

## **ABSTRACT**

Aim: Anxiety disorders are twice as common among women, and those with anxiety disorders are 2-3 times more likely to have a substance abuse disorder than the general populace.

However, little data exists on the sexually dimorphic effects of cannabinoids. In male humans and rodents, low acute doses of cannabinoids are anxiolytic while high and/or chronic doses are anxiogenic. In the dose response curve (DRC), we examined whether the biphasic effects of cannabinoids observed in males are also present in females. In the CB1R antagonism study, CP55,940-induced CB1R activation was antagonized via the CB1R-selective antagonist rimonabant to test the hypothesis that sexually dimorphic CB1R activation underlies sex differences observed in response to CP55,940 administration.

Methods: Male and female adult Wistar rats received 0, 0.001, 0.01, 0.075 or 0.125 mg/kg i.p. of the THC agonist CP55,940 in the DRC. Thirty minutes later, rodents were tested for 10 minutes in the elevated plus maze (EPM) and their behavior analyzed with Med Associates tracking software. Western blot analysis assessed changes to p-DARPP-32 (Thr34), p-ERK, p-CREB and cFOS following sacrifice. In the CB1R antagonism study, rodents received 3.0 mg/kg of the CB1R antagonist rimonabant, followed thirty minutes later by 0.075 mg/kg i.p. CP55,940 and methods were thereafter as described for the DRC.

Results: In the DRC, we found main effects of dose and sex on percent open arm time and percent open arm entries. Male manifested a bi-phasic, dose-dependent response as expected, while females had a dose-dependent anxiogenic reaction to CP55,940. Sex and dose effects were observed in multiple brain areas and proteins. The CB1R antagonism study demonstrated a potentiating effect of pretreatment with the CB1R antagonist rimonabant on anxiety, but a restorative effect on locomotion. Dose and sex effects were observed for changes in protein expression in multiple brain regions.

Conclusion: Sex differences were observed in the effect of CP55,940 on anxiogenic and anxiolytic responses, and in the effects of rimonabant. Although males showed biphasic dose dependent responses, females showed only an anxiogenic response to CP55,940. Further research is needed to understand the underlying mechanisms responsible for these differences.