Effects of the non-psychoactive cannabinoid cannabidiol in a mouse model of migraine

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Objective

The objective of the present research is to test the hypothesis that cannabidiol (CBD) can be effective as a pharmacotherapy for the treatment of migraine.

Introduction

CBD, the main non-psychoactive component of the *Cannabis sativa*, has therapeutic potential over a wide range of disorders that result from an equally wide range of CBD pharmacological actions. In particular, CBD has been reported to hold anxiolytic and antidepressant effects, to modulate neuronal transmission, and to deliver pain relief. Therefore, CBD may serve as a potential treatment for migraine, a complex condition characterized by the tendency to have headache with sensory disturbances associated with various symptoms including comorbid anxiety and depression.

Surprisingly there is limited research on CBD for migraine and there is no scientific evidence to prove that CBD is an effective treatment.

Methods

Migraine model and animals:

The effects of CBD are examined using a calcitonin-gene related peptide *(CGRP)-induced headache model* that mimics the complex migraine symptomatology using C57BL/6J mice. As migraine has a strong sex bias toward females, the experiments are conducted both in male and female mice.

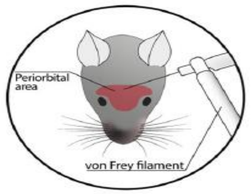
***Drugs*:**

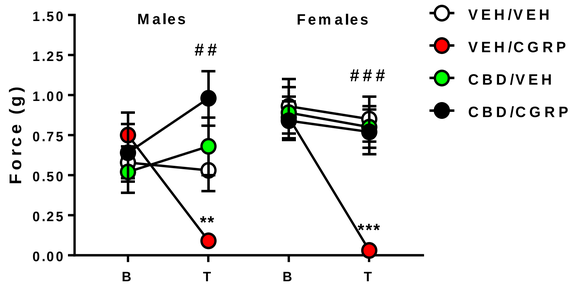
- Intraperitoneal (ip) CGRP (0.1 mg/kg) , CBD (30.0 mg/kg) and capsazepine (CPZ, 10 mg/kg)

Behavioral assays and measures:

- Cephalic allodynia measured by periorbital application of von Frey filaments
- Spontaneous pain assessed by facial grimace
- Light sensitivity (photophobia) assessed in the dark/light box
- Anxiety-like behavior assessed in the elevated-plus maze (EPM)
- Conditioned Place Aversion (CPA)

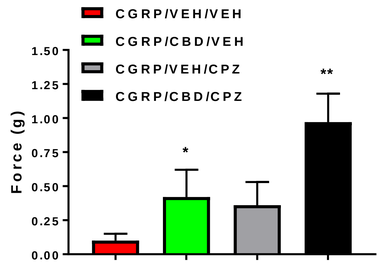
1. CBD effects on CGRP-induced cephalic allodynia





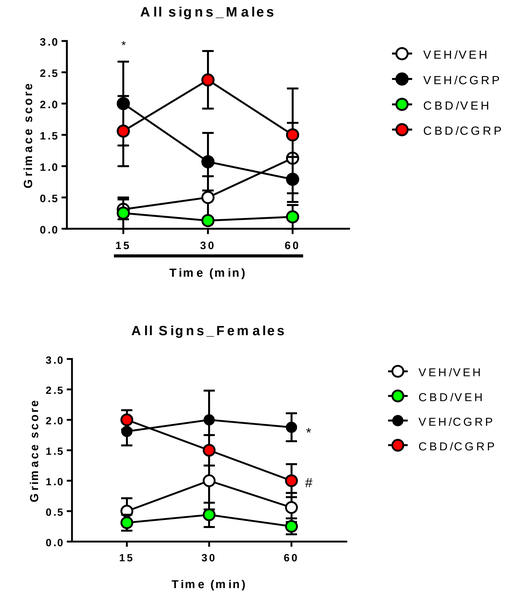
Cephalic allodynia, as measured by periorbital application of von Frey filaments, induced by peripherally administered CGRP (0.1 mg/kg) was successfully blocked by CBD (30 mg/kg, ip) both in male and female mice (N=8/group). B=baseline, T=test. **p<0.01, ***p<0.001 vs. VEH/VEH. ##p<0.01, ###p<0.001 difference VEH/CGRP-CGRP/CBD.

