Evaluation of cannabidiol effects on oxycodone-induced analgesia and reward-related behaviors in rats

Ariana C. Brice-Tutt[1], Wendi Malphurs[1], Azin Behnood-Rod[1], Cassidy Kramer[1], Alexandria S. Senetra[3], Robert M. Caudle[2,4], Marcelo Febo[4,5], Adriaan W. Bruijnzeel[5], Abhisheak Sharma[3], Barry Setlow[5], Niall P. Murphy[1], and John K. Neubert[1,4]

Affiliations: [1]Department of Orthodontics and [2]Department of Oral and Maxillofacial Surgery. [3]Department of Pharmaceutics. [4]Department of Neuroscience and [5]Department of Psychiatry. University of Florida, Gainesville, FL 32610

Introduction

- ~20% of US adult population has chronic pain[1]
- Limited effective therapies for treating chronic pain[2,3]
- Opioids are commonly used analgesics
- ~25% chronic pain patients misuse prescription opioids, with ≥10% meeting the criteria for substance use disorder[4]
- The overlap in neural circuitry mediating pain inhibition and reward complicates the use of opioids for long-term pain control
- Cannabinoids are potential alternative therapeutics for pain
- Cannabidiol is interesting due to an apparent lack of psychoactive effects
- Cannabidiol has been suggested to have opioid sparing properties[5]

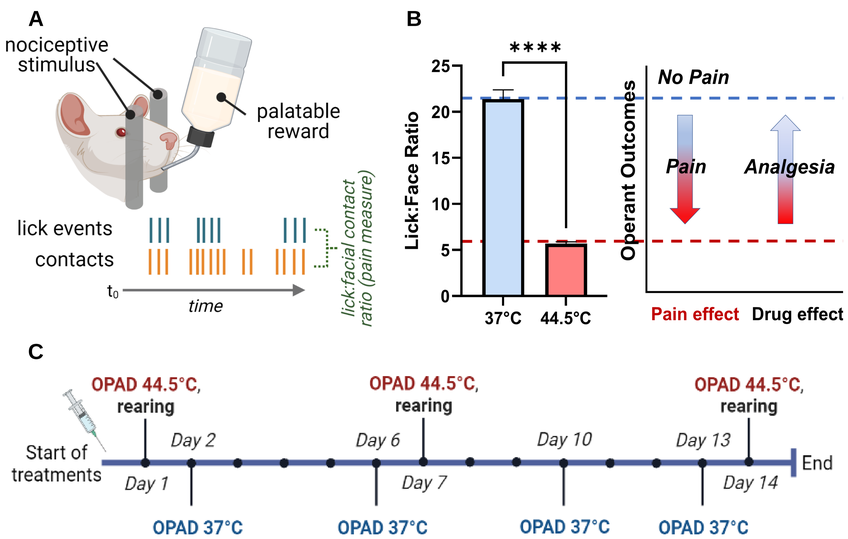
Objective

Investigate the effect of chronic oxycodone (OXY) and cannabidiol (CBD) treatment, alone or in combination, on pain- and reward-related behavior

Methods

- Male and female Sprague Dawley rats (N = 109)
- Operant-based reward-conflict paradigm - Orofacial Pain Assessment Device (OPAD, Fig. 1A)
- 14 day drug treatments (i.p.): Vehicle (1:1:18 ethanol, Cremaphor, PBS), CBD (3.2 or 10 mg/kg), OXY (0.56 mg/kg), or CBD + OXY combinations.
- Animals tested 20' post-drug using OPAD (10') (Figure 1C).
- Rearing monitored in vertical activity chambers after OPAD (30' post-drug) (10').
- Drug-seeking behavior tested using conditioned place preference (CPP) assay (Fig. 4B).
- All data are presented as mean ± SEM with significance set at $p<0.05$
- Data were analyzed by ANOVA or mixed effects analysis (as appropriate) with significant results further analyzed using Tukey's post hoc tests. Direct comparisons were analyzed using paired sample t-tests.

Figure 1. OPAD pain-behavior testing.



