Effects of oleoylethanolamide and N-oleoylsulfamide in a model of alcohol relapse in the context of PTSD

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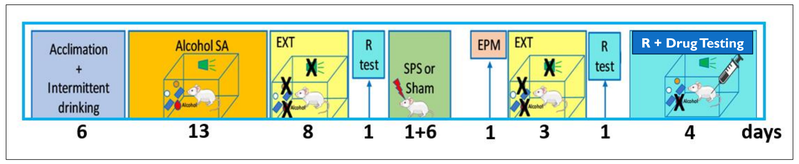
Background

Alcohol use disorder (AUD) is frequently co-morbid in patients suffering from post-traumatic stress disorder (PTSD). Few therapeutic options are available for the individual disorders, and there are currently no drugs specifically shown to treat AUD in patients with comorbid PTSD. This is in part because it has been challenging to produce reliable animal models that allow evaluation of pharmacological interventions for the comorbidity. Oleoylethanolamide (OEA), an endocannabinoid-like lipid signaling molecule, which functions as a satiety factor, has been reported to decrease alcohol self-administration (SA) in rats and preclinical manifestations associated with stress exposure such as stress-induced anxiety-like behavior and prepulse inhibition. N-oleoylsulfamide (NOS) is a compound licensed by Galea Therapeutic, which like OEA, binds at peroxisome proliferator-activated receptors-a (PPAR-a).

Objective

To test the validity of a model of alcohol relapse combined with exposure to Single Prolonged Stress (SPS) using OEA and N-oleoylsulfamide

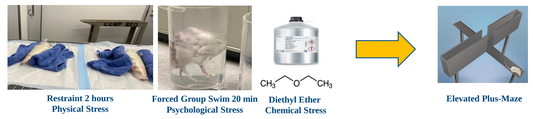
Methods & Study Design

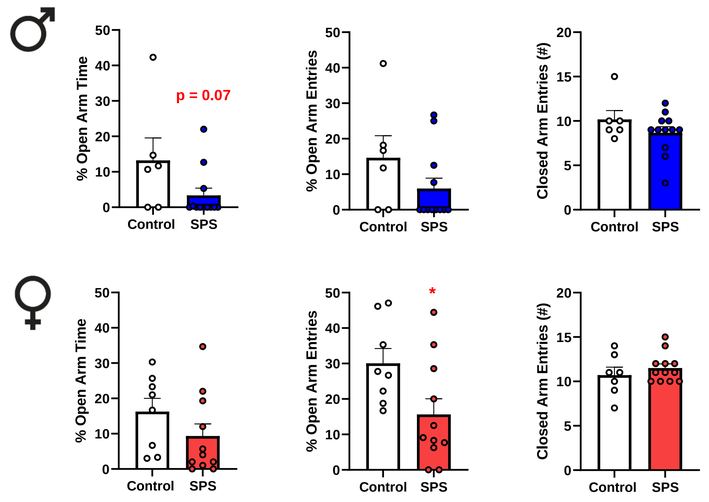


Animals. Male (N=18) and female (N=19) Sprague Dawley rats.
Drugs. OEA and N-oleoylsulfamide were administered intraperitoneally at 4mg/kg, and 1 and 4 mg/kg, respectively. Both drugs were suspended in a vehicle made of 5%Tween 80 + water.
SPS. SPS consisted of a combination of physical stress (Restraint for 2 hours), motivational stress (group swimming for 20 min) and chemical stress (diethyl ether exposure), all done in the same day.
Procedures. All rats were trained to self-administer alcohol (20% v/v, 0.1 ml) in 30-min daily sessions under a fixed ratio 1 (FR-1) reinforcement schedule over 13 sessions. Alcohol delivery was paired with the illumination of a cue light and a tone turned on for 5 sec. Responses were extinguished for 8 consecutive days when rats entered the chambers, but no alcohol, cue light, or tone were presented. Following the last extinction day, rats returned to the chambers where responses were paired to cue light and tone, but no alcohol was present (reinstatement, R). SPS or Sham control procedures took place after reinstatement. Rats were then assessed for their anxiety-like behavior in the elevated plus-maze (EPM) on day 9 following the onset of the SPS/Control procedures. Rats returned to the operant chambers and a second reinstatement took place after 3 consecutive extinction sessions. Finally, the reinstatement of alcohol-seeking behavior was evaluated following the administration of OEA and N-oleoylsulfamide according to a Latin Square design.

