# Effects of NEPE14 on Conditioned Behavior and Nociception

**Jessye Garriet, Tamara Morris[1], Alastair Deng, Jessica Cucinello-Ragland[2], Scott Edwards[2], and Peter Winsauer[1]**

Louisiana State University Health Science Center, [1]Department of Pharmacology, and [2]Department of Physiology

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## Introduction

As the highly addictive and dangerous effects of opioids are becoming more widely known, cannabinoids have been discussed as a potential replacement for opioids in the reduction of pain. Therefore, our research examined the effects of a Non-Euphoric Phytocannabinoid Elixir (NEPE14) on thermal nociception and conditioned behavior in a group of Sprague-Dawley rats after sublingual (s.l.) and intraperitoneal (i.p.) administration. A model of Complete Freud's Adjuvant (CFA)-induced hyperalgesia was also used to assess the effects of NEPE14 on chronic inflammation-induced mechanical and thermal pain in two group of subjects (saline versus NEPE14). In the behavioral experiments, the subjects served as their own control and were tested for antinociception after the behavioral session.

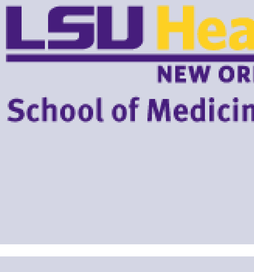
## Materials


### NEPE 14

(Non-Euphoric Phytocannabinoid Elixir)

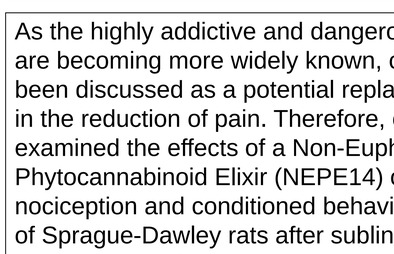
- This Elixir contains an extract from the plant, *Cannabis sativa*, which has over a hundred cannabinoids: delta-9-THC being one of them.

### Operant Chamber



- Behavioral testing is conducted in the operant chamber.
- Subjects are trained to respond under a fixed-ratio 30 (FR-30) schedule of reinforcement.

### Water Bath



- Used to measure tail withdrawal latency.
- Trained to keep tail in 40°C water for 20 seconds.
- On drug days we use 50°C.

### [1]The Harvard Schedule

| Monday | Tuesday | Wednesday | Thursday | Friday |
|---|---|---|---|---|
| Baseline (No drug) | Drug (NEPE14) | Baseline (No drug) | Vehicle (Water /THC vehicle) | Drug (NEPE14) |

## Methods

- Nine Sprague-Dawley rats were trained to respond under a fixed-ratio 30 (FR-30) schedule for food reinforcers.
- To assess the effects of NEPE14, subjects were injected with it 30 minutes prior to the behavioral testing sessions based on the [1]Harvard schedule to establsh complete dose-effect curves.
- Immediately after these behavioral sessions, warm-water tail-withdrawal latency (in seconds) was assessed using 40 or 50 °C water.
- Overall response rate, running rate and pre-ratio pause duration (PRP) were recorded.

## Results

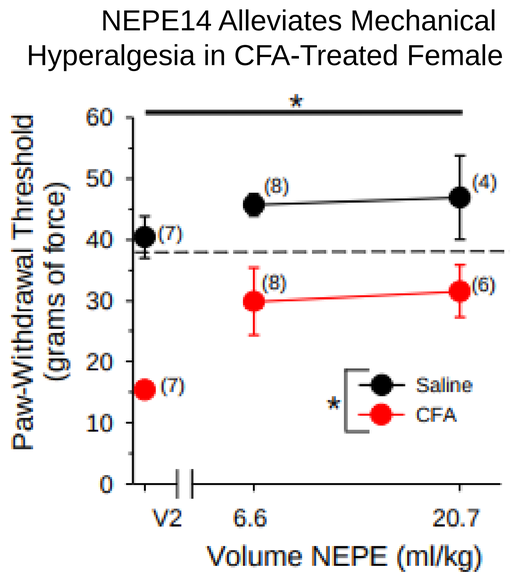



**Figure 1. Graphs show the reduction of mechanical and thermal hyperalgesia by NEPE14 administration in CFA- treated female rats. Paw-withdrawal threshold increased on both measures of hyperalgesia as the volume of NEPE 14 administered increased compared to saline administration. For mechanical hyperalgesia, there was a main effect of NEPE14 volume (p= 0.0433) and a main effect of CFA (p<0.0001). When tested for thermal hyperalgesia there was a main effect of dose (p=0.0261) and a main effect of CFA (p=0.0181). These results show that NEPE14 alleviated both mechanical and thermal hyperalgesia in CFA-treated female rats.**

**KEY**

**•Overall Rate: the total number of responses emitted per second**
**•PRP: the length of pauses before each ratio**
**•Running Rate: Overall rate minus pre-ratio pausing**

**•Tail-Withdrawal Latency: time (in seconds) from tail immersion to tail withdrawal.**

**•Paw-Withdrawal Threshold: Grams of force required to produce hindpaw withdrawal following application of the Von Frey filament.**
**•Paw-Withdrawal Temperature: Degrees Celsius required to produce hindpaw withdrawal following cold plate thermal sensitivity testing.**

