Applying behavioral economic approaches to study THC-opioid interactions in a rat model

Katherine E. Driver[1], Barry Setlow[2], Marek Schwendt[1], Lori A. Knackstedt[1]
Departments of Psychology[1] and Psychiatry[2], University of Florida, Gainesville, FL

Center *for* Addiction Research & Education
UNIVERSITY *of* FLORIDA

INTRODUCTION

- In 2020, more than 60,000 lethal overdoses were primarily attributable to opioids[1]. Opioid use disorder (OUD) lacks an effective, broad-spectrum treatment. Limited clinical research suggests that while co-use of cannabinoids can decrease rates of opioid dependence and severity of withdrawal, it can also increase rates of anxiety and depression[2].
- OUD is considered a qualifying condition for the use of medical marijuana in several US states.
- However, well-controlled, translational animal models are necessary to investigate the neural and behavioral consequences of cannabinoid-opioid co-use and to determine the efficacy and safety of cannabinoids for OUD treatment.
- The present study is the first comprehensive investigation of the effects of Δ9-tetrahydrocannabinol (THC) on behavioral and neural corelates of chronic oxycodone use in animals.
- Specifically, this study investigates the effects of daily Δ9-tetrahydrocannabinol (THC) consumption (1) on behavioral economic demand for intravenously self-administered (IVSA) oxycodone, (2) on oxycodone-associated withdrawal symptoms, (3) on the magnitude of cue-elicited oxycodone-seeking, and (4) on self-administration and seeking of a natural non-drug reinforcer.

METHODS

- **Subjects:** Adult male and female Sprague-Dawley rats (n = 48).
- **Sucrose self-administration:** 11 rats self-administered sucrose pellets (45mg) in standard 2-lever (active/inactive) operant chambers 6 days/week for 4 weeks. The ratio of responding for sucrose remained at FR-1 only.
- **Oxycodone IVSA training:** 23 rats self-administered oxycodone solution in standard 2-lever operant chambers. Rats received oxycodone (0.1 mg/kg/infusion) on an FR-1 schedule for 3 hours daily for the first 6 days. Upon completion of criteria for FR-1 (minimum 6 days on FR-1, with 2 consecutive days reaching a criterion of 10 infusions or more), rats advanced to an FR-3 schedule. After completing the necessary criteria on FR-3 (minimum 6 days on FR-3 reaching a criterion of 10 infusions or more), rats entered the demand curve.
- **Oxycodone IVSA demand curve:** The behavioral demand component of the experiment followed the same weekly schedule of sessions: 6 days/week, 3 hours/day. However, this stage involves quarter-log unit increases in FR value (FR-6, FR-10, FR-18, etc.) every 2 days. Once each rat had completed 2 consecutive sessions receiving 0 infusions of oxycodone, it returned to an FR-3 schedule for 2-3 days in order to re-assess low-cost oxycodone seeking.
- **Somatic signs of withdrawal (SSW)**: Approx. 22 hours following the second demand curve session rats were filmed for 20 minutes. Raters blind to experimental condition score the videos for counts of 5 withdrawal-related behaviors.
- **Gelatin:** Upon entering the demand curve, rats began to receive daily vehicle or THC gelatin. Sucrose rats began to receive daily vehicle or THC gelatin during the third of the 4 weeks of sucrose self-administration. Rats were provided with 10g of gelatin containing 1.0 mg/kg THC in 0.1 ml/kg ethanol or 0.1 ml/kg of 100% ethanol in the home cage for 60 minutes following a 1-hour rest period.
- **Home cage abstinence:** All rats, upon completing all self-administration procedures, were subject to 13-15 days of abstinence from all drugs, treatments, and reinforcers in order to investigate incubation of craving for oxycodone. Rats did not undergo any form of experimental extinction procedure.
- **Cue-primed reinstatement test:** Following the abstinence period, rats in the oxycodone groups completed a 2-hour relapse test in the operant chambers. This test involved the presence of the standard cues produced when an infusion is achieved during IVSA, but no drug is delivered to the animals.

