Analgesic effect of a novel cannabidiol formulation in preclinical models of chronic pain

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Abstract

Chronic pain is a debilitating experience linked to a variety of disease and conditions that approximately 20% of Americans and 25% of Canadians suffer from daily. Given the current opioid epidemic consuming both Canada and the United States, pain management practitioners are searching for new, non-opioid and non-addictive treatments for conditions that fall under the umbrella of chronic pain. One of these treatment options is cannabidiol, the major non-psychoactive constituent of cannabis and which has shown to be therapeutically beneficial in multiple clinical and preclinical conditions and shows an improvement of quality of life for patients. We sought to evaluate the efficacy of a novel cannabidiol formulation in reducing pain in mice in a few models of chronic pain. This cannabidiol/aloe vera formulation was tested in preclinical models of a chemotherapy-induced cold hypersensitivity, osteoarthritis, bladder pain, and neuropathic pain. Our results show that this formulation was indeed effective at reducing the cold hypersensitivity experienced by mice in the chemotherapy model, effective at reducing the intensity of mechanical allodynia in our model of neuropathic pain as well as effective at reducing spontaneous pain and urination volume in the bladder pain model. Future studies will aim to examine the effectiveness of this formula at reducing the activation of human sensory neurons.

Methods

OA model: The injection of mono-iodoacetate (250 micrograms per knee) and the scoring of the mechanical allodynia was performed as previously described (He et al., Osteoarthritis et al., 2017)

Interstitial Cystitis model: We followed the model of Bon et al (Bon et al. J. Urol 2003)). Spontaneous pain was scored based on the scale developed by Chen et al (Chen et al. Mediators of Inflamm. 2015). Mechanical sensitivity was assessed by the application of von Frey filaments to the abdomen. Urination frequency and volume were measured according to the model of Wood et al. (Wood et al. J Urol 2001)

The Neuropathic pain model was set as described by Petitjean et al. (Petitjean et al. Cell Reports 2019).

The Chemotherapy model was as developed by Polomano et al (Polomano et al. PAIN 2001).

The Cannabidiol-Aloe vera extract was provided by Desert Harvest Inc.

Effect of the CBD-Aloe Vera formulation on a mouse model of osteoarthritis pain

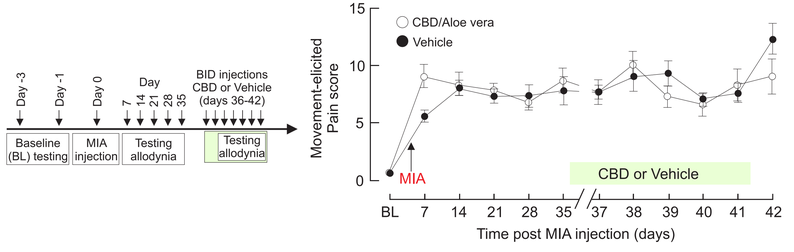

Figure 1. A preclinical model of knee osteoarthritis, in which the injection of a chemical (mono-iodoacetate) in the knee joint produces the loss of cartilage-producing cells (chondrocytes), and triggers mechanical allodynia, where gentle flexion and extension of the knee causes pain. The allodynia after MIA injection was measured for 5 weeks before treatment with the CBD-aloe vera or vehicle formulation began. After week 5, mice were injected for 7 days b.i.d. and allodynia measurements began a day later.

Effect of the CBD-Aloe Vera formulation on a mouse model of interstitial cystitis

Interstitial cystitis (IC) is a chronic and painful bladder condition characterized by spontaneous pain and sensitivity to touch, as well as frequent urination. A validated mouse model of IC has been used for many years and consists of a single injection of cyclophosphamide, which causes a bladder pain condition associated with spontaneous pain, pain upon mechanically stimulating the abdomen, and increased urination frequency and volume.

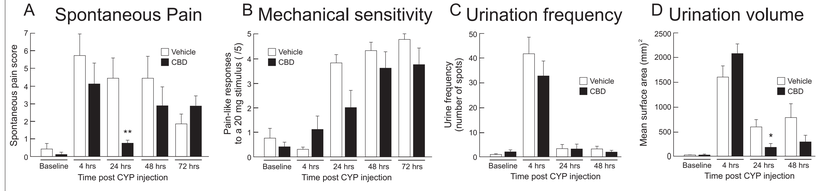

Figure 2. A preclinical model of interstitial cystitis. A) We observed a significant transient reduction in spontaneous pain score after CBD administration 24 hours post CYP. B) There was no significant difference in mechanical sensitivity following CBD administration or C) urination frequency. However, we did observe a significant transient reduction in urination volume following CBD administration 24 hours post-CYP injection.

