CANNABINOID PHARMACOKINETICS FOLLOWING EXPOSURE TO CANNABIS SMOKE IN YOUNG ADULT AND AGED MICE

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INTRODUCTION

Older adults represent the fastest-growing group of cannabis users in the US[1]. With Alzheimer's disease (AD) cases projected to increase[2], there is an urgent need to determine how cannabis affects AD pathology and age-related cognitive impairments. Cannabinoids have been shown to attenuate markers of AD-relevant pathology and neuroinflammation in both cell culture and animal models; however, most of these studies utilize Δ9THC (the primary psychoactive component of cannabis) or synthetic cannabinoids rather than cannabis itself, and/or employ cannabinoid administration methods that do not model human cannabis ingestion[3].

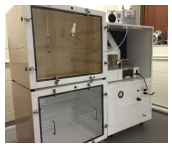
To begin to model cannabis use akin to human consumption in rodent models, the current study was designed to determine the pharmacokinetics of cannabinoids in mice exposed to cannabis smoke. **Specifically, experiments were designed to determine: A) the time course of plasma and brain levels of THC and its metabolites following passive cannabis smoke exposure in young C57BL/6J mice; B) how age affects THC and metabolite levels in mice of several strains commonly used in studies of AD-like pathology (FVB, 129, SW, and B6) and C) how dose affects THC and metabolite levels.**

Ongoing studies are determining the neurobiological effects of chronic cannabis smoke exposure in young adult and aged mice as well as the impact on AD-like tau pathology in rTg4510 mutant tau transgenic mice.

METHODS

Cannabis Smoke Exposure: Mice were exposed to smoke generated from sequentially burning 5 cannabis cigarettes (5.9% THC) over the course of an hour in a TE-10 Smoking Machine. Mice were placed into the upper chamber of the exposure apparatus (A.) while remaining in their home cages. Cigarettes were burned using an automated smoking machine (B.) from which the smoke was pumped into the exposure chamber.

A.



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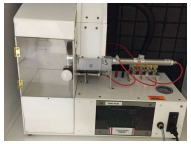

Sample Collection and Analysis: Following smoke exposure, the mice were euthanized via rapid decapitation and trunk blood and brain were collected at different timepoints. Plasma and brain homogenate samples were analyzed for Δ9THC (the primary psychoactive component of cannabis) as well as two major metabolites of Δ9THC (11-nor-9-carboxy-Δ9THC and 11-hydroxy-Δ9THC) using a validated ultraperformance liquid chromatography-tandem mass spectrometry method.

EXP. 1 CANNABIS SMOKE EXPOSURE IN YOUNG C57BL/6J MICE

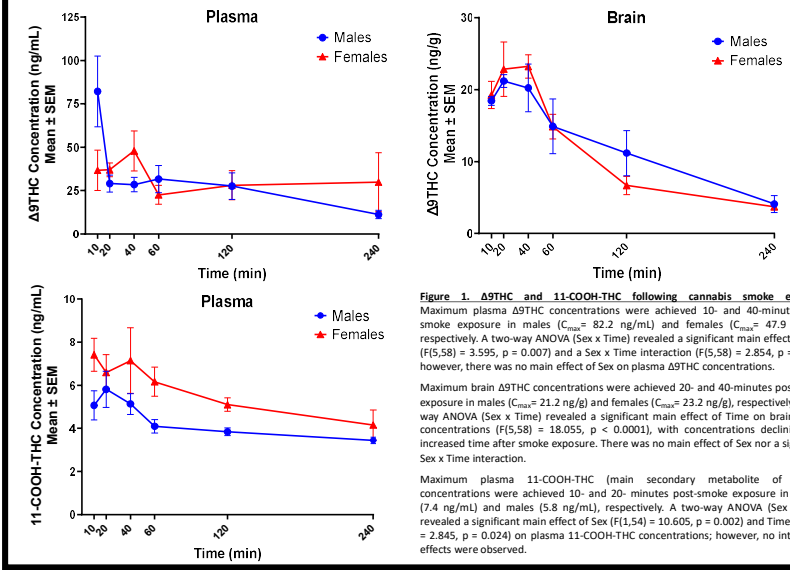

Figure 1. Δ9THC and 11-COOH-THC following cannabis smoke exposure
Maximum plasma Δ9THC concentrations were achieved 10- and 40-minutes post-smoke exposure in males (C_{max}= 82.2 ng/mL) and females (C_{max}= 47.9 ng/mL), respectively. A two-way ANOVA (Sex x Time) revealed a significant main effect of Time (F(5,58) = 3.595, p = 0.007) and a Sex x Time interaction (F(5,58) = 2.854, p = 0.023); however, there was no main effect of Sex on plasma Δ9THC concentrations.