Effects of THC on oxycodone self-administration and seeking

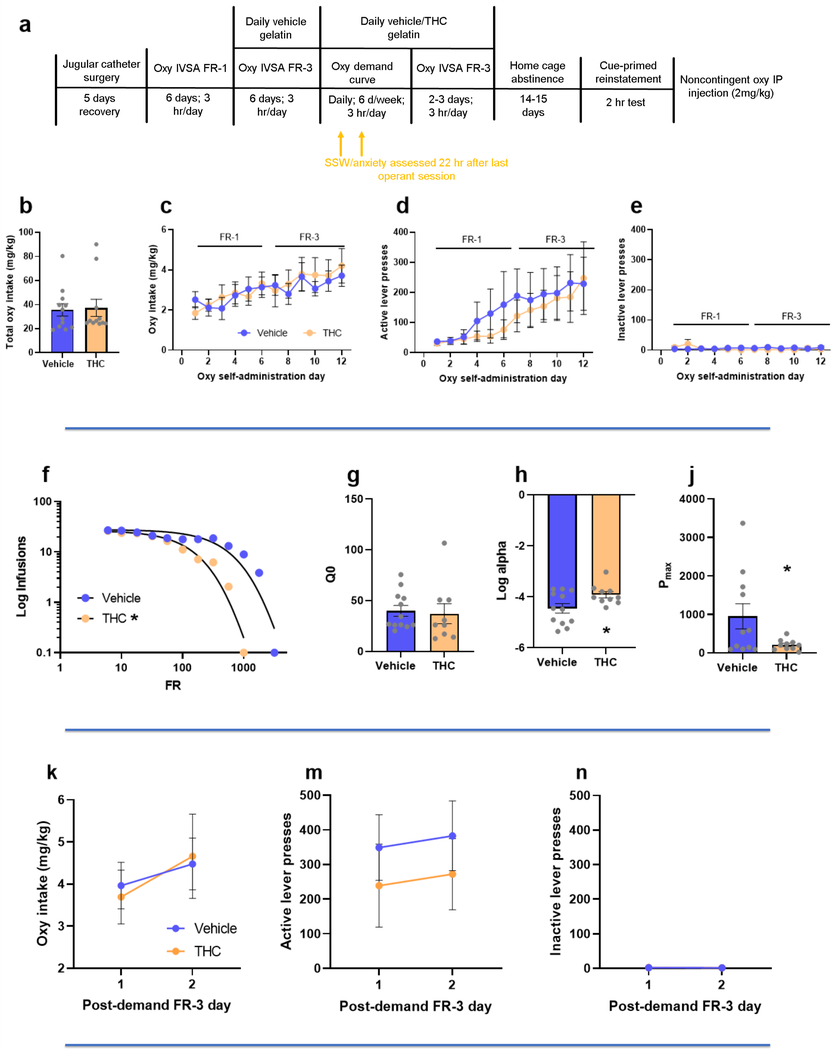

Fig. 1 (above/left) a. Oxycodone IVSA timeline (anxiety data not yet available). **b.** Rats to receive THC gelatin or vehicle gelatin did not differ in total intake, daily intake **(c)**, active lever pressing **(d)**, or inactive lever pressing **(e)** during oxycodone IVSA training. **f.** Behavioral demand for oxycodone was significantly decreased in rats consuming daily THC gelatin when compared to rats consuming vehicle gelatin. **g.** Q0 was not significantly different between groups. **h.** Log alpha was significantly between groups, as was Pmax **(j)**. **k.** Post-demand oxycodone intake, active lever pressing **(m)**, and inactive lever pressing **(n)** were not significantly different by group. **p.** Relapse test active lever pressing did not significantly differ by group; however, there appears to be a trend toward potential significance [t(17)=2.025, p = 0.05]. Relapse test inactive lever pressing did not significantly differ by group.

Effects of THC on sucrose self-administration

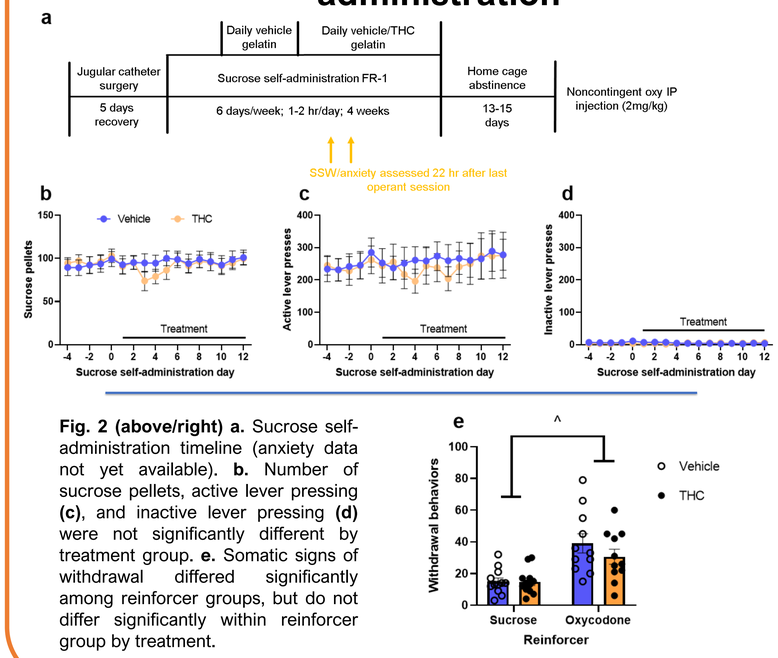

Fig. 2 (above/right) a. Sucrose self-administration timeline (anxiety data not yet available). **b.** Number of sucrose pellets, active lever pressing **(c)**, and inactive lever pressing **(d)** were not significantly different by treatment group. **e.** Somatic signs of withdrawal differed significantly among reinforcer groups, but do not differ significantly within reinforcer group by treatment.

CONCLUSIONS

- Rats that would later receive THC/placebo did not differ in oxycodone seeking or intake during IVSA training (before treatment started).
- THC increased demand elasticity for IVSA oxycodone.
- While Q_0 (the quantity demanded when the "price" is 0) was not affected by THC, P_{max} (the maximum “price paid”) for oxycodone was reduced by THC.
- THC did not reduce seeking behavior or intake for a naturally rewarding stimulus (sucrose).
- Our data suggest that THC can reduce motivation to seek oxycodone under high-effort conditions.

This work was supported by the Consortium for Medical Marijuana Clinical Outcomes Research (LAK) and R03 DA050118 (MS).

[1] National Institute of Drug Abuse (NIDA) (2022). *Overdose death rates*. https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis
[2] Wiese B, Wilson-Poe AR. Emerging Evidence for Cannabis' Role in Opioid Use Disorder. *Cannabis Cannabinoid Res*. 2018 Sep 1;3(1):179-189. doi: 10.1089/can.2018.0022.