**Effects of Restrain Stress and Allopregnalone 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 & Pescod, 2009). Although some therapeutic options decrease relapse rates, more effective treatments for relapse need further research.

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, allopregnalone (Purdy et al., 1991). Allopregnalone is a neurosteroid tied to 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 I) responsible for allopregnalone synthesis (Dazzi et al., 2002).

Finally, acutely stressed rats exhibit increased dopamine release in the prefrontal cortex after an injection of finasteride, further indicating allopregnalone’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 (littermate pair housed on a 12:12 light/dark cycle with lights on at 0700 hours. Rats were randomly assigned to one of three pretreatment conditions (saline, 100 mg/kg finasteride, or 25 mg/kg finasteride) following pseudo-random assignment to control or restraint stress conditions.

**Drugs:** Finasteride (Steraloids, Inc., Newport, RI) was dissolved in 30% CMC solution (pH 8.5) in a concentration of 30 mg/ml or 50 mg/ml (Allopregnalone (Sigma-Aldrich) was dissolved in saline in a concentration of 1 mg/ml.

**Pretreatment:** Rats received i.p. 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 last pretreatment injection rats received control or restraint stress procedure (no injections were administered on any days). During each 90-120 minutes after baseline, rats in the stress group were placed in restrain tubes for 30 minutes. After 30 minutes, rats were injected with 1 mg/kg amphetamine and placed back in the chamber for 120 minutes. Distance traveled was collected using a 30 x 30 phototube tracking system (MotionMonitor), and cummures recorded the time for a later score of stereotypy behavior averaged.

**Histological analysis:** Twenty four hours after restraint stress, rats were sacrificed by dislocation at the 24th hour and allowed to fixate for 24 hours. All rats received a saline injection (1 ml) and were placed in an open field chamber for 30 minutes. After 30 minutes, rats were injected with 1 mg/kg amphetamine and placed back in the chamber for 120 minutes. Distance traveled was collected using a 30 x 30 phototube tracking system (MotionMonitor), and cummures recorded the time for a later score of stereotypy behavior.

**RESULTS**

**Allopregnalone in Hippocampus**

**Allopregnalone concentrations following finasteride pre-treatment. A x 2 x 3 (condition x control x stress) x 2 (vehicle, 100 mg/kg finasteride, or 25 mg/kg finasteride) interaction revealed: no significant effect of dose (F(2, 10) = 1.124, p = 0.376), and no significant effect of condition (F(2, 10) = 1.064, p = 0.376). No main effect of condition (F(2, 10) = 1.064, p = 0.376). No interaction effect was observed.**

**Stereotypy was rated and effect of stress, not dose was found. Thus, rats that were stressd were alling very higher levels of stereotypy than control rats.**

**CONCLUSIONS**

- One hour of acute restraint stress decreased overall locomotor activity in an open field.
- Finasteride did not lower allopregnalone levels, regardless of dose.
- Pritchard et al. (unpublished) found similar results using a chronic stressor.

In conclusion, they found that stress must be increased for 5 days of restraint stress rats exhibited locomotor sensitization in response to an acute injection of 10 mg/kg amphetamine. However, no effect of finasteride on amphetamine sensitivity was observed after this chronic stressor.

**REFERENCES**


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