Effects of delta-9-tetrahydrocannabinol (THC) on Thermal Nociception and Conditioned Behavior in Sprague Dawley Rats

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Introduction

Cannabinoids have been suggested as a possible alternative to opioids for pain management and as an adjunct to opioid administration to reduce the many adverse effects associated with their administration (i.e., administered to produce opioid-sparing effects).

Although cannabinoids such as delta-9-tetrahydrocannabinol (THC) have been shown to produce antinociceptive effects, these effects have not typically been compared directly with its adverse effects – some of which include the disruption of cognitive and conditioned behaviors.

From the previous studies which showed the effects of THC on behavior and nociception as two separate aspects, it is now known that TCH is unable to produce the desired antinociceptive effects for some subsets of pain, such as capsaicin-induced hyperalgesia.

These types of studies are necessary if cannabinoids such as THC can be considered a valid option for pain management. The present experiment was conducted to directly compare the capacity of THC reduce thermal nociception and disrupt behavior in Sprague Dawley rats.

Methods

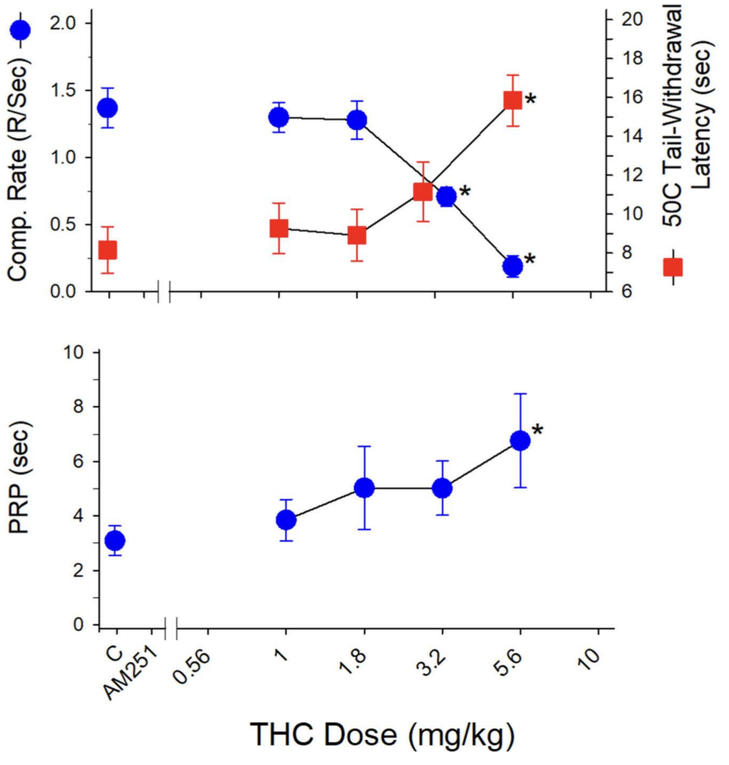
To assess the effects of THC on conditioned behavior, nine subjects were trained to respond under an operant schedule of reinforcement.

More specifically, subjects responded under a fixed-ratio 30 (FR-30) schedule of food pellet presentation; that is, every 30 responses on a response lever in the presence of a red stimulus resulted in the presentation of one food pellet. Behavioral sessions lasted 60 minutes and were conducted five days per week.

After the behavioral sessions, thermal antinociception was tested by dipping the rats' tails in either 40 or 50 °C water and measuring the tail-withdrawal latency from both water temperatures. Latency in tail withdrawal was carefully recorded with a hand-held stop-watch with a maximum test period of 20 seconds in order to avoid nerve damage.

The effects of THC on both conditioned behavior and nociception were tested by acutely injecting single doses 30 min prior to these procedures one to two times per week until an entire dose-effect curve was established. THC vehicle was also injected once per week as a control. The dependent measure when graphing the behavioral aspect was response rate in responses per second and pre-ratio pausing. When graphing the results for the antinociception aspect, the dependent measure was set as the tail-withdrawal time for both temperatures.

Effects of THC on Response Rate and Thermal Nociception



Key

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

Results

On day without injection (baseline days), the subjects were reliably able to respond at a steady rate with the FR-30 reward schedule as well as calmly keep their tails submerged in the 40 °C water for the entirety of the maximum set of 20 seconds.

As seen in the effects graphs, administration of 1 and increasing doses to 5.6 mg/kg of THC significantly and dose-dependently decreased response rate in the behavioral aspect when directly compared to prior vehicle injection. At 5.6 mg/kg dose, the subjects showed the maximum decrease in response rate.

In addition to this effect in behavior, THC also dose-dependently increased tail withdrawal latency at 50 °C from an 8.45 second mean when submerged during control conditions to a 15.84 second mean. Thus, THC in this instance was able to produce thermal nociception.

Calculation of the dose that produced a 50% change (ED50) in the dependent variables indicated that ED50 was 3.31 for response rate and 4.49 for tail-withdrawal latency.

Preliminary extended research and data (not shown on this poster) involving CB1 selective antagonist AM251 indicated that both the thermal antinociceptive and behavioral disruptive effects are mediated by CB1 receptors.

Conclusions

As has been previously proven by our laboratory as well as others, THC reliably and dose-dependently produces both a disruption to conditioned behavior and thermal antinociceptive effects in rats.

However, a direct comparison of these two effects in rats show that although significant antinociceptive effects can be attained, such results may only be reached at doses which also significantly affect any learned or conditioned behaviors.

The relative potency and effects shown here may have important consequences and updates for the use of THC as a proposed analgesic in human patients.

Acknowledgements

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This research project was supported through the School of Graduate Studies and Oleander Medical Technologies.