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Gut dysbiosis during methamphetamine exposure in SIV-infected, ART-treated rhesus macaques impacts metabolites associated with neurodysfunction via the microbiota-gut-brain axis

Among people with HIV (PWH) a high proportion suffer from methamphetamine (Meth) use disorder (MUD), worsening prognosis despite antiretroviral therapy (ART). Additionally, gut dysbiosis associated with HIV and MUD causes chronic systemic inflammation. We hypothesize that MUD impacts the microbiota-gut-brain axis (MGBA) via bacterial metabolite expression, increasing neuroinflammation and risk of developing HIV-associated neurocognitive disorder (HAND). Using the rhesus macaque model of SIV infection, this study aims to identify how MUD affects host-microbe interactions and gene expression in the CNS. The fecal microbiome of SIV-infected, ART-treated animals exposed to Meth was compared to SIV-infected, ART-treated animals using shotgun sequencing and bulk RNA-sequencing of the hippocampus. Ingenuity Pathway Analysis was used to analyze downstream impacts of changes in host gene expression. Spatial transcriptomics is in use for host transcriptomics profiling between groups in the colon and hippocampus, connecting gut dysbiosis to changes in host transcriptomics in both the brain and gut. We found significant increases of bacteria *Hallerella porci*, CAG-83 sp900545585, CAG-103 sp000432375, UBA5905 sp900764115, *Oribacterium* sp900772695, *Evtepia* sp004556345, and UBA3818 sp900557155 in Meth-exposed animals which produced metabolites, including γ -aminobutyric acid, butyric acid, and serine, related to host gene expression associated with HAND. This dysregulation is predicted to directly impact CREB signaling in neurons, salvage pathways, Alzheimer's disease, and nucleotide biosynthesis canonical pathways relating to activation of HIV, inflammation, and movement and cognitive disorders. Additionally, significant increases in plasma lipopolysaccharide binding protein indicates increased damage to the gut epithelium, resulting in additional inflammation and transmission from the gut to brain. In conclusion, increased neuroinflammation and risk of HAND in PWH with MUD could be closely associated with Meth-induced gut dysbiosis that significantly impacts metabolite concentrations and communication via MGBA.

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