GHSR protects the emergence of limited sex differences in anxiety-related behaviors in adult mice after long term THC administration during peri-adolescence

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Introduction

- Marijuana consumption during adolescence might increases the risk of developing mental illness, such as depression and anxiety, later in life [1]
- Heavy cannabis consumption has been correlated to changes in the hippocampus [2]
- During development for infancy to young adulthood, CB1R (the cannabinoid receptor 1) expression increases dramatically in regions such as the hippocampus [3]
- Ghrelin and its receptor GHSR are important for the ability of animals to cope with anxiety-inducing stressors [4]
- Ghrelin has neuroprotective properties, as it increases hippocampal neurogenesis [5]

Hypothesis

Aim of this Study:

to investigate the effects of chronic tetrahydrocannabinol (THC) administration during late adolescence (P42-55), in ghrelin receptor (GHSR-/-) knockout mice and their wild type littermates in relation to anxiety-like behaviors in adulthood

Methods

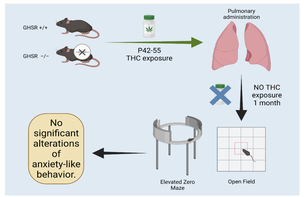
Mouse Model Used:

Mice were generated by breeding C57BL/6J mice with GHSR-/- mice in order to obtain an F1 generation of heterozygous GHSR knock-out animals [6].

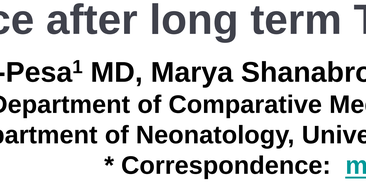
These progenies were subsequently used to generate GHSR +/+ (WT) and GHSR-/- (KO) animals used in this study.

Methods

Experimental Design:



- THC was daily administered to animals from 6 to 8 weeks of age.
- Behavioral testing was performed at 12 to 13 weeks of age during the light cycle
- To mimic smocking as a method of administration of THC, we used the Volcano® Vaporization device (below)

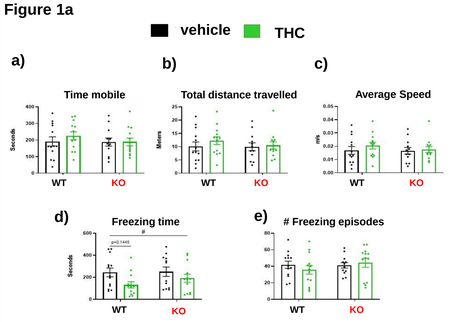


Behavioral assessments:

- Open field
- Elevated zero maze

Results

Figure 1a



Results

Figure 1b

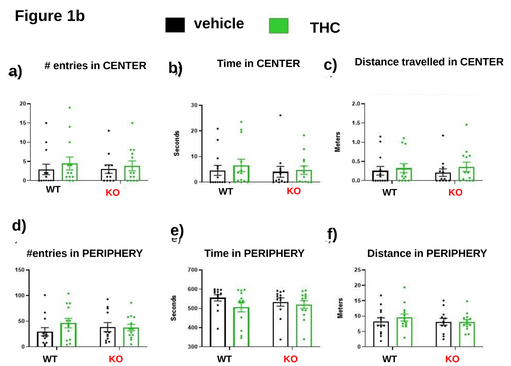


Figure 1a: *Open field*, general locomotion a) Time mobile. b) Total distance traveled. c) Average speed. d)Freezing time. e) Number of freezing episodes')

1b: *Open field, anxiety-related parameters.* a) Number of entries in the central zone. b) Time spent in central zone. c) Total distance traveled in central zone. d) Number of entries in peripheral zones. e) Time spent in peripheral zones. f) Total distance traveled in peripheral zones. WT-vehicle n=13, WT-THC n=13, KO-vehicle n=12, KO-THC n=13; Data are expressed as mean ± SEM *p< 0.05. Two-way ANOVA , post-hoc comparison indicated by p values when appropriate.

Figure 2

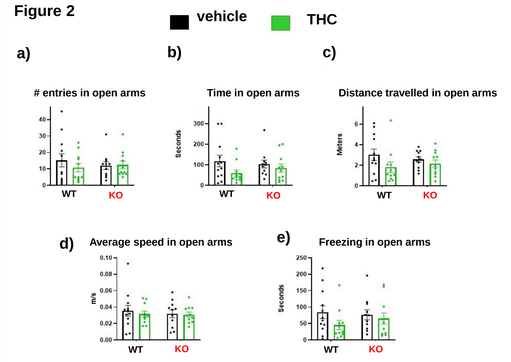


Figure 2. *Elevated Zero Maze.* WT-vehicle n=12, WT-THC 10 mg n=11, KO-vehicle n=11, KO-THC 10 mg n=11. a) Number of entries in open arms. b) Time spent in open arms. c) Distance traveled in open arms. d) Average speed in open arms. e) Time spent freezing in open arms. Data are expressed as mean ± SEM *p< 0.05. Two-way ANOVA

Summary

- In our experimental setting, parameters that evaluate general locomotion were unaffected by THC exposure in male and in female mice
- No differences among groups were found in the parameters of time spent in the open arms or distance travelled in open arms in elevated zero test

Conclusions

- Daily THC exposure during late adolescence did not lead to any significant alterations in anxiety-like behaviors, regardless of genotype, following a prolonged period of no exposure (1 month)
- Our data indicate that in presence of intact GHSR signaling, THC exposure during late adolescence has limited impact on anxiety-like behaviors in mice

Future Directions

- By employing additional behaviors tests, further research will investigate whether THC exposure in late adolescence affects behaviors related to sensory gating, compulsiveness, and mood regulation
- THC exposure will be coupled with a variety of adjunct treatments, such as sex hormone inhibitors and ghrelin, to address possible sex differences
- We will further investigate if any of the changes in behavior are associated with changes in area of the brain controlling them, such as the hippocampus, amygdala or the prefrontal cortex

References

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