THC attenuates weight loss in a pre-clinical animal model of activity-based anorexia.

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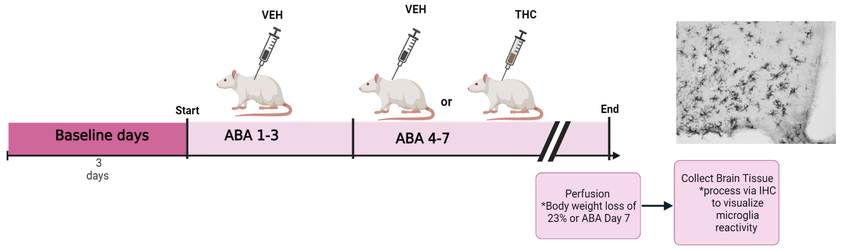
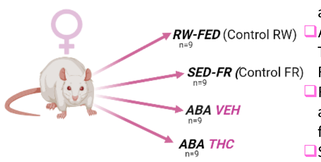
Introduction

- Anorexia Nervosa (AN) is a neuropsychiatric disorder that is characterized by increased hyperactivity, intense fear of weight gain, anhedonia, and chronic weight loss (1-2).
- To investigate the biological mechanism underlying AN, we used the preclinical activity-based anorexia (ABA) paradigm. ABA combines food restriction (FR) for 2 hr per day with unlimited access to running wheels (RW).
- ABA in rodents replicates some physiological symptoms of AN such as hyperactivity, extreme weight loss, and underconsumption of calories (3).
- D9-tetrahydrocannabinol (THC) is a phytocannabinoid that interacts with the endocannabinoid system. THC's orexigenic effect has been well documented in rodents. Recent literature has shown that an acute administration of THC in rodents acts via CB1R to increase food intake (4)(5).
- The endocannabinoid system (ECS) is a promising target for treating AN. The ECS plays an important role in feeding behavior, lipid synthesis, adipose tissue, and energy expenditure; all of which are dysregulated in AN patients (4).
- Several clinical studies have also tested the efficacy of cannabinoids to alleviate undereating. For example, one study found that a twice daily treatment of dronabinol increased weight gain by 2% in patients with AN relative to placebo (6).
- Few studies have shown efficacy to prevent weight loss in ABA. Thus far, only one study showed that THC reduced body weight loss and shifted markers of thermogenesis in BAT and lipid metabolism in WAT in directions consistent with reduced energy expenditure and lipolysis (7).
- We hypothesize that THC can "rescue" the rapid weight loss in rats exposed to ABA paradigm.

Methods





- ❑ABA-VEH - Day 1-7 VEH. 2 hr access to food (1-3pm). RW *ad-lib*.
- ❑ABA-THC – Day 1-3 VEH, day 4-7 THC. 2 hr access to food (1-3pm). RW *ad-lib.*
- ❑RW-FED - Day 1-7 VEH with free access to food and RW *ad-lib*. 2 hr food intake weighed (1-3pm)
- ❑SED-FR- Day 1-7. 2 hr access to food (1-3pm) and no access to RW.
- Body weight, food intake (FI) and RW activity were measured daily.
- Injections at 30 mins prior to dark onset.

Results

THC attenuated ABA-induced weight loss.

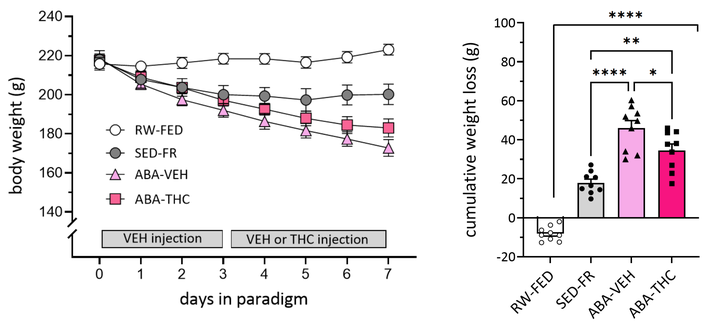
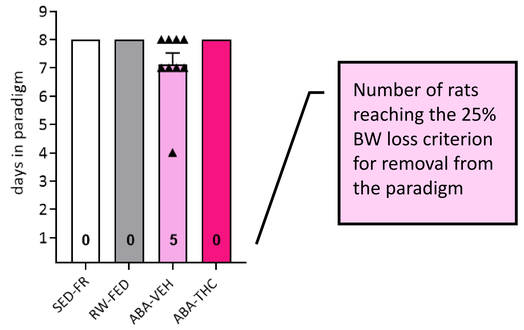


Fig. 1. Daily weight loss was greater in ABA rats compared to both control groups. THC treatment reduced cumulative weight loss in rats exposed to the ABA paradigm.

