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Role of nuclear receptors in epigenetic silencing of HIV in microglia and neuroprotection following methamphetamine exposure

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Methamphetamine (METH) selectively injures dopaminergic neurons. We previously demonstrated that healthy neurons silence HIV in microglial cells while damaged neurons resulting from METH exposure induce reactivation of latent HIV and microglial activation, thus supporting clinical findings that METH exacerbates the development of HIV-associated neurocognitive disorder (HAND) by indirectly inducing HIV expression. To explore cellular mechanisms that antagonize the effects of METH, we have used both an immortalized human microglial cell model (HC69) and induced pluripotent stem cells (iPSC)-derived human microglial cells (iMG). In both systems, overexpression of the nerve growth factor IB-like receptor Nurr1 (NR4A2) enhances rapid HIV silencing while knock down of Nurr1 inhibits HIV silencing. Mechanistically, we found that Nurr1 recruits the CoREST transcription repressor complex to the HIV LTR. This complex contains multiple epigenetic silencing factors including the histone deacetylases HDAC1/2 and the histone methyltransferases G9a and EZH2 and potently induces epigenetic silencing of HIV following proviral reactivation. Data from RNA-Seq analyses demonstrate that Nurr1 also down regulates numerous cellular genes involved in inflammation, cell cycle, and metabolism, thus promoting HIV latency and microglial homoeostasis. Additionally, we found that the ligand-dependent nuclear receptors RXR-α/β and the glucocorticoid receptor (GR) independently contribute to HIV epigenetic silencing. Simultaneous activation of Nurr1, RXR-α/β, and GR with specific agonist of each nuclear receptor completely shuts down HIV expression in both HC69 and iMG cells. Using an iPSC-derived neurons/HIV-infected iMG co-culture system, we are investigating if these agonists antagonize the effects of METH on HIV expression and microglial activation and protect neurons.