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Methamphetamine Increases Release of Pro-Inflammatory Cysteinyl Leukotrienes and Neurotoxicity of HIV-Infected Ipsc-Derived Microglia

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People living with HIV-1 (PWH) and methamphetamine (METH) use disorder (MUD) have an increased risk of developing neurocognitive impairment (NCI) compared to PWH without MUD and uninfected individuals. However, the cellular mechanisms underlying the combined effects of METH and HIV-1 are incompletely understood. We recently identified cysteinyl leukotrienes (CysLT), the CysLT synthase LTC4S and the CysLT receptor CYSLTR1 as critical components of HIV-induced myeloid cell neurotoxicity, and observed that ssRNA40, a mimic of the HIV-1 long terminal repeat (LTR), and METH induced increased expression of LTC4S and CYSLTR1. In the present study, we infected human microglia derived from induced pluripotent stem cells (iPSC) of four different donors with HIV-1 at multiplicities of infection (MOI) ranging from 0.01 to 1.0 and in the presence and absence of different concentrations of METH (1, 10 and 100 μM). The infection was allowed to proceed for 12 days. Conditioned media (CM) was collected every 3 days and concentrations of HIVp24 and CysLT were measured. Depending on donor, HIV MOI and METH concentration, productive infection became detectable on day 3 or 6 post infection (dpi) and METH increased infection and release of CysLTs at several time points. Testing of microglial CM in iPSC-derived mixed neuronal-astrocytic cell cultures showed that HIV and METH both caused loss of neurons with the combination of HIV and METH resulting in the most pronounced toxic effect. Therefore, METH may increase HIV neurotoxicity and NCI by promoting the pro-inflammatory CysLT cascade in the brain. (Supported by NIH R01 DA052209 to M.K.)