Maximum brain Δ9THC concentrations were achieved 20- and 40-minutes post-smoke exposure in males (C_{max}= 21.2 ng/g) and females (C_{max}= 23.2 ng/g), respectively. A two-way ANOVA (Sex x Time) revealed a significant main effect of Time on brain Δ9THC concentrations (F(5,58) = 18.055, p < 0.0001), with concentrations declining with increased time after smoke exposure. There was no main effect of Sex nor a significant Sex x Time interaction.

Maximum plasma 11-COOH-THC (main secondary metabolite of Δ9THC) concentrations were achieved 10- and 20- minutes post-smoke exposure in females (7.4 ng/mL) and males (5.8 ng/mL), respectively. A two-way ANOVA (Sex x Time) revealed a significant main effect of Sex (F(1,54) = 10.605, p = 0.002) and Time (F(5,54) = 2.845, p = 0.024) on plasma 11-COOH-THC concentrations; however, no interaction effects were observed.

EXP 2. CANNABIS SMOKE EXPOSURE IN DIFFERENT MOUSE STRAINS AND AGES

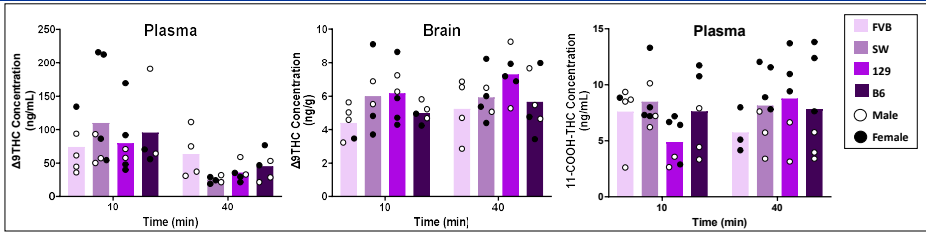

Figure 2. Strain differences in young adult mice following cannabis smoke exposure
A two-way ANOVA (Strain x Time) revealed a significant main effect of Strain (F(3,34) = 2.972, p = 0.045) on brain Δ9THC concentrations. Tukey post hoc comparisons revealed that 129 mice had significantly greater brain Δ9THC concentrations than FVB mice (p = 0.041). A main effect of Strain was not observed in plasma Δ9THC or plasma 11-COOH-THC concentrations. There was a significant main effect of Time (F(1,34) = 9.731, p = 0.004) on plasma Δ9THC, however, with concentrations decreasing 40 minutes post smoke exposure, whereas brain Δ9THC and 11-COOH-THC concentrations remained elevated.

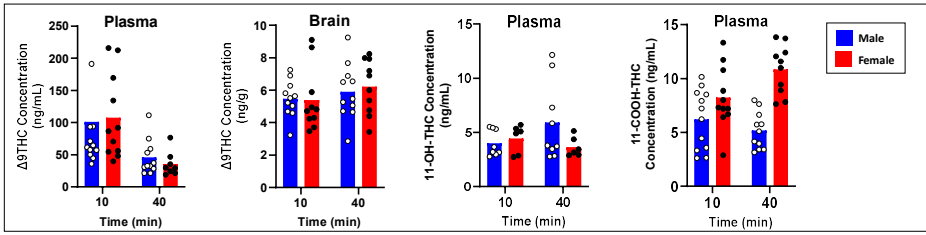

Figure 3. Sex differences in young adult mice following cannabis smoke exposure
Collapsed across strain, a two-way ANOVA (Sex x Time) revealed a significant main effect of Sex (F(1,40) = 26.386, p < 0.0001) on plasma 11-COOH-THC concentrations and a significant Sex x Time interaction (F(1,40) = 6.046, p = 0.018; however, there were no Sex differences in plasma and brain Δ9THC or plasma 11-OH-THC concentrations.