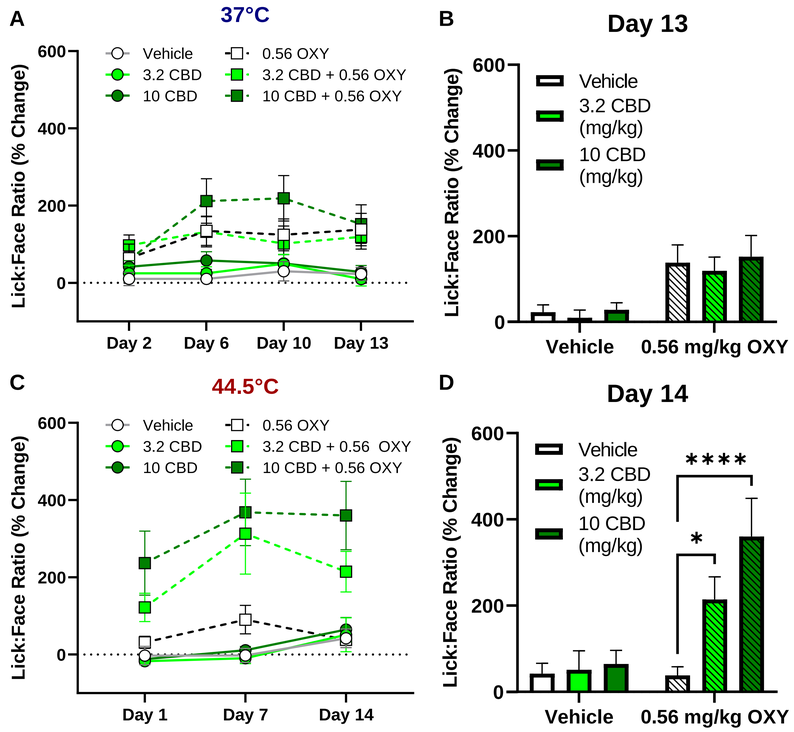
(A) The OPAD is a reward-conflict operant paradigm. **(B)** Baseline results demonstrate a significant effect of temperature (Paired t-test, P<0.0001), with 44.5°C responses reflecting thermal pain (compared to 37°C). The dashed color lines represent responses at neutral (blue, $Base_{37°C}$) and hot (red, $Base_{45°C}$) conditions. **(C)** Treatment and testing timeline.

Acknowledgements

This work was funded by NIH NIDA Grant #1R01DA049470-02S1

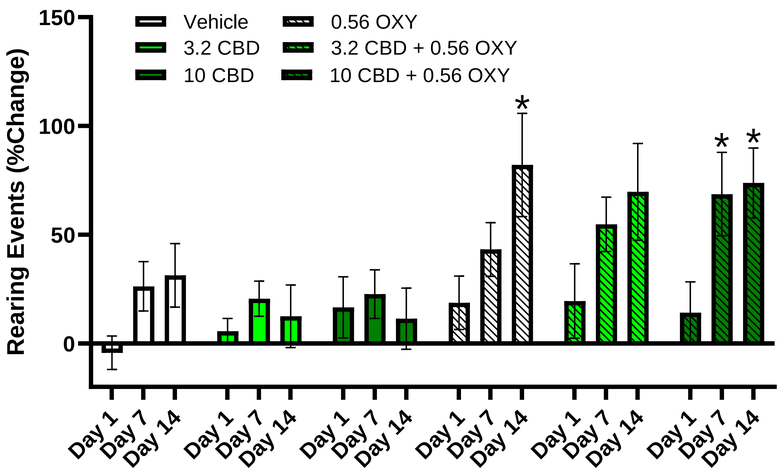
Results

Figure 2. CBD dose-dependently enhances the antinociceptive effect of OXY against thermal pain



