Effects of Cannabis and Psychedelics on Microglia

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Microglia, the brain's resident immune cells, are increasingly recognized for their physiological, as well as immunological, roles. The regulation landscape for certain psychoactive substances, such as cannabis and psychedelics, is rapidly evolving, whether for recreational or medicinal purposes. However, these compounds are still understudied, particularly when it comes to these important cells. Our goal is to understand how administration of cannabis and psychedelics, such as lysergic acid diethylamide (LSD), affect microglial physiological functions.

Methods: In a first experiment, whole cannabis plant was administered to adult, male, C57BL/6J mice for 15 min (one 15 sec puff every 5 min; 3 puffs total; 0.15 g flower/puff). Four groups were utilized, mice that received control air vapor, and mice exposed to either: high CBD/low THC [CBD], high THC/low CBD [THC], or balanced THC/CBD [Balanced] cannabis strains. Brains were isolated 30 min post-cannabis exposure onset, when THC levels peak in the brain. We stained the tissue against IBA1 and TMEM119. We looked at IBA1+ cell density, nearest neighbor distance and spacing index (changes in number and distribution), specifically focusing on the prefrontal cortex. We further investigated IBA1 and TMEM119 colocalization, as well as IBA1+ cell morphology. In a second experiment, chronic (7-day) low-dose (0.03mg/kg) or single high-dose (0.2mg/kg) LSD was administered intraperitoneally to adult, male, C57BL/6J mice undergoing chronic (14 days, 2h/day) and/or acute restraint stress (2h), and brains were extracted 24 hours after the last injection. Sections containing the prefrontal, primary sensorimotor, and primary motor cortex were processed for 2D and 3D electron microscopy analyses.

Results: Our preliminary data indicates that the distribution and spacing of microglia, as ascertained by nearest neighbor distance, was altered differently in the infra- and prelimbic cortices. Specifically, density and distribution of IBA1+ cells in the infralimbic area, but not the prelimbic cortex, were altered in CBD high strain *versus* others. In the prelimbic cortex, all IBA1 + cells analyzed colocalized with TMEM119, indicating these cells were likely resident or homeostatic. Furthermore, in the prelimbic area, although there were no changes in density or distribution, microglial morphology was altered, potentially indicating changes in microglial surveillance (reduced in CBD). In addition, preliminary results indicate chronic LSD exposure leads to accumulation of lipid bodies and lysosomes in microglia associating with neuronal cell bodies—indicating an activity and neuroprotective shift in the microglial population. Chronic stress-induced deficits in dendritic spine density and microglial trogocytosis of pre-synaptic structures were observed, and may be rescued with LSD treatment.

Discussion: Our preliminary data indicates that acute cannabis exposure modifies microglial morphology in the prelimbic cortex, laying the foundation for future work conducted upon stress, infection or disease. Our preliminary data on LSD also reveal a change in microglial activity with stress and LSD exposure suggesting microglia may underlie many of the neuroprotective and pro-cognitive effects of psychedelics.

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