The sigma-1 receptor antagonist S1RA ameliorates blood-brain barrier impairment synergistically induced by HIV-1 NL4-3 and methamphetamine

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Methamphetamine (METH) use is frequent among individuals with HIV-1. The molecular mechanisms mediating the combined effects of HIV-1 infection and METH use on the central nervous system remain largely unknown. The sigma-1 receptor (Sigma1R) has been shown to bind METH and its upregulation has been implicated in METH-induced blood-brain barrier (BBB) breakdown. Since HIV-1 can also disrupt the BBB, we aimed to determine whether Sigma-1R antagonist (S1RA) reduces synergistic BBB damage caused by HIV-1 infection and METH. Pretreatment of brain pericytes with S1RA for 6 hours attenuated the METH and HIV-1 induced increase in BBB permeability to 10 kDa fluorescein isothiocyanate (FITC)-dextran in contact models 24 hours post-infection. Inhibition of Sigma1R reduced levels of the proinflammatory cytokine IL-6 but did not affect replication as indicated by HIV-1 p24 protein release levels. METH upregulated CXCR4 mRNA levels and four IFN-stimulated genes (ISGs) including proinflammatory chemokine ligand 2 (CCL2) in infected pericytes which was identified by using a custom RT2 Profiler PCR Array with 42 ISGs. Pretreatment with S1RA resulted in a significant reduction of proton leakage and mitochondrial network fragmentation in brain pericytes measured using the Seahorse XF Cell Mito Stress Test and morphometric ImageJ plugin tool MiNA, respectively. These results provide evidence that HIV-1 and METH may synergistically contribute to BBB impairment via molecular mechanisms involved in pericyte Sigma1R.

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