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Cannabinoid modulation of the microbiota-gut-brain axis in HIV/SIV infection

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Background. HIV infection leads to disruption of the microbiota-gut–brain axis signaling which can potentially lead to chronic systemic immune activation including neuroinflammation and HIV associated neurocognitive disorders. Although people living with HIV infection use cannabis for alleviating symptoms associated with HIV disease, we hypothesized that cannabinoids may inhibit neuroinflammatory responses by modulating the microbiota-gut–brain axis and endocannabinoid levels. **Methods.** We performed metabolom (plasma) and colonic microbiome (metagenomics) profiling of uninfected (n=7) and SIV-infected rhesus macaques (RMs) administered vehicle (VEH/SIV; n=7) or delta-9-tetrahyrodcannabinol (Δ^9-THC) (THC/SIV; n=7). **Results.** Relative to controls, THC/SIV macaques had significantly ($p<0.05$) high plasma concentrations of endocannabinoids (2-Arachidonoyl ethanolamide), N-acyl ethanolamines [linoleoyl ethanolamide (LEA)] and N-acyl taurines [Oleoyltaurine (OT)] at five months post-SIV infection (5MPI). Further, relative to VEH/SIV RMs, plasma concentrations of both LEA and OT were significantly ($p<0.05$) higher in THC/SIV RMs at 5MPI. In addition, THC/SIV macaques showed higher levels of gut bacteria derived tryptophan and other neuroprotective metabolites in plasma at 5MPI compared to uninfected control and VEH/SIV macaques. Microbiome profiling confirmed enrichment of phylum *Firmicutes* and *Bacteriodetes* and reductions in class *Gammaproteobacteria* in THC/SIV RMs. In addition, we successfully identified select bacterial species responsible for the production of neuroprotective tryptophan metabolites in colon of THC/SIV RMs. Finally, THC/SIV had significantly higher numbers of beneficial *Lactobacillus* and *Bifidobacterial* species and butyrate (neuroprotective) producing bacterial species in colon compared to VEH/SIV RMs. **Conclusions.** Our findings demonstrate that cannabinoids may suppress systemic and neuroinflammation in HIV/SIV infection by differentially modulating the microbiota-gut-brain axis.