Effect of the CBD-Aloe Vera formulation on a mouse model of neuropathic pain

Chronic neuropathic (NeP) pain follows a lesion to the nervous system and typically remains once the initial injury has subsided. It is characterized by spontaneous pain, and more importantly, pain caused by light touch, also known as mechanical allodynia. Several validated mouse models of NeP exist. One commonly used model is the chronic constriction injury of the sciatic nerve model. Upon loose ligature of the sciatic nerve, mice develop a state of mechanical allodynia that is, as in humans, resistant to common analgesics.

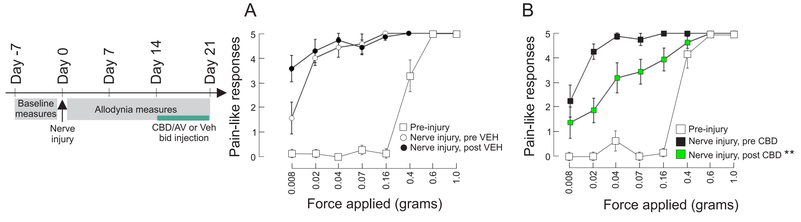

Figure 3. A preclinical model of nerve injury-induced mechanical allodynia, in which gentle stimuli evoke a pain-like reaction. In prelinical and clinical tests, von Frey filaments are used to assess mechanical sensitivity. A) Absence of anti-allodynic effect of the vehicle used to suspend the CBD/Aloe vera mixture. B) In the CBD/Aloe vera-treated group, 7 days of b.i.d. led to a significant reduction in the allodynia displayed by the mice.

Effect of the CBD-Aloe Vera formulation on a mouse model of chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling pain condition resulting from chemotherapy for cancer. Treatment options for established CIPN are also limited. Annually 165, 544 patients survive cancer in the United Kingdom, and more than 1 million in the United States. Approximately 60% of patients undergoing chemotherapy develop chronic pain symptoms, including hypersensitivity to touch and to cold stimuli.

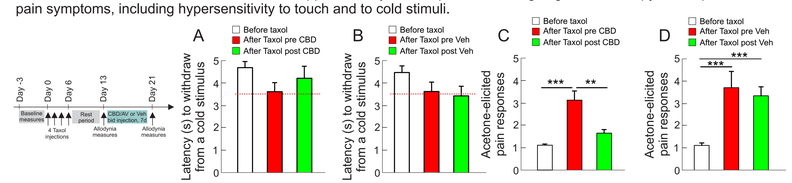

Figure 4. A preclinical model of chemotherapy-induced cold hypersensitivity. A and B) Systemic administration of the chemotherapeutic agent Paclitaxel (Taxol) causes a small and non-significant reduction in the latency to withdraw from a cold stimulus (ice). Upon chronic administration of the CBD-Aloe vera mixture (green bar, left graph), there is a partial attentuation of this hypersensitivity. Chronic administration of the vehicle (green bar, right graph) did not change the cold hypersensitivity. C and D) Brief application of acetone to the plantar surface of the paw produces a cooling sensation that can become painful after chemotherapy. The number of painful reactions was recorded for 30 seconds after acetone application. The administration of Taxol produces a significant increase in the number of painful responses produced by acetone (red bar, left graph). Interestingly, chronic administration of the CBD/Aloe vera mixture reduces these acetone-elicited pain behaviors (green bar). Administration of the vehicle (green bar, right graph) however, had no effect on acetone-elicited pain responses.

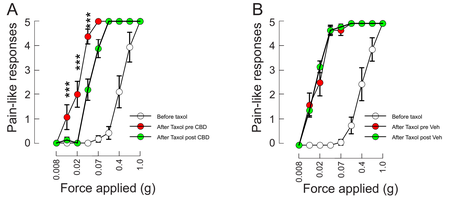

Figure 5. A preclinical model of chemotherapy-induced mechanical allodynia, in which gentle stimuli evoke pain-like reactions. In preclinical and clinical tests, von Frey filaments are used to assess mechanical sensitivity. A) Systemic administration of the chemotherapeutic agent Paclitaxel (Taxol) produces a significant mechanical allodynia (red circles). Upon chronic administration of th CBD-Aloe vera mixture, there is a partial yet significant reduction of this allodynia (green circles). B) In the vehicle (Veh)-treated mice, no attenuation of the mechanical allodynia could be observed.

Conclusions

- The formulation attenuates some of the symptoms of IC, with a transient reduction of the spontaneous pain and urination.
- We observed no change in the pain elicited by flexion and extension in the mouse model of OA by the CBD or vehicle formulations.
- Although the formulation does not abolish the mechanical allodynia caused by NeP, it significantly reduces the intensity of the pain experienced by the animals after nerve injury.
- Although the formulation does not abolish the mechanical allodynia in CIPN it significantly reduces it.

Future studies will examine the effect of this combination on pain neurons obtained from human donors.

Acknowledgements

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