2. Effect of TRPV1 blockade on the anti-allodynic properties of CBD



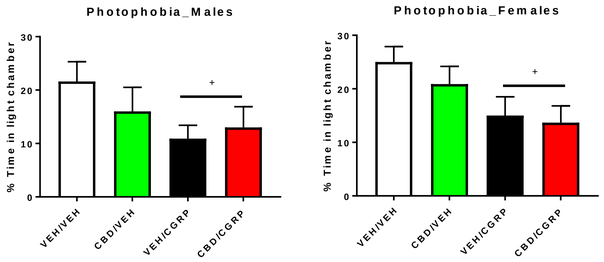
As analgesic effects of CBD have been ascribed to TRPV1 receptors, we chose to test whether the observed anti-allodynic responses to fine touch induced by CBD were prevented by the TRPV1 antagonist CPZ. **CPZ (10 mg/kg) enhanced the anti-allodynic effect of 30 mg/kg CBD** (N=7-8/group). *p<0.05, **p<0.01 vs. CGRP/VEH/VEH.

3. CBD effects on facial discomfort



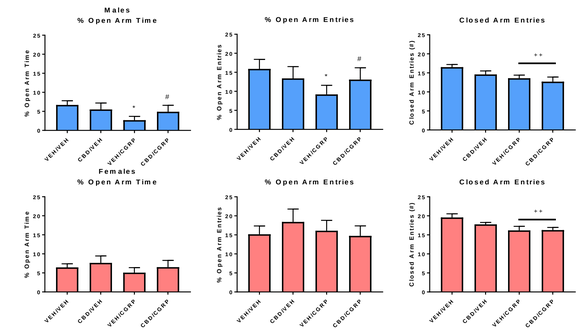
Effect of CBD on CGRP-induced facial grimace in male and female mice. Signs of discomfort examined were orbital tightening, nose bulge, cheek bulge, ear position and whisker change. **CBD (30 mg/kg) blocked facial grimace in female mice at 60 min time point** (N=8/group). *p<0.05 vs. VEH/VEH. #p<0.05 difference VEH/CGRP-CGRP/CBD.

4. CBD effects on CGRP-induced photophobia



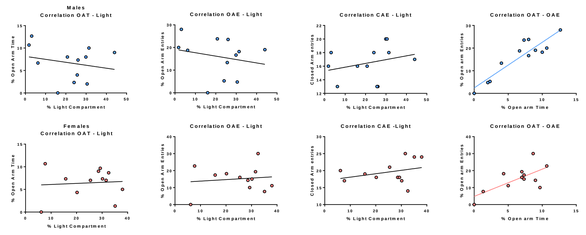
CBD (30 mg/kg) failed to reverse CGRP-induced photophobia both in male and female mice (N=12/group). +p<0.05 vs. VEH/VEH. #p<0.05 difference VEH/CGRP-CGRP/CBD.

5. CBD effects on CGRP-induced anxiety



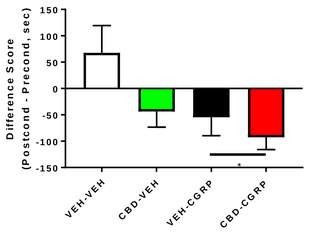
Effect of CBD on CGRP-induced anxiety in male and female mice using elevated plus maze. **CBD (30 mg/kg) reversed anxiety-like behavior induced by CGRP only in male mice** (N=12/group). *p<0.05 vs. VEH/VEH. #p<0.05 difference VEH/CGRP-CGRP/CBD.

6. Anxiety-Photophobia Correlations



Anxiety parameters did not correlate with photophobia. As the two symptoms were assessed in the same mice, lack of correlation indicates proper assessment of both symptoms.

7. CBD effects on CGRP-induced CPA



CBD (30 mg/kg) failed to reverse CGRP-induced CPA in male mice (N=8/group). *p<0.05, main effect of "pre-treatment" factor.

Conclusions

We demonstrate that:

- CBD successfully relieves migraine-like pain and anxiety associated with headache pain
- CBD fails in providing protection from other migraine-like traits such as photophobia and CPA
- CBD anti-allodynic properties are not mediated by CBD-induced TRPV1 activation

Additional research is needed to demonstrate the suitability of CBD as a treatment for migraine and to identify the mechanisms underlying CBD anti-headache properties.

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