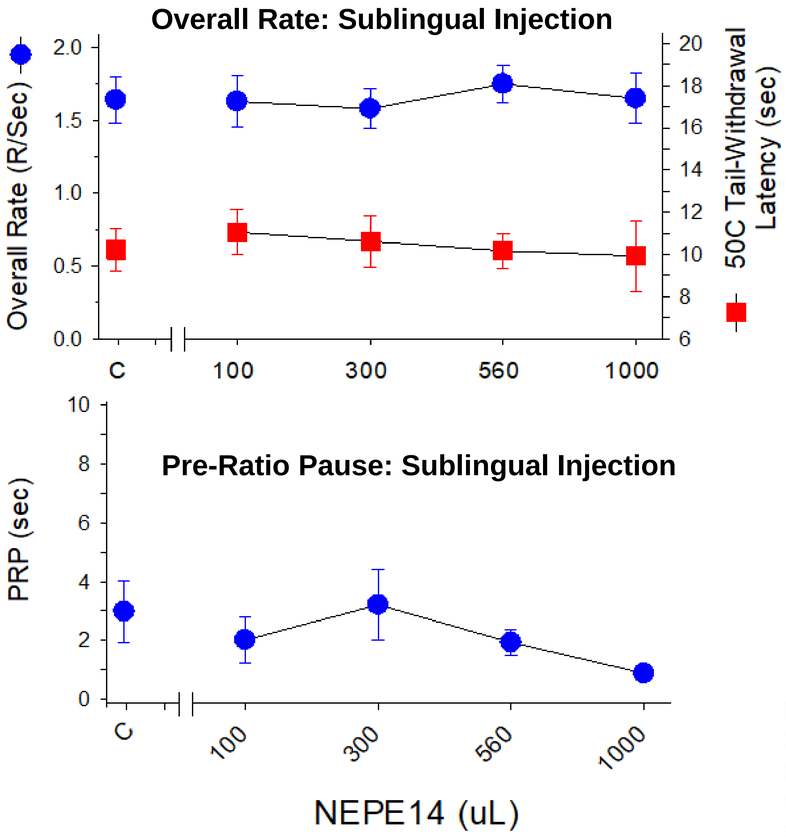



**Figure 2. Acute administration of NEPE14 (100-1000 ul s.l.) did not significantly affect response rate, PRP or tail-withdrawal latency in subjects that did not have inflammatory pain.**

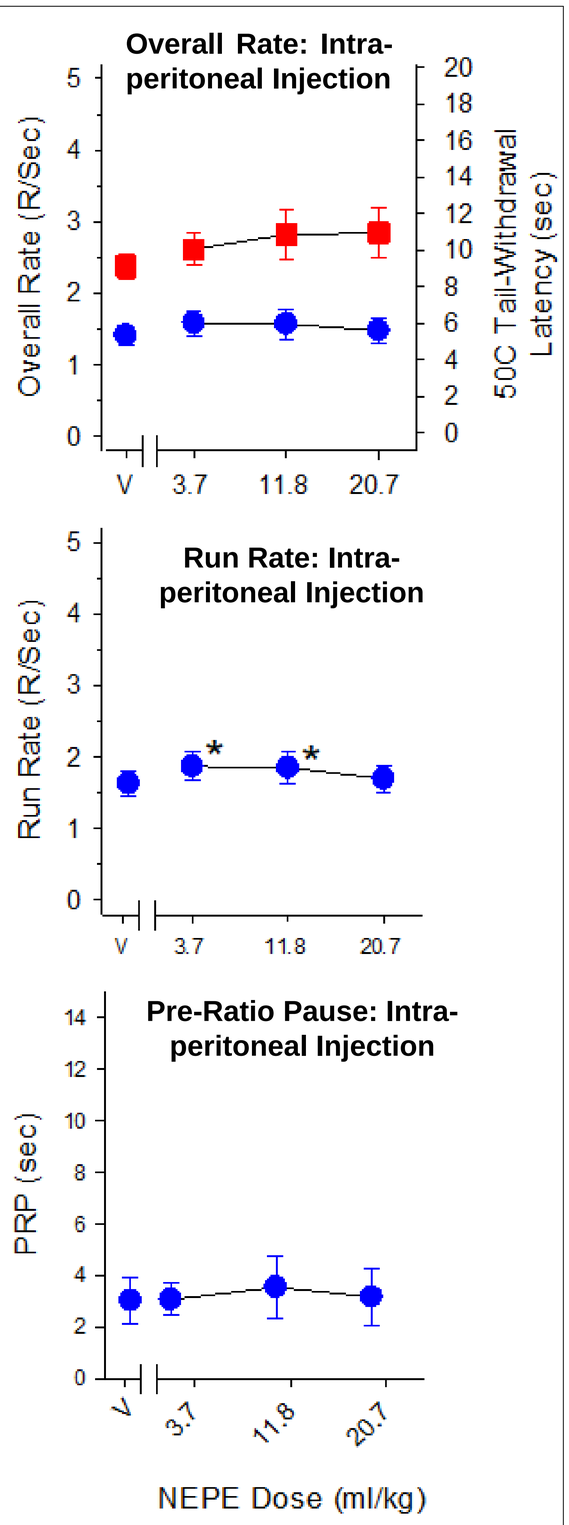



**Figure 3. Acute administration of NEPE14 (3.7-20.7 ml/kg i.p.) did not significantly affect overall rate, PRP, run rate or tail-withdrawal latency compared with vehicle (V). However, there was a small, but significant, increase in running rate at the 3.7 and 11.8 ml/kg volumes. These data indicate that the i.p. route of administration for NEPE14 did not produce antinociception in the absence of inflammation.**

## Conclusions

- NEPE14, administered i.p. or s.l., did not significantly affect either conditioned behavior or tail-withdrawal latency in the absence of chronic inflammatory pain.
- However, i.p. NEPE14 decreased chronic CFA-induced mechanical and thermal hyperalgesia, suggesting that it may be effective for treating chronic inflammatory pain. These same doses that were effective for reducing hyperalgesia did not disrupt conditioned behavior.
- These effects suggest that certain cannabinoid products such as NEPE14 may have potential for treating inflammatory pain in humans.

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