IMPACT OF THC VAPE ON THE PROTEOMIC PROFILE OF EXTRACELLULAR VESICLES IN THE BRAIN

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Abstract

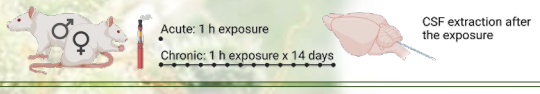
Background: With legalization of cannabis in the US, there is an urgent need to more clearly understand the drug's effects on central signaling mechanisms. Extracellular (EVs) vesicles have been identified as intercellular signaling mediators, which contain a variety of cargo, including proteins, enzymes, and RNA transcripts. The focus of these studies was to examine whether the main psychoactive component in cannabis, Δ9-tetrahydrocannabinol (THC), alters EV cargo in the brain.

Methods: In vitro studies were first conducted to determine whether THC can act on primary epithelial cells derived from the dorsal third ventricle of rats. Next, to examine the impact of THC in vivo, male and female rats were exposed to aerosolized THC or vehicle in vapor chambers. The first cohort of rats (n=12/group/sex) received a single session of exposure, and the second cohort (n=12/group/sex) received 14 consecutive daily sessions of exposure. CSF was collected from the cisterna magna, and EVs were extracted with SBI SmartSEC and then processed for label free quantitative proteomics analyses via high resolution tandem mass spectrometry. Quantitative LFQ mass spectral data were analyzed using Progensis QI Proteomics software.

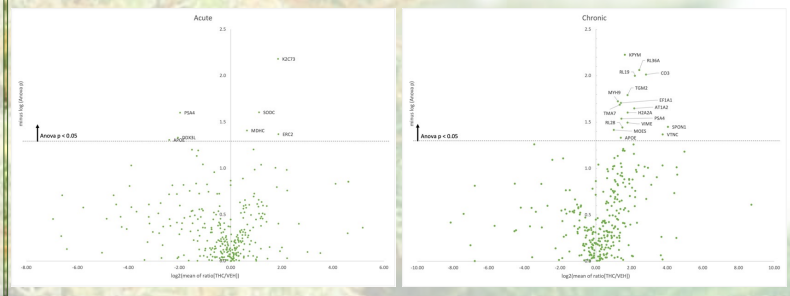
Results: Cannabinoid receptor (CB1R) expression was localized in the choroid plexus, and THC upregulated the expression of c-fos, CB1R mRNA, and mir-204, a transcript localized in EVs. In the THC vape exposed rats, multiple EV proteins were identified as being differentially expressed following either acute or chronic exposure. Interestingly, exponential effects were found with some proteins between acute exposure and chronic exposure expression.

Conclusions: Our findings reveal that cannabinoids can modulate intercellular signaling mechanisms in the brain, with differential effects following single or chronic exposure. Our data further support the contention that THC can act on CB1 receptors in the choroid plexus to mediate EV signaling, which may then integrate into different brain regions to modulate cellular function.

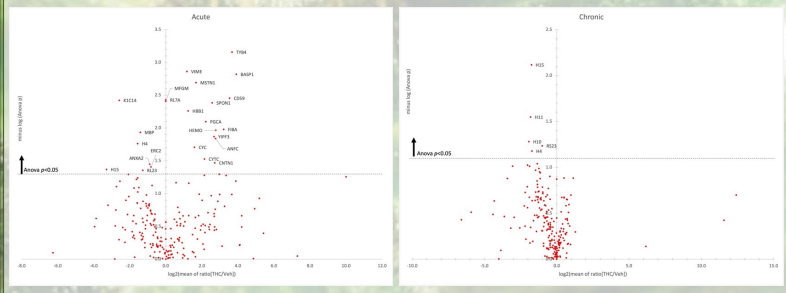
Timeline of vapor exposure experiment



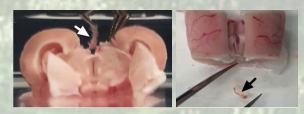
Change in Extracellular protein content of CSF in Male subject

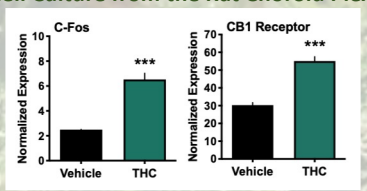


Change in Extracellular protein content of CSF in Female subject

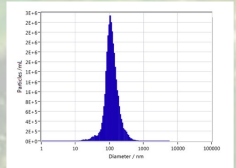


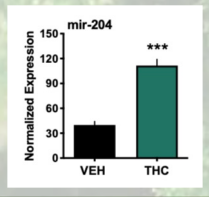
Effect of THC on Primary Epithelial Cell Culture from the Rat Choroid Plexus

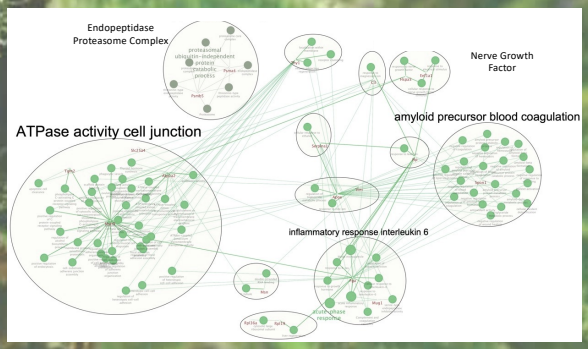




Quantification and visualization of EVs from CSF of rats







Conclusion

THC triggers cellular activation mechanisms:

→ Leads to variations in the release and/or uptake of EVs.

→ EV cargo include fundamental messengers of proteins involved in essential physiological processes, such as ionic exchange, cell development and immunological states.

→ Sex and length of exposure differentially modulated EV protein expression.

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