THC slows progressive weight loss in a rodent model of anorexia nervosa

Alexis A. Perrini and Lisa A. Eckel

Program in Neuroscience, Department of Psychology, Florida State University, Tallahassee, FL.

Introduction

Anorexia nervosa (AN) is a serious illness characterized by caloric restriction, hyperactivity and profound weight lost. Available treatments are largely ineffective, relapse is common, and full recovery occurs in only half of AN patients[1]. **These poor outcomes highlight a critical need for more effective treatments.**

The endocannabinoid system could be an important therapeutic target for AN as it plays an important role in regulating energy homeostasis[2-4], and clinical studies report impaired endocannabinoid signaling in AN patients[5]. Additional studies involving the pre-clinical rodent model of activity-based anorexia (ABA) have shown that daily treatment with tetrahydrocannabinol (THC), initiated on the first day of the ABA paradigm, promotes a modest decrease in weight loss in female rats[6-7].

The primary goal of the current study was to determine whether THC treatment, initiated following 12-15% weight loss in the ABA paradigm, could rescue the ABA phenotype in female rats. Prior to conducting this study, we first examined whether THC's orexigenic effect is influenced by stage of the estrous cycle based on studies suggesting sex differences in THC's orexigenic effect.

Methods

Expt. 1: Is THC's orexigenic effect influenced by estrous cycle stage?

A within-subjects design was used to examine the effects of THC on food intake in cycling female rats. Stage of the estrous cycle was monitored daily by examining vaginal cytology samples under a light microscope. Testing began when all rats displayed 2 consecutive 4-day estrous cycles. On 4 separate test days, i.p. injections of THC (1mg/kg) or vehicle were administered 30 min prior to dark onset when individual rats were in estrus or diestrus. At dark onset, food intake was measured at 1, 2, and 21 h.

Expt. 2: Can THC treatment rescue the ABA phenotype?

Female rats were housed in custom cages equipped with running wheels and feeding niches that provided access to powdered chow. Following adaptation to the cages and drug injections, animals were exposed to the **ABA paradigm, which combines restricted daily access to chow (90 min/day at dark onset) with unlimited access to running wheels.** These conditions promote hypophagia and hyperactivity, which result in rapid weight loss.

At study onset, rats were assigned to treatment groups: vehicle or THC (1 mg/kg). Each day, animals received acute i.p. injections of their assigned drug 30 min prior to their 90-min access to food. Rats in the THC group were given THC injections after a 12-15% body weight loss. Rats were maintained on this restricted feeding schedule with unlimited access to running wheels either for 7 days or after losing 22% of their body weight, whichever occurred first.

Results

THC increased food intake at 1 and 2 h post-injection in diestrous, but not estrous, rats.

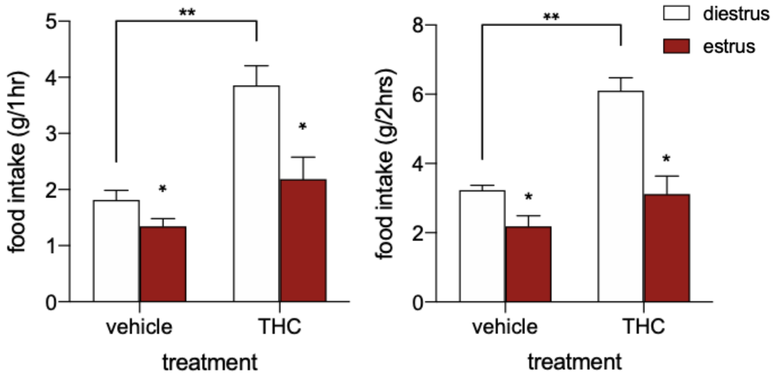

Fig. 1: As expected, food intake was decreased when rats were in estrus (*Estrus < diestrus, $p < 0.05$). THC increased food intake in diestrous rats, but not in estrous rats (**THC > vehicle, $p < 0.05$).