Results

1.





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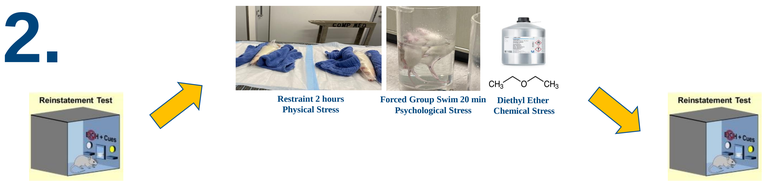
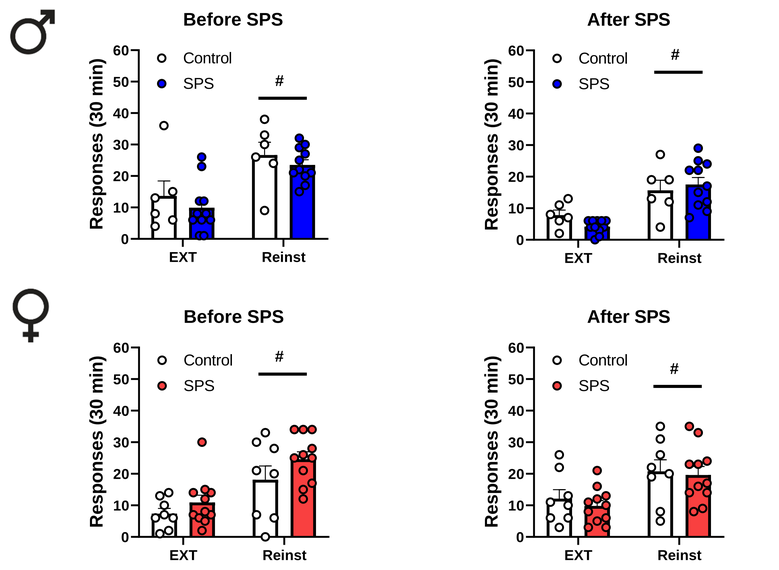
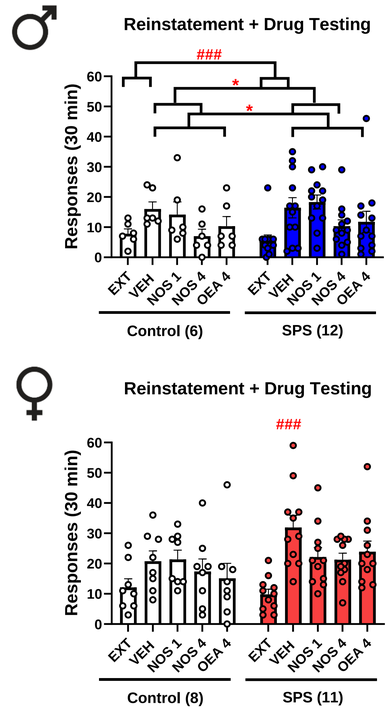




Results

3.



Conclusions

- **SPS induces substantial anxiety-like behavior in male and female rats.**
- **Overall, SPS exposure does not alter cue-induced reinstatement.**
- **PPAR-a agonists reduce alcohol-seeking behavior both in SPS-exposed and Control male rats.**
- **OEA and N-oleoylsulfamide could represent potentially novel pharmacotherapies for AUD-PTSD comorbidity.**

Acknowledgements

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