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Long term delta-9-tetrahydrocannabinol administration inhibits neuroinflammation in chronically SIV-infected rhesus macaques through regulating interferon responses and miRNA mediated pathways

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Background. HIV/SIV associated neurocognitive dysfunction (HAND) represents a major comorbidity affecting up to 30-40% of patients on anti-retroviral therapy. Mechanisms proposed to mediate HAND include chronic inflammation, glial cell activation, and neuronal injury. While cannabinoids have been approved for the treatment of neuroinflammatory disorders like multiple sclerosis, its impact on HIV/SIV induced neuroinflammation remains unknown and unexplored. We hypothesized that cannabinoids inhibit neuroinflammatory responses by modulating proinflammatory gene and microRNA expression. **Methods.** We profiled gene (RNA-seq) and microRNA (OpenArrays) expression in basal ganglia (BG) of uninfected (n=5) and SIV-infected rhesus macaques (RMs) administered vehicle (VEH/SIV; n=6) or Δ^9-THC (THC/SIV; n=6). **Results.** Relative to controls, 145 and 49 mRNAs ($p<0.05$) were up and downregulated, respectively in BG of VEH/SIV RMs. Interestingly, fewer mRNAs were upregulated in THC/SIV RMs (99-up and 85-down). Gene enrichment analysis showed differential enrichment of biological functions involved in interferon-beta/gamma response/signaling, MyD88-TLR receptor signaling, RIG-1 pathway, immune response and cytokine-receptor interactions in the VEH/SIV RMs. We focused on Wolframin syndrome-1 (WFS1) and μ-crystallin (CRYM), two neuroprotective genes that were significantly upregulated in BG of THC/SIV RMs. Using immunofluorescence, we localized WFS1 and CRYM protein expression to neurons and confirmed enhanced and reduced expression in BG of THC/SIV and VEH/SIV RMs, respectively. Additionally, miR-155 and miR-142-3p showed significantly higher expression in BG of VEH/SIV RMs. WFS1 was validated as a target of miR-142-3p in HCN2 cells. **Conclusions.** Our findings clearly demonstrate that cannabinoids suppress neuroinflammation in chronic HIV/SIV infection by differentially modulating the expression of neuroprotective genes and microRNAs.