

Concurrent Evaluation of the Antinociceptive and Behaviorally-Disruptive Effects of THC in Rats

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Introduction

Cannabinoids, particularly delta-9-tetrahydrocannabinol (THC), have been increasingly proposed as a replacement for opioids in pain management and relief. However, the preclinical and clinical data assessing the antinociceptive effects of THC have been equivocal and many of the assessments have not taken into account the behaviorally-disruptive effects of THC.

There is previous data showing the effects of THC on behavior and antinociception separately. From these previous studies, however, it has been shown that THC fails to produce antinociceptive effects for certain types of pain, such as acute-pain or capsaicin-induced hyperalgesia in healthy humans.

In this present study, the antinociceptive effects of THC were studied concurrently with its behaviorally disruptive effects in rats to directly compare the relative potency of these effects. Determining the relative potency could also have implications for the medicinal use of THC in humans.

Methods



Behavioral Sessions:

1. Performance (60 minutes or 200 reinforcers): Subjects were trained to respond under a fixed-ratio 30 (FR-30) schedule of food pellet presentation (i.e. every 30 responses on a response lever in the presence of a green stimulus resulted in the presentation of one food pellet).
2. Injections: The effects of THC were tested by acutely injecting subjects with single doses 30 minutes prior to behavioral sessions one or two times per week. THC vehicle was injected once per week as a control.

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. Withdrawal latency was recorded daily using a stop watch with a maximum latency of 20 seconds to prevent nerve damage

Effects of THC on Response Rate and Thermal Nociception

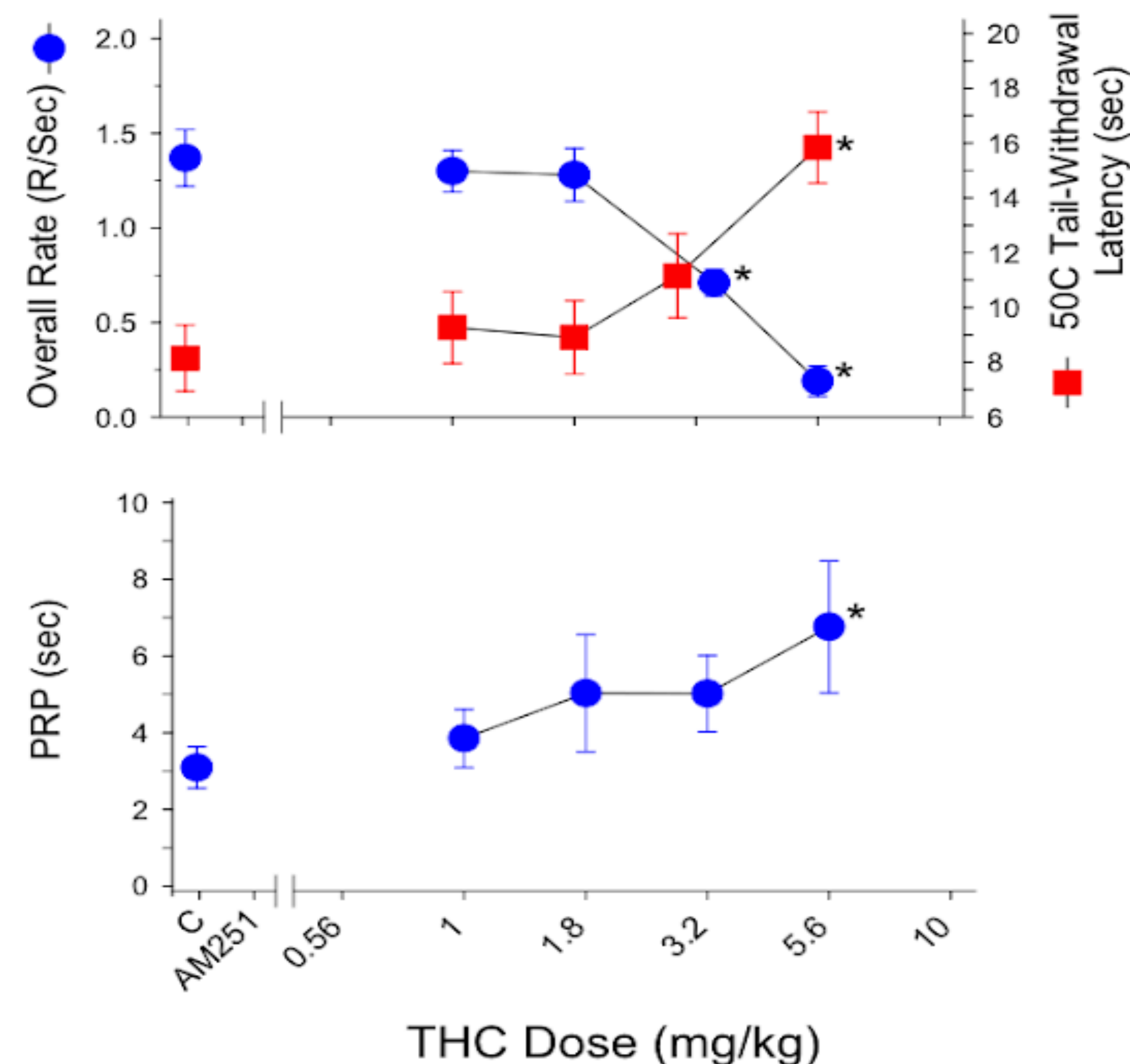


Figure 1. THC significantly and dose-dependently decreased overall response rate and increased tail-withdrawal latency. THC also significantly increased pre-ratio pausing (PRP), meaning as the dose of THC increased, the pause that occurs prior to each FR increased.

Results

- On days without injections (baseline days), subjects reliably responded under the FR-30 schedule of food presentation, and maintained their tails in the 40 °C water temperature for the maximum latency of 20 seconds.
- Administration of 1 to 5.6 mg/kg of THC significantly, and dose-dependently, decreased response rate under the FR-30 schedule compared to vehicle administration (control). The maximum decrease in responding was obtained after the 5.6-mg/kg dose.
- THC administration also significantly and dose-dependently increased tail-withdrawal latency from a mean of 8.45 seconds under control conditions to a mean of 15.84 seconds (i.e., produced thermal antinociception).
- Calculation of the dose that produced a 50% change (ED50) in the dependent variables indicated that the ED50 was 3.31 for response rate and 4.49 for the tail-withdrawal latency.
- Preliminary data (not shown) involving the CB1 selective antagonist AM251 indicate that both the thermal antinociceptive and behaviorally-disruptive effects are mediated by CB1 receptors.

Conclusion

1. THC can reliably produce thermal antinociceptive effects as dose increases.
2. THC dose-dependently produces behavioral impairment and disrupts conditioned behavior.
3. Overall these data show that THC can produce thermal antinociceptive effects; however, the doses which have antinociceptive effects either markedly decrease or eliminate conditioned behavior.

References:

Schindler EAD, Schnakenberg Martin AM, Sewell RA, Ranganathan M, DeForest A, Pittman BP, Perrino A Jr, D'Souza DC. In an exploratory randomized, double-blind, placebo-controlled, cross-over study, psychoactive doses of intravenous delta-9-tetrahydrocannabinol fail to produce antinociceptive effects in healthy human volunteers. *Psychopharmacology (Berl)*. 2020 Oct;237(10):3097-3107. doi: 10.1007/s00213-020-05595-9. Epub 2020 Jul 6. PMID: 32632491.

Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. *J Pharmacol Exp Ther*. 1991 Aug;258(2):517-23. PMID: 1650831.