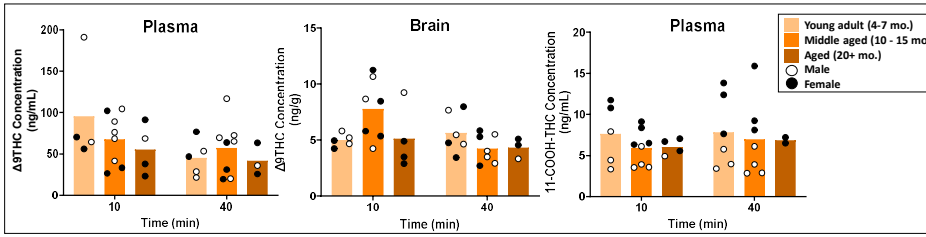

Figure 4. Age differences in young adult, middle aged, and aged B6 mice following cannabis smoke exposure
A two-way ANOVA (Age x Time) revealed a significant Age x Time interaction (F(2,26) = 3.741, p = 0.037) in brain Δ9THC concentrations; however, there was no main effect of Age on plasma or brain Δ9THC, or on plasma 11-COOH-THC concentrations. The same analysis conducted with young adult and middle aged FVB mice also revealed no main effect of Age on plasma and brain Δ9THC nor 11-COOH-THC plasma concentrations (data not shown).

EXP 3. EFFECT OF CIGARETTE DOSE ON THC AND METABOLITE LEVELS

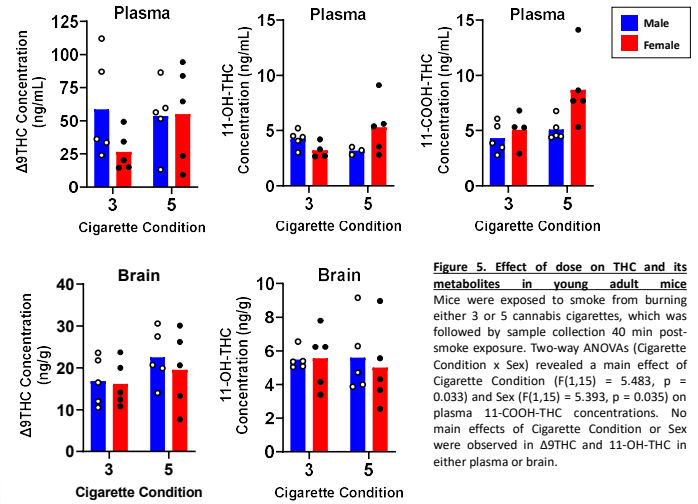

Figure 5. Effect of dose on THC and its metabolites in young adult mice
Mice were exposed to smoke from burning either 3 or 5 cannabis cigarettes, which was followed by sample collection 40 min post-smoke exposure. Two-way ANOVAs (Cigarette Condition x Sex) revealed a main effect of Cigarette Condition (F(1,15) = 5.483, p = 0.033) and Sex (F(1,15) = 5.393, p = 0.035) on plasma 11-COOH-THC concentrations. No main effects of Cigarette Condition or Sex were observed in Δ9THC and 11-OH-THC in either plasma or brain.

SUMMARY & CONCLUSIONS

- Passive cannabis smoke exposure in mice yields detectable levels of Δ9THC in both plasma and brain that are comparable with those in humans exposed to cannabis smoke[4]
- Peak plasma Δ9THC concentrations are achieved at 10- and 40-min time points in males (C_{max}= 82.2 ng/mL) and females (C_{max}= 47.9 ng/mL), respectively
- Peak brain Δ9THC concentrations are achieved at 20- and 40-min time points in males (C_{max}= 21.2 ng/g) and females (C_{max}= 23.2 ng/g), respectively
- There were significant strain differences in Δ9THC brain concentrations
- Δ9THC levels were not significantly affected by age in either B6 or FVB mice
- There were significant sex differences in plasma 11-COOH-THC concentrations, with females having higher levels than males in all three experiments
- No significant differences in plasma and brain concentrations of Δ9THC following 3 cigarette exposure; subsequent chronic smoke exposure studies will utilize a 3 cigarette dose

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