Results

THC treatment prolonged survival in the ABA paradigm.

Fig. 2. THC prolonged rodent survival in the ABA paradigm. ABA VEH group survival was lower compared to other groups.
*Survival was defined as meeting the 25% BW loss criterion before the end of the experiment.



THC treatment had no effect on food intake.

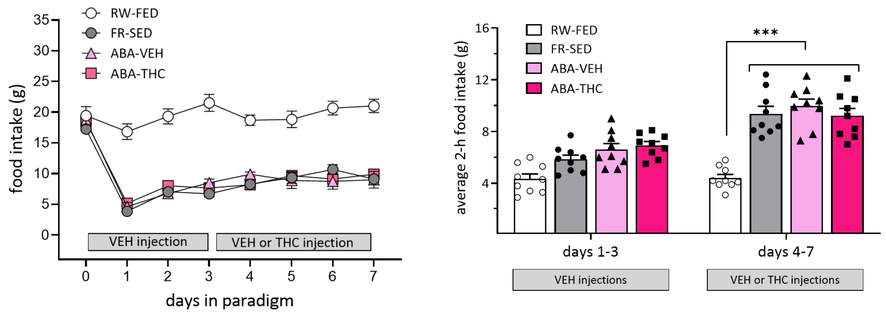


Fig. 3.. Daily food intake was similar in both ABA Groups and the FR-SED group. Average FI on days 1-3 was similar across all groups. Average FI on days 4-7 was increased in all the food restricted groups, relative to RW-FED group.

THC treatment reduced hyperactivity.

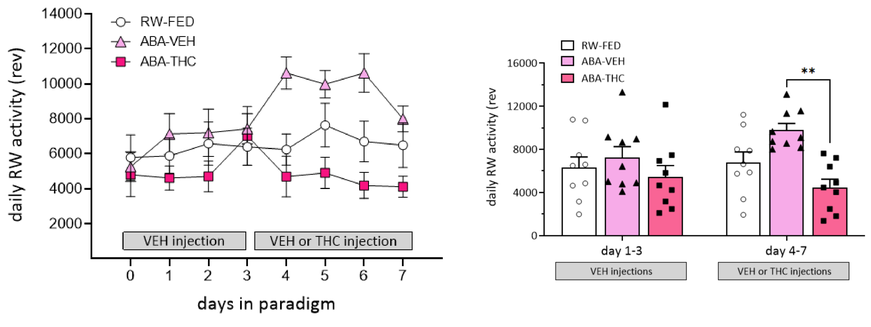


Fig. 4.. Daily THC treatment attenuated hyperactivity compared to RW-FED and ABA-VEH groups. On days 4-7, there was a significant decrease in daily running wheel activity in THC-treated rats.

THC reduced running wheel activity during light and dark phase.

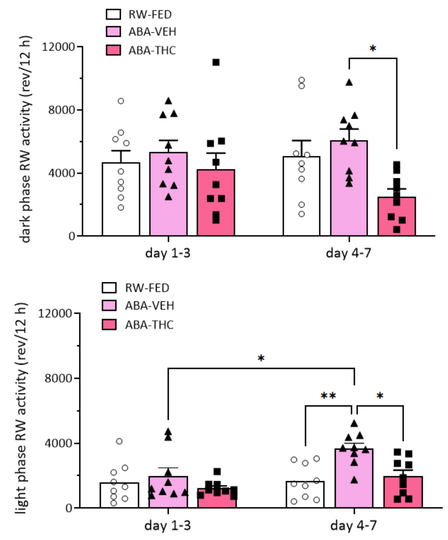


Fig. 5. During the dark phase, ABA-THC rodents ran significantly less than the ABA-VEH and RW-FED groups on days 4-7. During the light phase, ABA-VEH rats ran more than RW-FED rats. The hyperactivity observed in ABA-VEH rats was attenuated in ABA THC rats..

Discussion and Future Directions

- THC attenuated weight loss in ABA-THC animals, which increased the animal's survival in the ABA paradigm.
- This effect was mediated by THC's ability to decrease locomotor activity, rather than increasing food intake. THC 's anxiolytic properties could be contributing to our observed decrease in hyperactivity in ABA.
- Between the two ABA groups, THC had no effect on food intake which could have been due to a ceiling effect.
- In rodents, restricted eating has also been shown to promote a neuroinflammatory response that is well characterized in brain areas that regulate feeding behavior. This supports the rationale to study microglia reactivity (8) .
- Future studies will focus on quantifying brain tissue with IBA-1 to examine microglia expression in brain regions that modulate food intake, which could indicate that microglia reactivity may contribute to the maintenance of AN.

References

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