



A Ketogenic Diet Impairs Conditioned Place Preference for Cocaine in Sprague-Dawley Rats

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INTRODUCTION

RESULTS

DISCUSSION

BACKGROUND:

- Over 5.5 million people use cocaine in the U.S. (Lipari, 2018); chronic use is associated with drug addiction and increased health risks.
- Currently, there is no FDA approved treatment to effectively address cocaine addiction.
- Cocaine acts by blocking the reuptake of dopamine in the synapse.
- The resulting increase in dopaminergic signaling is critical for the locomotor stimulating and addictive properties of cocaine.
- High fat/low carbohydrate ketogenic diets (KDs) cause an upregulation of adenosine signaling in the brain (Masino et al., 2009).
- Increases in adenosine signaling reduces cocaine-induced reward.
- Previously our lab studied the effect of a KD on cocaine-induced locomotor responses (Martinez et al., 2019).
- A KD was seen to reduce cocaine-induced locomotor responses.

HYPOTHESIS: KDs positively impact brain processes that are negatively impacted by drug addiction, thereby reducing motivation to seek drugs of abuse.

PREDICTIONS: Male and female rats who are given a KD will show diminished conditioned place preference (CPP) for cocaine.

METHODS

ANIMALS: Male and female Sprague-Dawley rats were pair housed and subjected to a 12hr light-dark cycle with free access to food and water. The animals began their assigned diet at 5 weeks of age. Behavioral testing took place when the rats were between 8 and 10 weeks of age.

DIET: At 5 weeks of age, rats were randomly chosen to maintain a standard diet (SD; LabDiet 5001, Lab Supply, Fort Worth, TX) composed of 13.5% calories from fat, 58.0% calories from carbs and 28.5% calories from protein or switched to a ketogenic diet (KD; F3666, Bio-Serv, Flemington, NJ) composed of 75.1% calories from fat, 3.2% calories from carbohydrates, and 8.6% calories from protein. They remained on their assigned diet throughout the experiment.

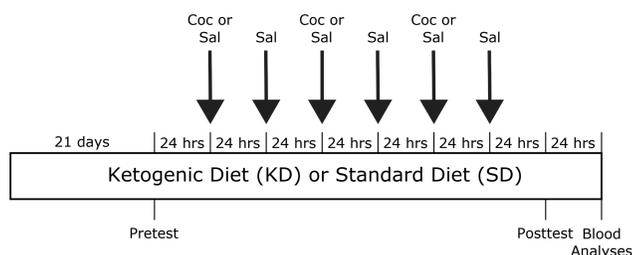
PHARMACOLOGICAL AGENTS: Cocaine Hydrochloride (Sigma-Aldrich) was dissolved in sterile saline to the working concentration of 10 mg/kg. Animals received intraperitoneal injections of 10 mg/kg of cocaine or saline.

BEHAVIORAL TESTING/MEASURES: A two chamber CPP apparatus was used for this experiment. During the Pretest and Posttest, the animal was allowed free access to both sides of the apparatus for 15 minutes while video recorded. Innate preference for apparatus side was determined from the Pretest. On conditioning days 1, 3, and 5, rats were injected with either saline or cocaine and placed into their initially non-preferred chamber. On days 2, 4, and 6, all animals were injected with saline and placed into their initially preferred chamber. For the Pretest and the Posttest, no animals were injected, and time spent in each chamber and total distance travelled were measured.

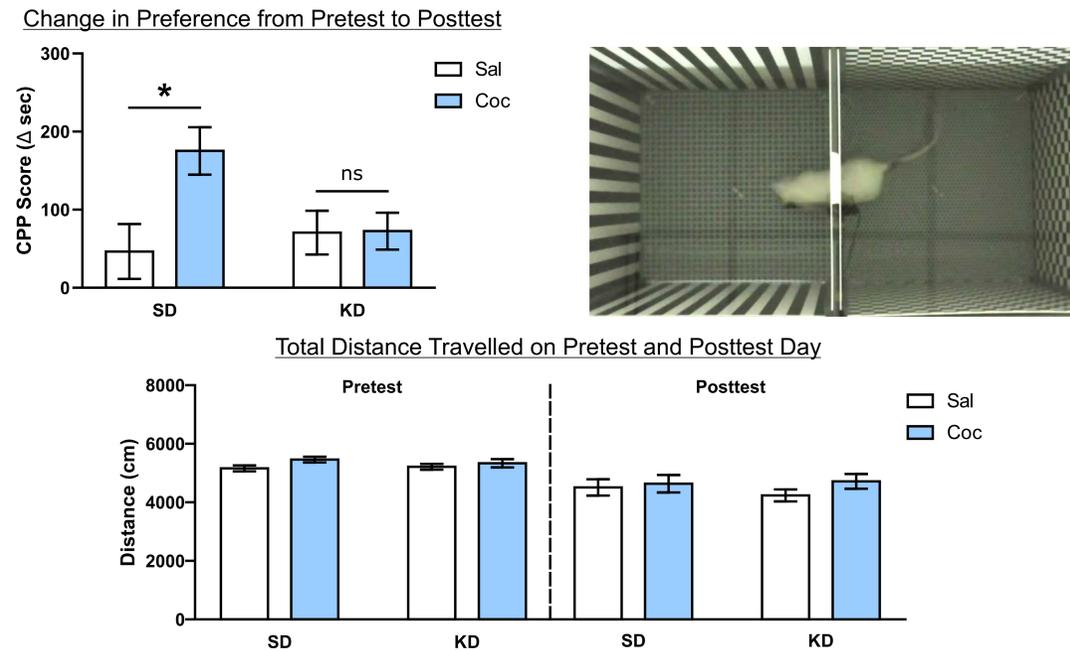
TREATMENT GROUPS:

