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Multiple long-term changes of neurotransmission-related gene expression correlate with behavioral impairment caused by methamphetamine and NeuroHIV

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Methamphetamine (METH) use is frequent among people living with human immunodeficiency virus type-1 (HIV-1) and aggravates HIV-associated neurocognitive disorders (HAND). Yet, pathological mechanisms underlying the combined effects of HIV-1 and METH are incompletely understood. Transgenic mice expressing a soluble viral envelope protein gp120 of HIV-1 in the brain (gp120tg) share key neuropathological features with NeuroHIV/AIDS patients. We previously exposed young gp120tg mice to an escalating METH binge regimen for 25 days and analyzed the animals 7 months afterwards. We found that METH exposure aggravated behavioral impairment in gp120tg mice and both gp120 and METH caused lasting differential expression of neurotransmission-related genes besides neuronal injury (Hoefer et al., Exp. Neurol. 2015). For this study, we correlated neurotransmission-related gene expression in cerebral cortex and hippocampus with gp120 and METH exposure and with behavioral performance. Significant correlations were found for gp120 and METH in both cortex and hippocampus, indicating that neurotransmitter receptors, such as Htr7 and Gria 3, as well as transporters, such as Slc7a11, and signaling factors, such as Grk6, Prkaca and Pik3cg, are affected by METH, HIV and their combination. However, behavioral outcomes for spatial learning and memory (Barnes Maze, % time in target quadrant, spatial strategy, errors) correlated most significantly with different genes of all three categories, such as receptors Gabra1, Gabrg3, Htr2b, transporter Slc32a1, and signaling factors Akt1, Pkb3, Sncaip. Thus, METH and HIV affect neurotransmission and behavior in a lasting fashion at multiple levels, and our study provides a framework for the future identification of causal mechanisms.

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