Cannabis-derived terpenes as novel neuropathic pain therapeutics: preclinical mouse studies and possible cannabinoid receptor involvement

Ortiz, Y.; McMahon, L.R.; Wilkerson, J.L.
Department of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, FL, USA

Consortium for Medical Marijuana Clinical Outcomes Research

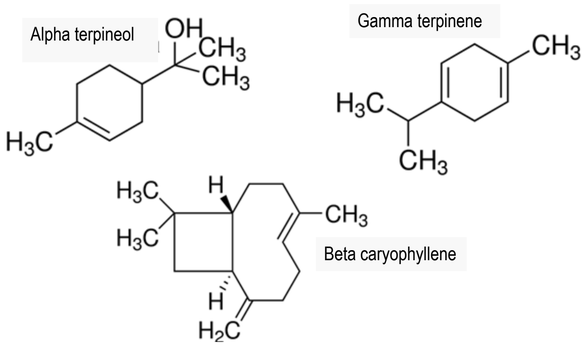
Introduction

- Anecdotal reports suggest cannabis may be an effective analgesic.
- Cannabis contains a multitude of compounds (i.e., terpenes) that have not been well studied and may hold therapeutic promise as pain therapeutics.
- We examined the ability of a subset of terpenes found in cannabis: γ-terpinene, α-terpineol, β-caryophyllene to reverse mechanical allodynia (i.e., light touch sensitivity) in mice experiencing paclitaxel chemotherapy-induced peripheral neuropathy (CIPN) and in the chronic constriction injury of the sciatic nerve (CCI) neuropathic pain model.
- Emerging studies suggest that these terpenes may have activity at cannabinoid receptors.
- To examine cannabinoid receptor involvement within both neuropathic pain models we also tested each terpene in mice lacking either functional cannabinoid type 1 receptors (CB_1R (-/-)) or cannabinoid type 2 receptors (CB_2R (-/-)).

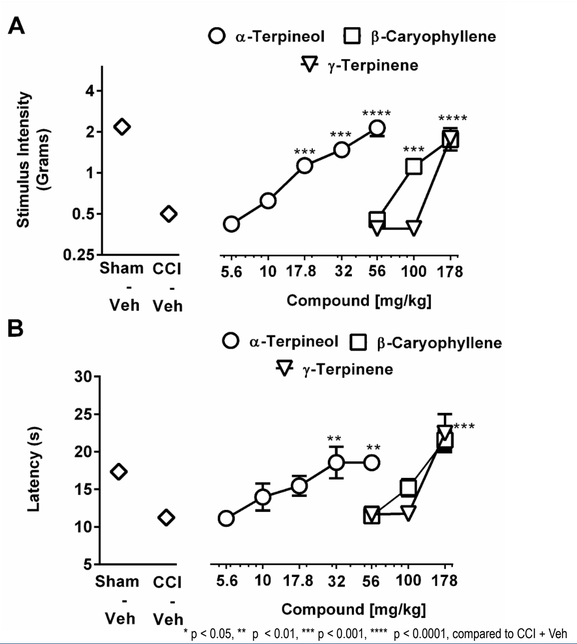
Materials & Methods

Animal Models of Neuropathic Pain: Male and female wildtype, CB_1R (-/-), CB_2R (-/-) mice on a C57BL/6J background were used in all experiments. Chronic constriction injury (CCI) of the sciatic nerve was used to elicit neuropathic pain. In separate mouse cohorts, intraperitoneal injection of 8 mg/kg paclitaxel, a chemotherapeutic, was given once every other day for 4 days Increased sensitivity to a light touch stimulus (allodynia) was assessed in the von Frey test. CCI mice were tested for increased sensitivity to thermal stimulus (thermal hyperalgesia) in the 52 C hot plate assay

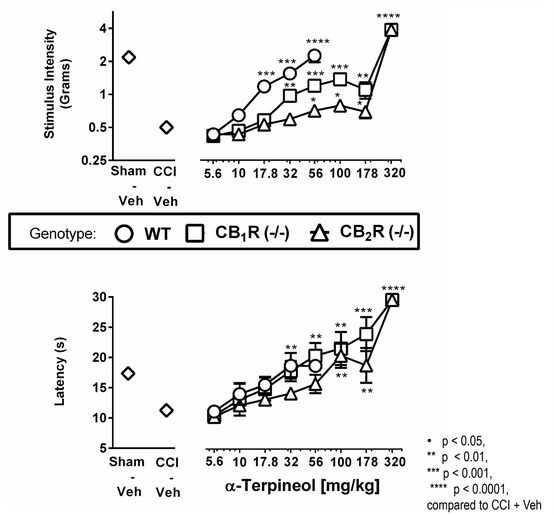
Compounds: The present study employed the terpenes alpha terpineol, beta caryophyllene, and gamma terpinene, purchased from Sigma Aldrich (St. Louis, MO). Compounds were administered intraperitoneally at a volume of 10 µL per gram of body mass.



