Evaluation of chronic combination oxycodone and cannabidiol treatment on pain behavior in an operant pain model

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Introduction

- ~20% of US adult population have chronic pain[1]
- Limited effective therapies for treating chronic pain[2,3]
- Opioids are commonly used for treating chronic pain
- ~25% chronic pain patients misuse prescription opioids with ≥10% meeting the criteria for substance use disorder[4]
- Intersection of pain inhibitory and reward neural circuitry complicates use of opioids for long-term pain control
- Cannabinoids are potential alternative therapeutics for pain
- Cannabidiol is interesting due to apparent lack of psychoactive effects

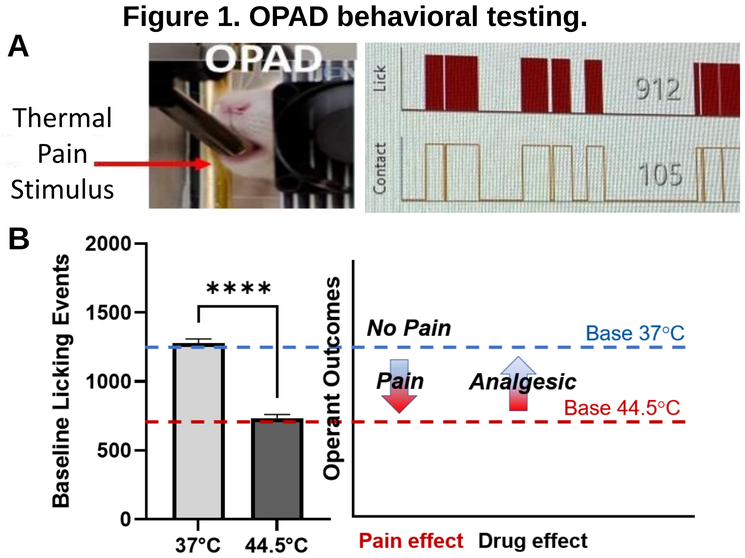
Objective

Investigate the effect of chronic oxycodone (Oxy) and cannabidiol (CBD) treatment, alone or in combination, on pain-related behavior using an operant orofacial reward-pain conflict model

Methods

- Male and female Sprague Dawley rats (N = 109)
- Operant-based reward-conflict paradigm - Orofacial Pain Assessment Device (OPAD, Fig. 1A)
- Thermal stimuli: non-nociceptive (37°C) or nociceptive (44.5°C)
- Positive reinforcer = sweetened condensed milk
- 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 administered daily for 14 days.
- Animals tested 20' post-drug using OPAD (10') on days 1,2,6,7,10, 13, and 14 of drug treatment (Figure 2A).
- Rearing activity monitored after OPAD (30' post-drug) using rearing chambers on Days 1, 7, and 14 (10').
- All data is presented as mean ± SEM with significance set at P<0.05
- Data analyzed by ANOVA (one-way or two-way with repeated measures (RM), as appropriate) with significant results further analyzed by Tukey's post hoc test. Direct comparisons analyzed by Student's t-test.

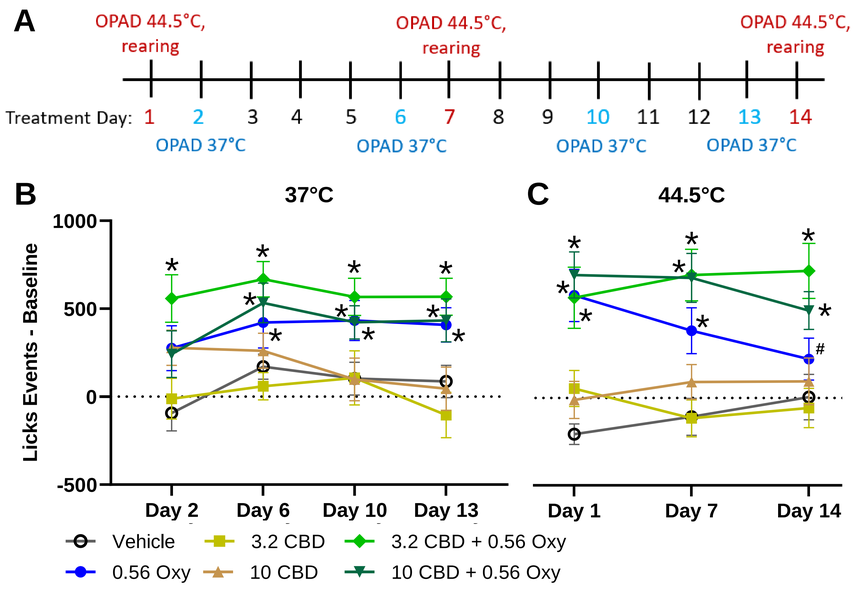
Figure 1. OPAD behavioral testing.



(**A**) The OPAD is a pain assay based on 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.