Results

The orexigenic effect of THC in diestrous rats was observed at 1 and 2h, but not at 21 h, post-injection.

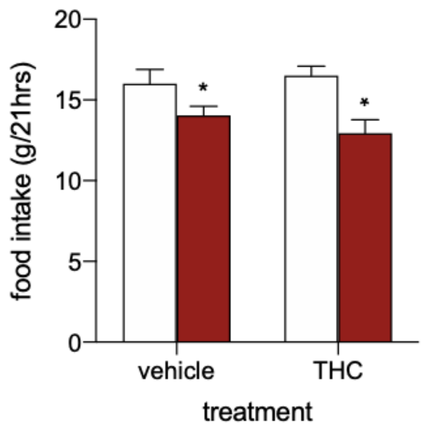

Fig. 2. As expected, an estrous-related decrease in 21-h food intake was observed (*Estrus < diestrus, $p < 0.05$). While THC produced a rapid increase in food intake within the first 2 h post-injection in diestrous rats, it failed to increase feeding at 21 h in both diestrous and estrous rats.

THC attenuated weight loss in the ABA paradigm.

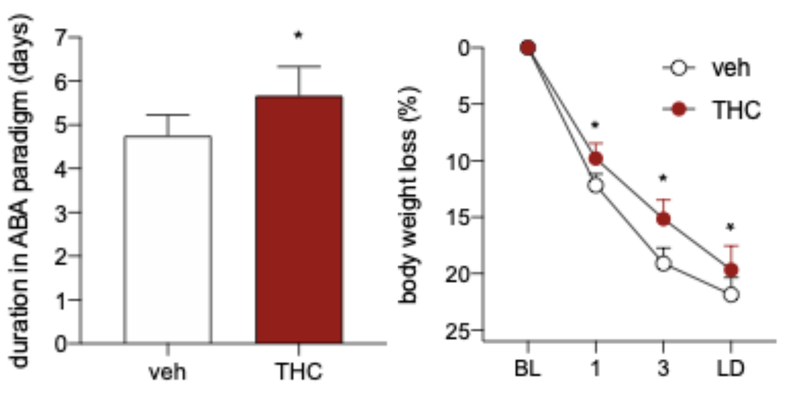

Fig. 3. THC-treated rats were able to stay in the ABA paradigm longer than control rats, due to THC's ability to slow progressive weight loss ($p < 0.05$).

THC attenuates running wheel activity in the ABA paradigm.

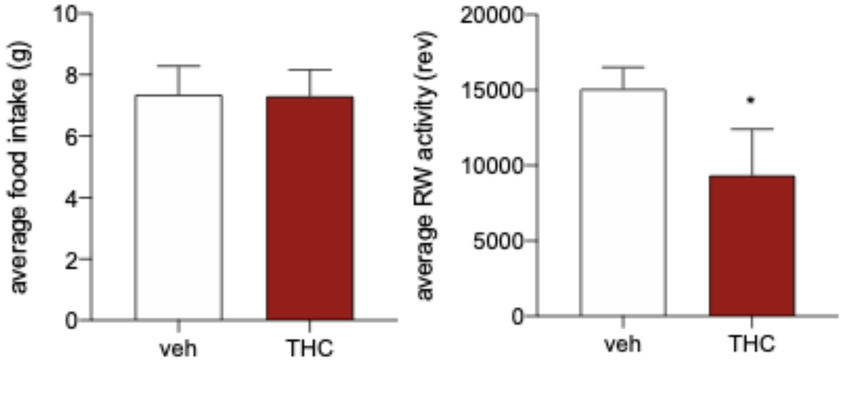

Fig. 4. THC increased survivability in the ABA paradigm by decreasing running wheel activity. THC-treated rats ran less than vehicle-treated rats ($p < 0.05$).

Food intake was increased and running wheel activity was decreased following the onset of THC treatment.

