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Methamphetamine modulates neurotoxicity of HIV-infected iPSC-derived microglia separately from viral production

The risk of developing neurocognitive impairment (NCI) is increased in people with HIV-1 infection (PWH) and methamphetamine (METH) use disorder (MUD) compared to PWH without MUD and uninfected individuals. However, the mechanisms conferring the combined effects of METH and HIV-1 are incompletely understood. In the present study, we assessed viral production and neurotoxicity of human microglia derived from induced pluripotent stem cells (iPSC) of four different donors. Microglia were infected with HIV-1 at multiplicities of infection (MOI) ranging from 0.001 to 0.1 and in the presence and absence of METH (10 μ M). Conditioned media (CM) was collected every 3 days and concentrations of HIVp24 were measured by ELISA. CM collected at the peak of viral production, if it occurred before day 12, or collected at day 12 of infection was tested for neurotoxicity using mixed cultures of iPSC-derived neurons and astrocytes at 50% final concentration. After 24 hours the neuroglial cell were fixed and neurons and nuclear DNA were fluorescence labeled. Analysis by quantitative microscopy showed that HIV and METH both caused loss of neurons with the combination of HIV and METH often resulting in the most pronounced toxicity. However, different HIV MOIs varied in their effect in that the highest MOI did not always produce the highest level of neurotoxicity. Therefore, while METH can increase HIV neurotoxicity, the extent of neuronal injury (and NCI) may depend on the HIV inoculum and the intensity of the host's response in the brain. (Supported by NIH R01 DA052209 and NS148274 to M.K., CIRM RAMP Program to N.E.C.)

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