Sex Differences and Effects of Modafinil and Allopregnanolone on a Rat Model of Methamphetamine Relapse

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Background

- Methamphetamine (METH) addiction is notoriously difficult to treat; in one study examining patients undergoing treatment for addiction, 58% admitted to relapsing within 6 months[1]
- METH causes a short term rise in brain dopamine levels, but causes long term deficits of dopamine in areas of the brain associated with drug addiction and reward (striatum), possibly contributing to its withdrawal effects[2]
- Modafinil (MOD) is a drug currently being investigated as a treatment for METH addiction due to its ability to block METH induced rises in dopamine levels[3] and reduce the severity of METH withdrawal symptoms[4]
- Some drugs, such as baclofen, are known to have a differential effect on attenuating drug-seeking behavior in males and females[5]
- Allopregnanolone (ALLO) is a progesterone metabolite shown to alter dopamine release in the striatum[6] and reduce drug-seeking behavior in female rats[7]

Objectives

- Investigate the effects of MOD on drug-seeking behavior using an animal model of relapse
- Analyze sex differences in receptivity to METH, susceptibility to relapse, and response to MOD and ALLO treatments

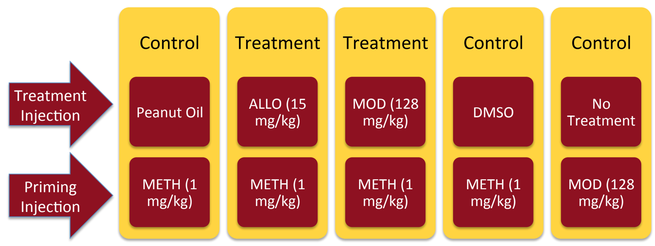
Methods

Figure 1. A rat with an IV infusion apparatus in an operant conditioning chamber. Both levers activate a stimulus light when pressed. One lever also activates a pump that delivers a 0.5 mg/kg METH IV infusion. 10 males and 8 females completed the experiment. One additional female completed an ALLO and ALLO control trial before being withdrawn for health reasons.

Procedure

Figure 2. Four phases of the relapse model. Rats pass through these distinct phases during the experiment.

Figure 3. Detail of treatment and primer schedule during reinstatement phase. Every other session a saline priming injection was given in place of METH. The order of the MOD, ALLO, and control treatments (DMSO and peanut oil) were randomized for each rat, though the MOD priming control was always done in the last session.



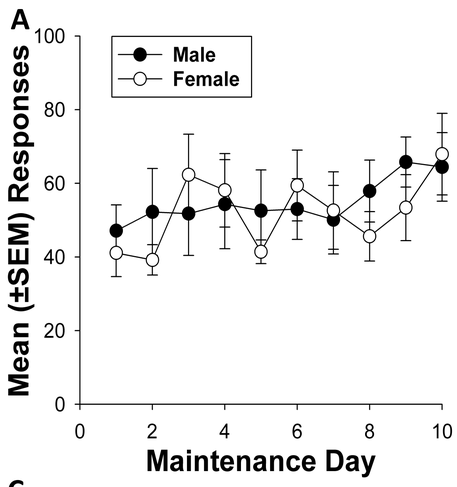
Acquisition
- 0.5 mg/kg METH infusions available in daily 5 hr sessions
- Peanut butter on lever aids acquisition of METH seeking behavior
- Begins maintenance phase after stability criteria met (>25 infusions over 3 days)

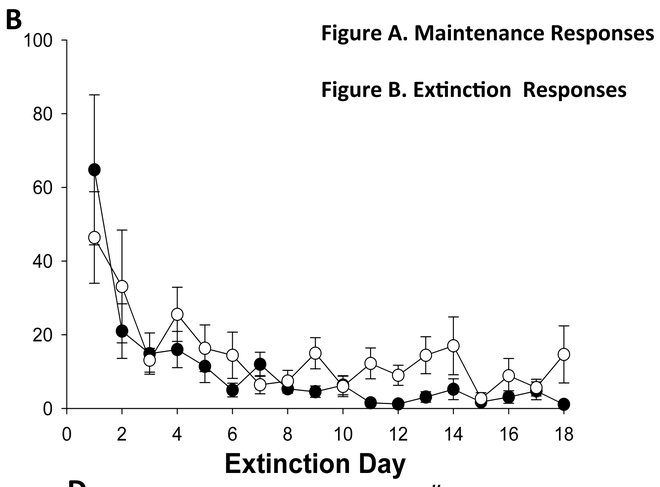
Maintenance
- 0.5 mg/kg METH infusions available in daily 2 hr sessions
- Begins extinction phase after 10 days