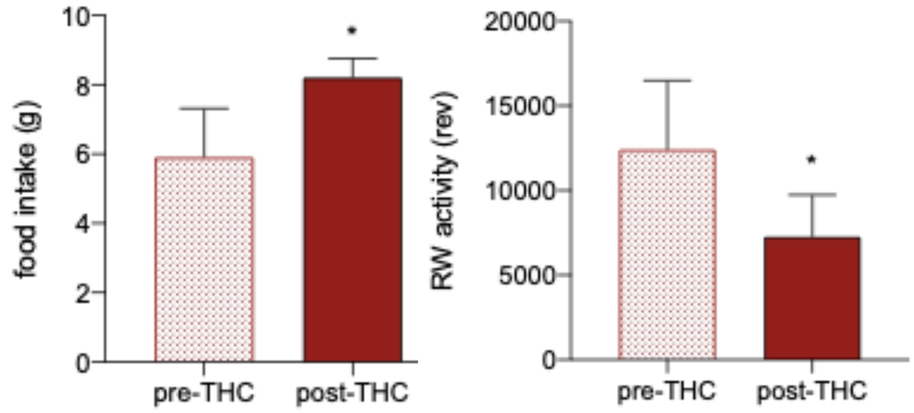

Fig. 3. Rats treated with THC showed an increase in food intake post THC-5injection compared to vehicle injections during injection acclimation ($p < 0.05$).

Discussion

- THC's orexigenic effect varies across the estrous cycle, with estrous rats being less sensitive to THC than diestrous rats.
- We conclude that hormonal changes across the estrous cycle influence the orexigenic effect of THC, and this may explain the reported sex differences in THC-induced feeding. Given estradiol's known anorexigenic effect, it is likely that the peri-ovulatory increase in estradiol secretion is responsible for decreasing sensitivity to THC during the estrous stage of the cycle.
- Additional studies are underway to determine whether THC stimulates feeding in satiated female rats, and whether this effect is modulated across the estrous cycle.
- Future studies are planned to investigate THC-induced feeding conjointly with maladaptive eating behaviors in rodent models of anorexia nervosa, binge eating, and obesity.
- The within-subject comparison of THC's ability to increase appetite in ABA rats (Fig. 5), suggests that prolonging the period of THC treatment may have promoted a greater attenuation of weight loss in the ABA paradigm. Future studies will incorporate a longer duration of food access in order to extend the ABA testing phase.
- Our data demonstrate that daily THC treatment slows weight loss in the ABA paradigm by decreasing energy expenditure.
- Future studies will examine other cannabinoids, like cannabidiol (CBD), an important component of medical marijuana as it lacks THC's psychotropic effects.

References

1. Andries, A., Støving, R.K. (2011). Cannabinoid-1 receptor agonists: a therapeutic option in severe, chronic anorexia nervosa? *Neuropsyc* 1:467-476.
2. Koch, JE. (2001). D^9-THC stimulates food intake in Lewis rats: Effects on chow, high-fat and sweet high-fat diets. *Pharmacol, Biochem, Behav.* 68:539-43.
3. Cota, D, et al. (2003). The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest*, 112: 423-31.
4. Williams, CM & Kirkham, TC. Observational analysis of feeding induced by D^9-THC and anandamide. *Physiol & Behav.* 2002; 76: 241-50.
5. Monteleone, AM, et al., 2015. Deranged endocannabinoid responses to hedonic eating in underweight and recently weight-restored patients with anorexia nervosa. *Am J Clin Nutr* 101(2), 262-269.
6. Verty, AN, et al., The cannabinoid receptor agonist THC attenuates weight loss in a rodent model of activity-based anorexia. *Neuropsychopharm.* 2011; 36:1349-58.
7. Scherma, M., et al., 2017. Cannabinoid CB1/CB2 receptor agonists attenuate hyperactivity and body weight loss in a rat model of activity-based anorexia. *Br. J. Pharmacol.* In press.

This work was supported by the Consortium for Medical Marijuana Clinical Outcomes Research (LAE) and a T32 grant MH093311 (AAP).