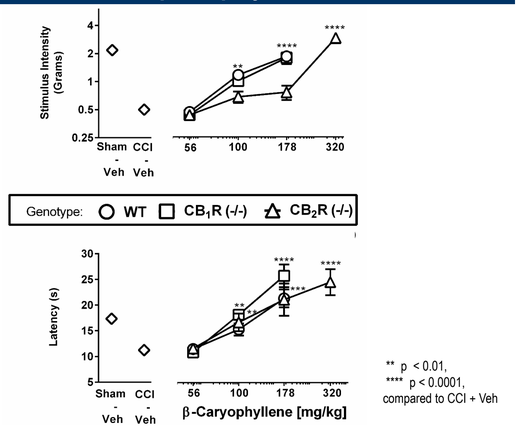
Terpenes reverse CCI-induced allodynia and thermal hyperalgesia



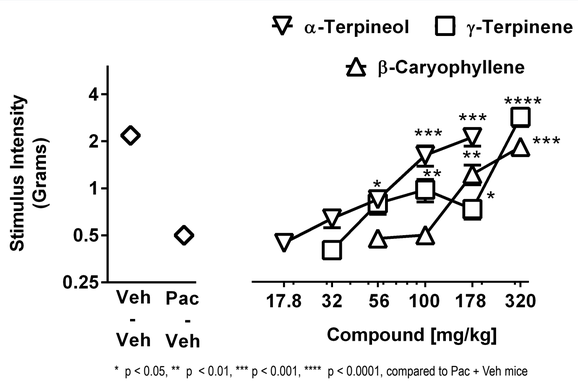
Alpha terpineol reversal of CCI allodynia: CB_1, CB_2 receptors play a role



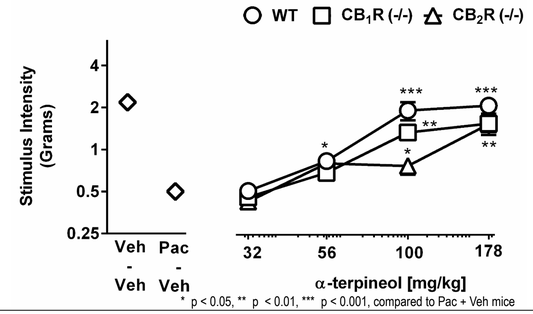
Beta caryophyllene reversal of CCI allodynia: CB_2 receptors play a role



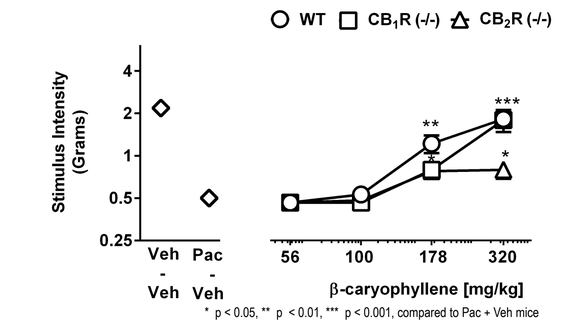
Terpenes reverse CIPN-induced allodynia



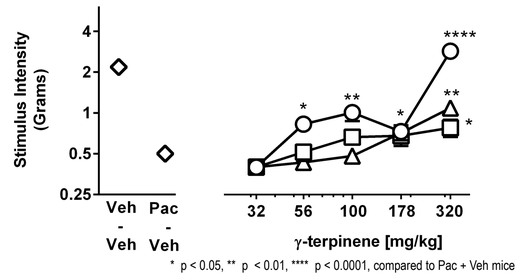
Alpha terpineol reversal of CIPN allodynia: CB_2 receptors play a role



Beta caryophyllene reversal of CIPN allodynia: CB_2 receptors play a role



Gamma terpinene reversal of CIPN allodynia: CB_1, CB_2 receptors play a role



Summary and Conclusions

- Each terpene dose-relatedly reversed mechanical allodynia in both models.
- Both CB_1R (-/-), CB_2R (-/-) mice treated with α-terpineol displayed a significant rightward shift in potency to reverse mechanical allodynia in both models.
- β-caryophyllene-induced reversal of mechanical allodynia underwent a significant rightward shift in potency in CB_2R (-/-) mice.
- Both CB_1R (-/-) and CB_2R (-/-) mice treated with γ-terpinene displayed a significant rightward shift in potency to reverse CIPN mechanical allodynia. These findings suggest these terpenes may have differential cannabinoid receptor activity.
- Cannabis-based terpenes may yield novel analgesics.

Acknowledgements

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