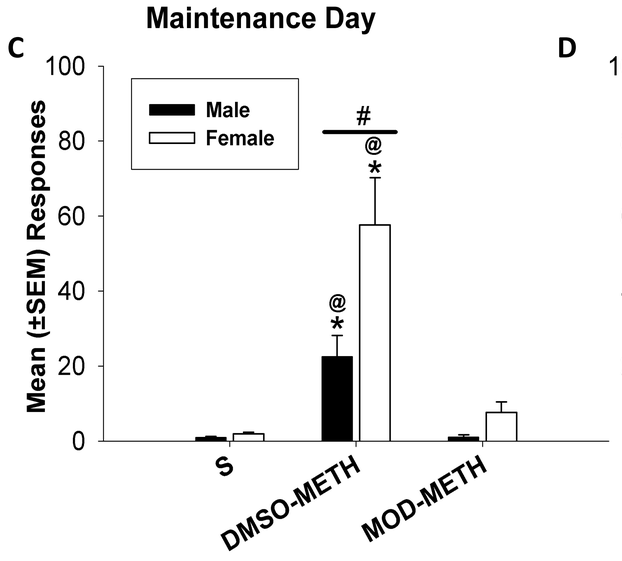
Extinction
- METH is replaced with saline , but daily 2 hr sessions continue
- Pump, stimulus light, and house light continue to operate
- Begins reinstatement phase after 18 days

Reinstatement
- Drug pump, stimulus light, and house light are unplugged
- Lever presses continue to be recorded in daily 2 hr sessions
- Treatments are given 30 minutes prior to session via IP injection, priming injections are given at the start of session

Results







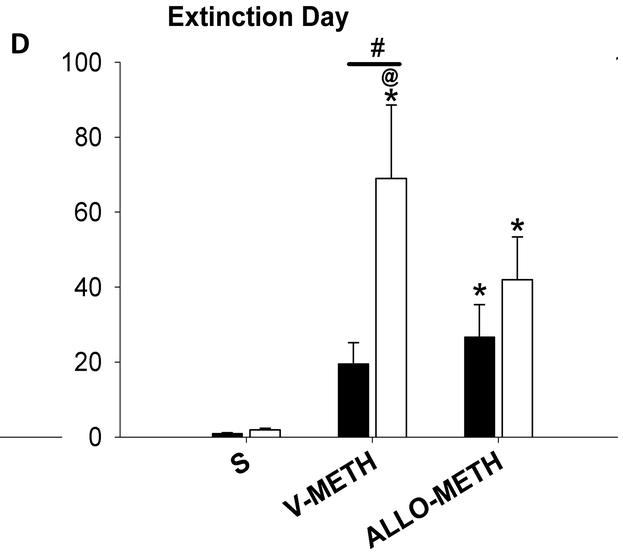


Figure C. MOD Treatment. Mean responses on previously METH-paired lever after saline, METH, and METH priming injection with MOD treatment. * indicates significant difference from saline priming injection, # indicates significant difference between sexes with control treatment, @ indicates significant difference from MOD treatment.

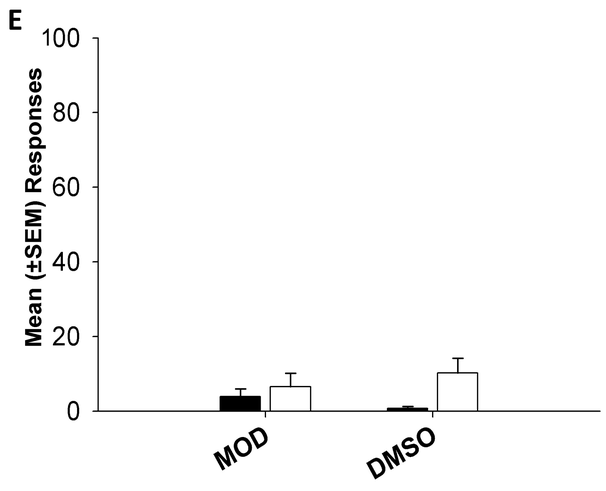


Figure D. ALLO Treatment. Mean responses on previously METH-paired lever after saline, METH, and METH priming injection with ALLO treatment. * indicates significant difference from saline priming injection, # indicates significant difference between sexes with control treatment, @ indicates significant difference from ALLO treatment.

Figure E. MOD priming injection control. Mean responses on previously METH-paired lever after MOD priming injection and control priming injection.

Conclusions

- No sex differences were observed in the maintenance or extinction phases (Figs A and B)
- Mod attenuated drug-seeking behavior in both male and female rats (Fig C)
- When a METH priming injection was given after a MOD treatment, the mean response was not different than the mean response after a saline priming injection (Fig C)
- ALLO attenuated drug-seeking behavior in only female rats (Fig D)
- Female rats had more responses than male rats after a METH priming injection with control treatment (Figs C and D)
- When MOD itself was used as a priming injection, it did not cause an increase in lever presses compared to the control injections (Fig E)
- The results suggest that MOD may be an effective drug for treating METH addiction by preventing relapse
- Since MOD did not potentiate drug-seeking behavior itlself, it may not induce METH relapse
- Results also illustrate that gonadal hormones, like ALLO, play a role in drug addiction and may help to explain sex differences in drug-seeking behavior

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