The Effect of Chronic Cocaine on Behavioral Sensitization and Allopregnanolone Levels in Rat Serum and Brain Samples

Griffin M. Sansbury, Minna H. McFarland, Kate C. Musselman, Donita L. Robinson
Bowles Center for Alcohol Studies, Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

Introduction

- Neurosteroids are steroids produced de novo in the brain that affect neuronal excitability. Chronic use is often associated with decreased levels of neurosteroids.
- Allopregnanolone, (3α,5α)-3-hydroxy-5-pregnan-20-one, is a progesterone-derived neurosteroid that is a positive allosteric modulator of GABA<sub>B</sub> receptors with potential to affect dopaminergic transmission.
- Human studies have demonstrated the possibility of elevated Basal plasma and cerebral concentrations of allopregnanolone in both sexes.

Animals were euthanized 24 hours after the final injection. Specifically, elevating circulating allopregnanolone via progesterone administration mediated a reduction in drug craving and stress responsivity. Chronic cocaine confers sensitization in rats. In humans, it is associated with decreased levels of pregnenolone, a precursor to allopregnanolone. Basal plasma and cerebral concentrations of allopregnanolone are elevated in female rats compared to males.

This study aims to elucidate the mechanism of an allopregnanolone-mediated inhibition of drug reinstatement observed in humans by testing whether chronic cocaine reduces allopregnanolone in an animal model.

We hypothesize that chronic cocaine administration will sensitize subject’s locomotion and stereotyped behavior while attenuating allopregnanolone levels in serum and specific brain regions involved in the mesolimbic dopamine pathway and neurosteroidogenesis.

Materials and Methodology

**Experimental design:**
- 32 Sprague-Dawley rats: 16 male, 16 female
- Drug regimen: 2 days of saline IP injections, followed by 14 days of 15 mg/kg cocaine HCl or saline IP injections (once/day)
- Immediately after injections, animals were placed in operant boxes for 2 hours to measure locomotor activity. Distance traveled was measured via Anymaze software and stereotyped behavior was scored by the experimenter.
- Animals were euthanized 24 hours after the final injection.

Allopregnanolone was extracted from serum and brain samples and ELISAs were used to quantify allopregnanolone.

**Results**

- **Figure 1. Locomotor activity**
  - Female Locomotor Activity
  - Male Locomotor Activity
  - There was a main effect of treatment on locomotion as cocaine-treated females travelled significantly further distances than saline-treated females (p<0.001). This was also replicated within the males (p<0.001). There was no treatment x time interaction.

- **Figure 2. Stereotyped behavior**
  - Female Stereotyped Behavior
  - Male Stereotyped Behavior
  - There was a main effect of treatment on stereotyped behavior as cocaine-treated females received higher stereotypy scores than saline-treated females (p<0.001). This was also replicated within the males (p<0.001). Within the females, there was a significant treatment x time interaction between days 3 and 9 (p<0.05).

- **Figure 3. Allopregnanolone Levels in Serum and Brain Regions**

**Conclusions**

- Chronic cocaine increased locomotor and stereotyped behavior compared to saline, but sensitization was only observed in stereotyped behavior.
- Chronic cocaine did not significantly affect allopregnanolone levels in serum nor in any brain region.
- We found potent sex differences in allopregnanolone levels in serum, olfactory tubercle, and the prefrontal cortex, consistent with literature.
- We found a lack of a sex difference in the dorsal striatum, ventral striatum, and midbrain, potentially elucidating sex differences in addiction and reinstatement.

**Future Directions**

- Does allopregnanolone decrease spontaneous dopamine release within the mesolimbic dopaminergic pathway? Is this effect sex-dependent?
- Can allopregnanolone restore chronic cocaine-mediated increases in dopamine release?

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**References**