B) and preference F_{Stress} (1, 62) = 26.77, P<0.05] in males. Social stress also increased (C) alcohol consumption [F_{Stress} (1, 30) = 5.419, P<0.05] and (D) preference [F_{Stress} (1, 29) = 7.219, P<0.05] in female mice. Two-Way repeated measures ANOVA, *, P<0.05; **, P<0.001; ***, P<0.0001. Sidak test. N = 29 - 35/group for males and N = 16-17/group for females.

Systemic NorBNI administration attenuates stress-escalated alcohol consumption



Male and female C57BL/6J mice were subject to SDS and IA alcohol consumption for 3 weeks. Mice were systemically injected with Vehicle or NorBNI (10mg/kg) and alcohol consumption was measured 3h post injection. A) NorBNI selectively reduced alcohol consumption (A) but not water consumption [$F_{Stress \times Drug}$ (1,24) = 13.85, p<0.05], ***, P<0.0001, Bonferroni's post-test. N = 10-16/group) (B) in stressed males . C) NorBNI also selectively reduced alcohol (C) but not water consumption (D) in stressed females. [$F_{Stress \times Drug}$ (1,17) = 6.56, p<0.05], ***, P<0.001, Bonferroni's post-test. N = 10/group)

Infusion of NorBNI into the BNST attenuates stress-escalated alcohol consumption



SDS increased alcohol consumption (A) although this increase did not reach statistical significance. Two-Way RM ANOVA, [F_{Stress}(1,13) = 2.774, p = 0.12]. B) Water consumption was not affected by SDS. Infusing NorBNI into the BNST significantly reduced alcohol consumption in stressed mice but not in unstressed controls. Two-Way RM ANOVA [F_{Drug}(1,13) = 2.774, p = 0.0005], ***, p<0.05, Sidak post test, n = 6—9/group. Water consumption was not affected by NorBNI.

Conclusion and Future Directions

- SDS increased alcohol consumption in males though this effect did not reach statistical significance.
- Bilateral infusions of 2.5μg NorBNI into the BNST reduced stress-escalated alcohol consumption. Water consumption was not affected.
- This experiment will be confirmed in a second independent cohort of cannulated mice
- Future experiments will use chemogenetic approaches in KORCre knockin mice to determine whether KORs located on the terminals of BLA glutamatergic projections into the BNSt regulate stress-escalated alcohol consumption.

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