Effects of Cannabinoids and a Cannabinoid Extract on Thermal Nociception and Conditioned Behavior

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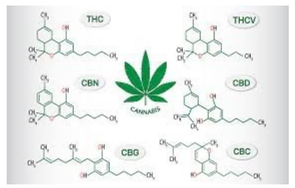
Introduction

Cannabinoids have been considered as alternatives to opioids, and therefore, have been tested for their antinociceptive effects and potential as analgesics. However, data on the effectiveness of cannabinoids for treating pain are still lacking, and few preclinical studies have compared their relative potency for producing antinociception with their well-known capacity for disrupting conditioned behavior.



Therefore, our research aimed to examine the antinociceptive and behavioral effects of Δ9-tetrahydrocannabinol (Δ9-THC), Δ8-THC, (-)-CP 55,940 (CP), and a cannabis-derived mixture (NEPE14) in Sprague-Dawley rats.

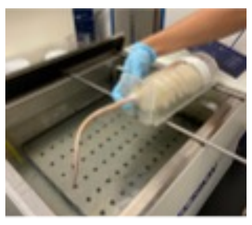
Methods

Behavioral Sessions:

1. **Operant Conditioning:** Nine male Sprague-Dawley rats were trained to respond under a fixed-ratio 30 (FR-30) schedule, with food pellets serving as the reinforcer.
2. **Injections:** Thirty minutes prior to the session, subjects were administered cannabinoids or NEPE14 twice a week along with a control injection once per week.

Thermal Antinociception:

1. **Tail-Withdrawal Procedure:** Subjects were trained to maintain their tails in a warm-water bath set at 40 °C for the maximum latency of 20 seconds. On test days, subject tails were dipped in either 40 or 50 °C.
2. Tail-Withdrawal latency was recorded daily with a maximum latency of 20 seconds to prevent nerve damage.



Results

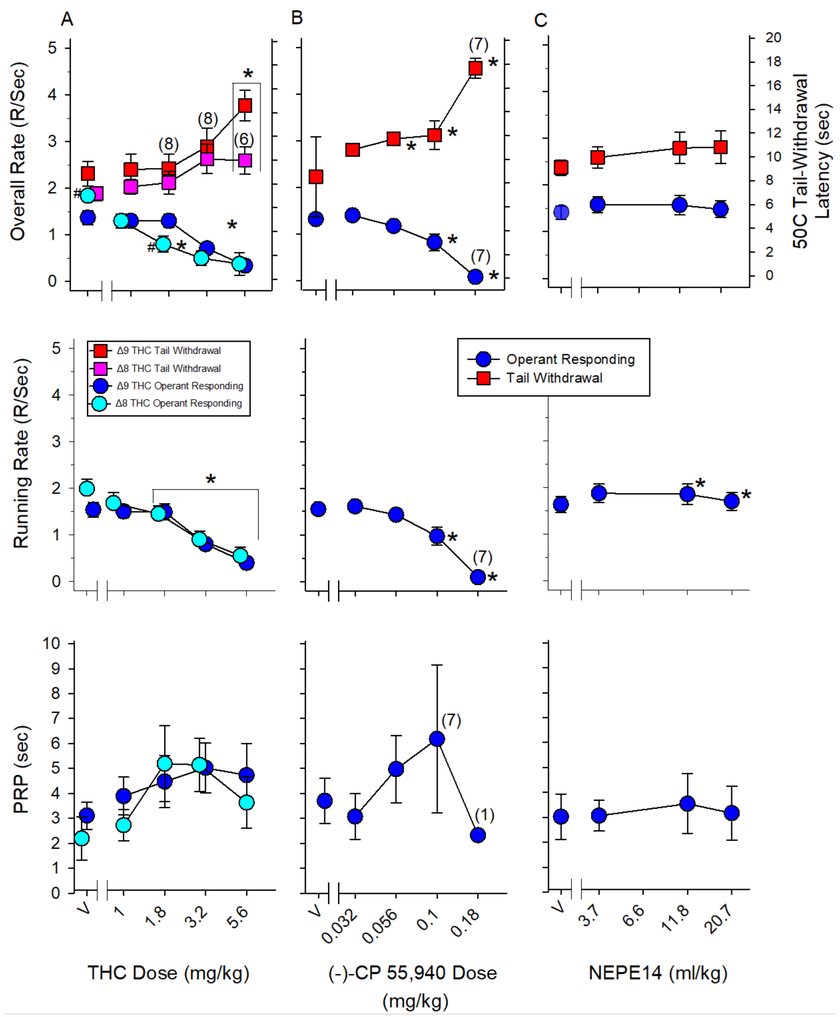


Figure 1. Effects of i.p. administration of two isomers of THC (column A), (-)-CP 55,940 (column B), and NEPE14 (column C) on overall response rate (top row for each drug), running rate (middle row), and pre-ratio pausing (PRP; bottom row) in male subjects (n=9) responding under a fixed-ratio 30 (FR-30) schedule of food presentation. Tail-withdrawal latency (antinociception) was also measured for these drugs after the behavioral session and is plotted using the righthand axis and square symbols in the top row of panels.

Key

- **Overall Rate: average number of responses per second**
- **Running rate: average rate minus pre-ratio pausing**
- **PRP: average length of pause prior to initiating each ratio**
- **Tail-Withdrawal Latency: average number of seconds between tail immersion and tail withdrawal**

1. Acute administration of Δ9-THC, Δ8-THC (1-5.6 mg/kg for both) and CP (0.032-0.18 mg/kg) significantly and dose-dependently decreased overall response rate and running rate; PRP was not affected.
2. There was not a significant difference between Δ9-THC and Δ8-THC for operant responding. However, there was a significant difference between Δ9-THC and Δ8-THC for tail withdrawal latency (main effect).
3. Both THC isomers and CP also increased tail-withdrawal latency compared to vehicle.
4. In contrast, NEPE14 (3.7-20.7 ml/kg i.p.) did not significantly decrease response rates or increase tail-withdrawal latency even though the volumes administered contained doses of Δ9-THC that had effects alone (e.g., the 11.8 ml/kg volume contained 3.2 mg/kg of Δ9-THC).

Conclusion

1. Δ9-THC, Δ8-THC, and (-)-CP 55,940 significantly reduced thermal nociception, suggesting these cannabinoids may be effective for treating some types of pain.
2. However, only CP produced antinociceptive effects that were more potent than their disruptive effects on conditioned behavior.
3. The cannabinoid extract, NEPE-14, did not reduce thermal nociception or cause a disruption of behavior, despite the injection volumes containing effective doses of Δ9-THC.

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