An Evaluation of the Antinociceptive and Behaviorally-Disruptive Effects of Delta-9-tetrahydrocannabinol in Sprague Dawley Rats

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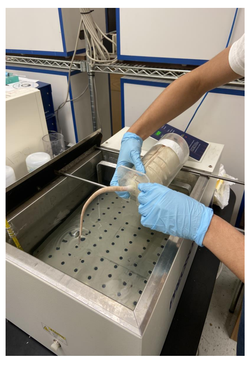
Introduction

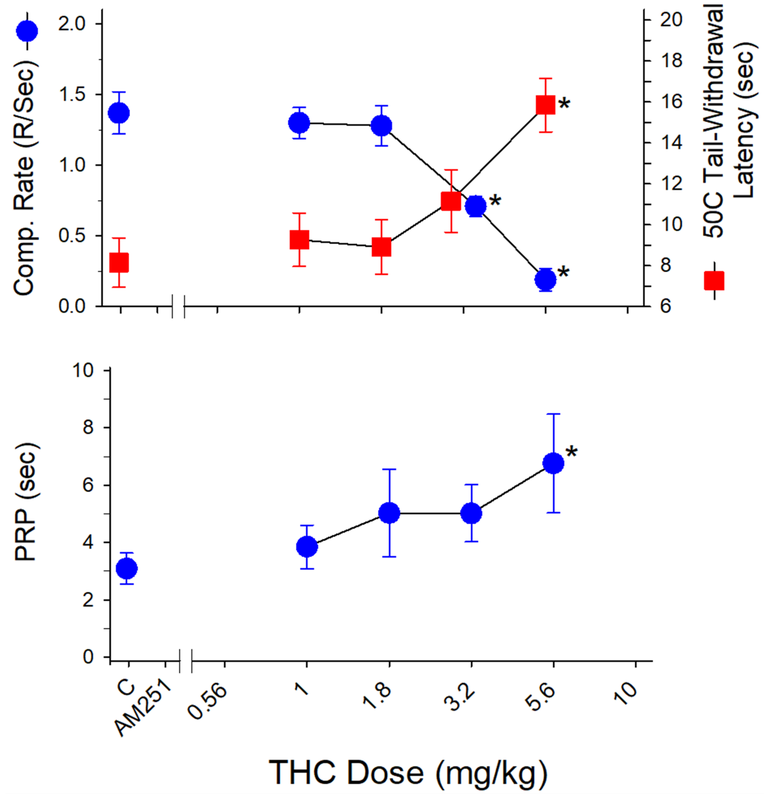
As the dangerous and addictive effects of opioids have become more widely recognized, researchers are investigating many novel alternative drugs for mitigating pain. Cannabinoids, specifically delta-9-tetrahydrocannabinol (THC), are among the most popular of these alternatives. Although THC can produce antinociceptive effects (i.e., reduce pain), it can also produce disruptions in conditioned behaviors. Other researchers have studied THC's effect on either antinociception or conditioned behaviors independently. However, our experiments were conducted to directly compare and contrast the antinociceptive and behaviorally-disruptive effects of THC in outbred Sprague Dawley rats.

Methods

- Nine mildly food-deprived subjects were trained to respond under a fixed-ratio 30 (FR-30) schedule of food pellet presentation, and to maintain their tails in 40 °C water for 20 sec in preparation for tests of thermal antinociception.
- Subjects were weighed before and after the 60-min (or 200 reinforcer) behavioral session, with test for thermal antinociception immediately following the post-session weighing.
- Injections were conducted under the 'Harvard' schedule: Monday, baseline and 40 °C; Tuesday, THC (30 min ps) and 50 °C; Wednesday, baseline and 40 °C, Thursday, vehicle and 50 °C; Friday, THC and 50 °C.
- The dependent measures for the operant schedule of FR responding were response rate in responses per second and pre-ratio pausing (PRP). The dependent measure for the test of thermal antinociception was tail-withdrawal latency from both water temperatures.



Effects of THC on Conditioned Behavior and Thermal Antinociception



Key

- Overall Rate: the number of responses per second.
- PRP: the length of pauses between each response
- Tail-Withdrawal Latency: the number of seconds the occurs between tail immersion and tail withdrawal.

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.

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 CB1 selective antagonist AM251 indicate that both the thermal antinociceptive and behaviorally-disruptive effects are mediated by CB1 receptors.

Conclusions

- As previously reported by our laboratory and others, THC dose-dependently disrupts conditioned behavior and produces thermal antinociceptive effects in rats.
- However, a direct comparison of these effects in the present study indicates that significant antinociception may only occur at doses that markedly decrease or eliminate conditioned behavior.
- The relative potency of these effects may also have important ramifications for the use of THC as an analgesic in humans.

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