Effects of Restraint Stress and Allopregnanolone Inhibition on Amphetamine Locomotor Sensitivity

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INTRODUCTION

The chronic, recurring nature of addiction remains a worldwide problem. Even after apparently successful clinical treatment and long-term abstinence, individuals may still relapse many months or years later. Although many individual differences exist among substance abusers, relapse tends to occur during periods of high stress (Sinha et al., 2006). Behavioral training and therapy can help cope during these high stress times, but pharmacological interventions have not been shown to be effective (Ross & P seiselow, 2009). Although some therapeutic options decrease relapse rates, more effective treatments for relapse need further evaluation.

The effect of stress on use of and relapse to drugs of abuse likely stems from coupled stress and reward circuits in the brain. Stress leads to increased release of stress-related hormones including 3α, 5α-tetrahydroprogesterone or, allopregnanolone (Purdy et al., 1991). Allopregnanolone is a neurosteroid that inhibits several brain circuits involved with stress and reward. Elevated levels of this neurosteroid occur throughout the mammalian brain and periphery after cocaine administration, and rats show enhanced dopamine release in the nucleus accumbens after an injection of finasteride, which inhibits the enzyme (5α-reductase) responsible for allopregnanolone synthesis (Dazzi et al., 2002). Finally, acutely stressed rats exhibit increased dopamine release in the prefrontal cortex after an injection of finasteride, further indicating allopregnanolone’s involvement with brain reward systems (Devoto, 2012). Based on this information, we hypothesized that administration of finasteride would result in increased stress induced amphetamine locomotor sensitization.

METHODS

Subjects: Thirty adult male Long-Evans rats (Iffa Credo) were pair housed on a 12:12 light-dark cycle with lights on at 07:00. Rats were randomly assigned to one of three pre-treatment conditions (saline, 100 mg/kg finasteride, or 25 mg/kg finasteride) followed by pseudo-random assignment to control or restraint stress conditions.

Doses: Finasteride (Zeinon, Inc., Newport, RI) was dissolved in 20% CMC-45% glycerol in a concentration of 15 mg/ml or 25 mg/ml. 5α-Pregnanolone (Sigma) was dissolved in saline in a concentration of 1.0 mg/ml.

Pretreatment: Rats received subcutaneous injections of either vehicle, 100 mg/kg finasteride, or 25 mg/kg finasteride both 48 hours and 24 hours before stress procedure.

Acute stress: Twenty-four hours after the pretreatment injection rats received control or restraint stress procedures (no injections were administered on the day). During the 90-120 minute time period after behavior, rats in the stress group were place in restraints tubes for 30 minutes. After 30 minutes, rats were injected with 0.5 ml/kg 5α-pregnanolone and placed back in the chamber for 120 minutes. Distance traveled was collected using a 1 × 1.8 phototransistor tracking system (Watsonetics, Inc.) and scanners recorded the number of crossing points for each rat during this period.

RESULTS

Allopregnanolone in Hippocampus

Allopregnanolone concentrations following finasteride pre-treatment. A 2 x 3 (condition x stress) ANOVA (vehicle, 100 mg/kg, 25 mg/kg) between subject design revealed no significant effect of dose (F < 1, p > 0.05), and no significant effect of condition (F < 1, p > 0.05). Non-representative standard error.

CONCLUSIONS

• One hour of acute restraint stress decreased overall locomotor activity in an open field.
• Finasteride did not lower allopregnanolone levels, regardless of dose.
• Pritchard et al. (unpublished) found similar results using a chronic stressor. Following 5 days of restraint stress rats exhibited locomotor sensitization in response to an acute injection of 1.0 mg/kg amphetamine. However, no effect of finasteride on amphetamine sensitization was observed after this chronic stressor.
• Stereotypy was rated and effect of stress, not dose was found. Thus, rats that were stress-stressed all demonstrated higher levels of stereotypy than control rats.
• Corticosterone levels did not elevate in response to stress.

Limitations in our study may have been due to our timing of finasteride pretreatment, stressor type, or duration of stress. In addition, more thorough lipid extraction will be taken into consideration for future research.

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REFERENCES


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FINISHER Dose in mg/kg

Corticosterone in Plasma

Corticosterone concentrations during restraint stress. Time: 1 hr after restraint stress, 6 hr after restraint stress. Rats were injected with 0.5 ml/kg 5α-pregnanolone at 1 hr before restraint recovery. Mixed ANOVA with between subject factor of condition (control vs. stress) and time (vehicle, 100 mg/kg, 25 mg/kg) between subject design revealed no significant effect of dose (F < 1, p > 0.05), and no significant effect of time (F < 1, p > 0.05). Non-representative standard error.