Sex	Diet Group	Drug Group	Sample Size
Female	SD	Saline	12
Female	SD	Cocaine	10
Female	KD	Saline	10
Female	KD	Cocaine	10
Male	SD	Saline	8
Male	SD	Cocaine	12
Male	KD	Saline	8
Male	KD	Cocaine	10

TIMELINE:

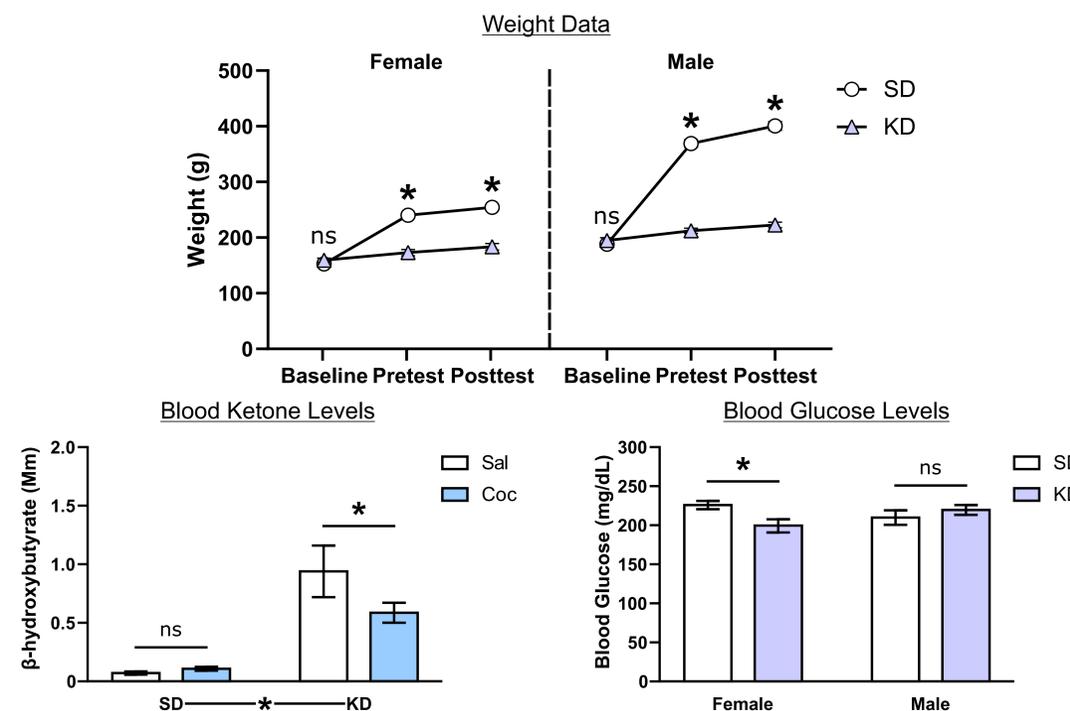


BEHAVIORAL MEASURES



Mean (SEM +/-) of CPP score (change in duration in time spent in the initially non-preferred side from Pretest to Posttest) and the total distance travelled during the Pretest and Posttest. SD animals injected with cocaine had significantly higher CPP scores than SD animals injected with saline. This effect was not seen in the KD animals. SD and KD animals were equally able to perform the locomotor functions required of this task.

PHYSIOLOGICAL MEASURES



Mean (SEM +/-) of weight, blood ketone levels and blood glucose levels. As expected, males weighed more than females. There was no significant difference at Baseline, but during the Pretest and Posttest SD rats had significantly higher weights than KD rats. As anticipated, KD rats had significantly higher ketone levels than SD rats. Females on the SD had significantly higher blood glucose levels than females on the KD; this difference was not observed in the males.

BEHAVIORAL MEASURES:

- A KD blocked the formation of a CPP for cocaine.
- This indicates that motivation for cocaine was reduced by this kind of diet.

PHYSIOLOGICAL MEASURES:

- As expected, a KD elevated blood ketone levels.
- Ketosis was induced in animals on a KD.
- A KD interfered with weight gain.
- As expected, SD and KD rats still gained weight over time, but the KD animals weighed less overall than SD animals.
- Even though KD animals weighed less, they were still equally able to perform the basic locomotor functions required for this task.

FUTURE DIRECTIONS

- Our lab is currently investigating the effects of a KD on natural rewards such as sexual behavior



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- Martinez, L. A., Lees, M. E., Ruskin, D. N., & Masino, S. A. (2019). A ketogenic diet diminishes behavioral responses to cocaine in young adult male and female rats. *Neuropharmacology*, 149, 27–34. <https://doi.org/10.1016/j.neuropharm.2019.02.001>
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