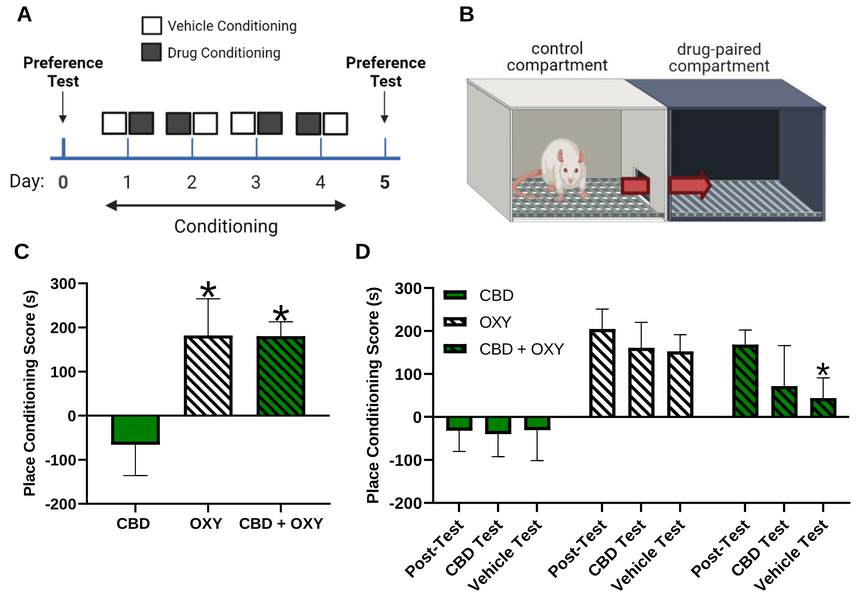
(A) At 37°C, there was a significant day x treatment interaction ($F_{(30, 398)} = 2.26$) on the lick:face ratio, but **(B)** no significant interaction between CBD and OXY. **(C)** At 45°C there was also a significant day x treatment interaction ($F_{(15, 302)} = 3.75$) on the lick:face ratio **(D)** and a significant interaction between CBD and OXY ($F_{(2, 97)} = 4.30$) on day 14. *= P<0.05, ****=P<0.0001, Two-Way ANOVA w/ Tukey's post hoc.

Figure 3. No effect of CBD on OXY-induced behavioral sensitization



There was a significant interaction between treatment and day on time spent rearing. ($F_{(10,206)} = 2.11$), but no significant interaction between CBD and OXY was found. * = significantly different from Day 1, P<0.05, Two-way RM ANOVA with Tukey's post-hoc.

Figure 4. CBD does not affect the acquisition of OXY-induced CPP but attenuates the persistence of CPP expression



(A) Drug conditioning design and timeline. **(B)** Conditioned place preference (CPP) paradigm. **(C)** Animals conditioned with OXY alone, or in combination with CBD demonstrated a significant increase in preference for the drug-paired chamber. **(D)** Animals conditioned with CBD + OXY experienced extinction of CPP following vehicle administration * = P < 0.05, paired sample t-test.

Conclusions

- Alone, CBD had no effect on any behavior tested
- CBD dose-dependently enhanced the analgesic effects of OXY
- CBD had no effect on the ability of OXY treatment to produce behavioral sensitization or CPP, suggesting CBD neither potentiates nor attenuates the rewarding properties of OXY
- CBD co-administration with OXY during conditioning appeared to produce a less persistent CPP.
- These results suggest that CBD has opioid-sparing properties that are specific to painful conditions.
- Future studies will assess potential mechanisms behind CBD and OXY interactions (receptor expression, PK), and the effects of CBD on OXY in other models of pain (mechanical hypersensitivity, chronic pain) and reinforcement (self-administration).

References

1. Dahlhamer J, *et al.,* Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(36):1001-6.
2. Abdel Shaheed C, *et al.*, Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. JAMA Intern Med. 2016;176(7):958-68.
3. Chou R, *et al.,* The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4):276-86.
4. Vowles KE, *et al.,* Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-76.
5. Jesus CHA, et al., Cannabidiol enhances the antinociceptive effects of morphine and attenuates opioid-induced tolerance in the chronic constriction injury model. Behav Brain Res. 2022;435:114076.