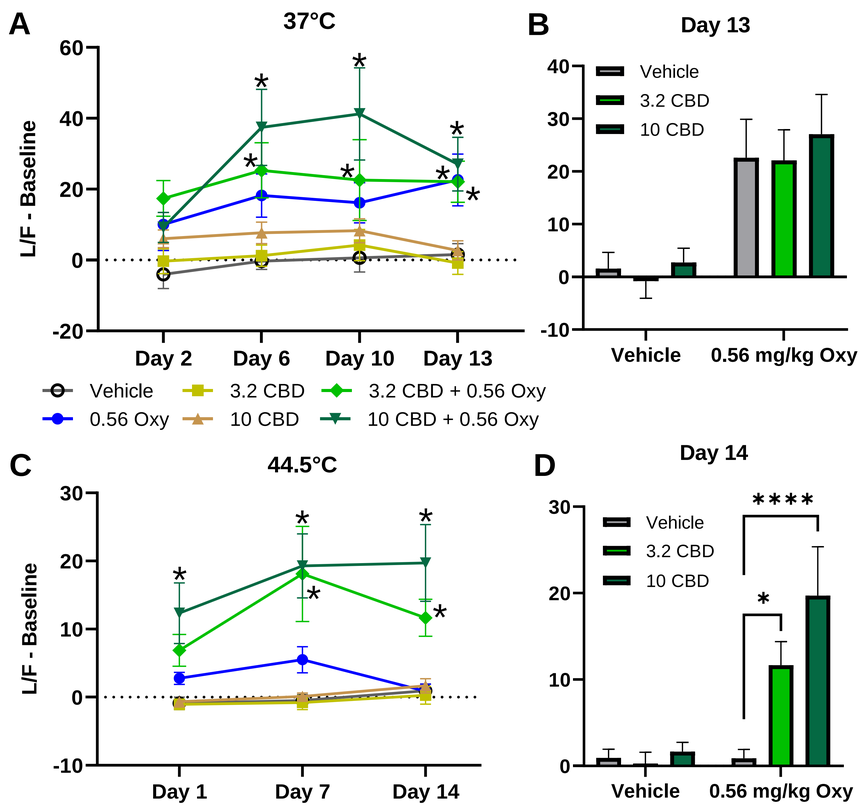
Results

Figure 2. Effects of CBD and Oxy on licking events under non-nociceptive (37°C) and nociceptive (44.5°C) conditions.



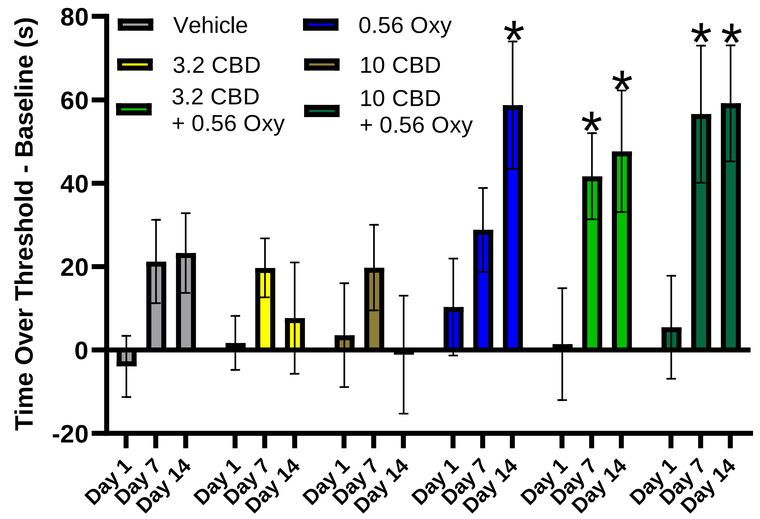
(**A**) Treatment and testing timeline. There was a significant main effect of treatment on licking events at (**B**) 37°C ($F_{(5,102)}$ = 9.08) and (**C**) 44.5°C ($F_{(5,102)}$ = 13.5). * = significantly different from baseline, # = significantly different from Day 1, P<0.05, Two-way RM ANOVA w/ Tukey's post-hoc.

Figure 3. Effects of CBD and Oxy on the lick activation/ face contact ratio (L/F) at 37°C and 45°C, as a measure of thermal nociception.



(**A**) At 37°C, there was a significant main effect of time ($F_{(2, 306)}$ = 4.21) and treatment ($F_{(5, 102)}$ = 7.29) on L/F (Two-way RM ANOVA w/ Tukey's post hoc; *P<0.05 from baseline). (**B**) However, on day 13, there was no significant interaction between CBD and Oxy. **(C)** At 45°C there was also a significant main effect of time ($F_{(2, 206)}$ = 3.99) and treatment ($F_{(5, 103)}$ = 12.51) on L/F (Two-way RM ANOVA w/ Tukey's post hoc, *P<0.05 from baseline). (**D**) On day 14, there was a significant interaction between CBD and Oxy ($F_{(2, 103)}$ = 5.84) on L/F (Two-Way ANOVA w/ Tukey's post hoc, *P<0.05, ****P<0.0001)

Figure 4. Effects of CBD and Oxy on rearing behavior



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

Conclusions

- Oxy treatment, alone and in combination with CBD, generally increased licking behavior at 37°C and 44.5°C (Fig. 2B and C)
- While Oxy treatment had generally little effect alone at 37 °C on L/F ratio and no effect at 44.5 °C, when combined with CBD, the L/F ratio was significantly increased at both temperatures (Fig 3).
- There was no significant interaction between Oxy and CBD on 37°C L/F ratio or rearing behavior; however, there was a significant interaction on L/F ratio testing at nociceptive temperatures (44.5°C).
- These results suggest CBD may potentiate the analgesic effects of Oxy in a manner specific to nociceptive conditions.
- Future studies will assess potential mechanisms behind CBD and Oxy interactions (receptor expression, PK, neural activation), the effects of CBD on Oxy reinforcement and reward, and in other models of pain (mechanical hypersensitivity, chronic pain conditions).

Acknowledgements

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