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HIV infection enhances the addiction-related actions of opioids: Brain substrates and cellular mechanisms

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Antiretroviral therapy (ART) has shifted HIV to a survivable infection. Nevertheless, ART-maintained patients suffer from chronic HIV-related diseases, including neurocognitive impairment (HIV-NCI). Opioid overdose deaths are higher, and the likelihood of using opioid-replacement strategies to facilitate abstinence is lower in HIV-infected individuals. We hypothesize that opioids facilitate HIV-NCI pathogenesis, and that HIV modifies brain responses to opioids. EcoHIV is a chimeric mouse-tropic HIV that can infect mice to precipitate HIV-NCI-like behavioral abnormalities. C57BL/6J mice were implanted with morphine or placebo pellets, EcoHIV/mock-inoculated, their performance in a radial-arm water maze (RAWM) assessed, and brain tissue collected for single nuclei RNA sequencing (snRNA-seq). Morphine-treated HIV-infected mice demonstrated deficits in RAWM performance, consistent with opioid-induced exacerbation of HIV-related cognitive deficits. This cognitive deficit was related to HIV burden, and was accompanied by dysregulated gene expression in the prefrontal cortex. Next, the effects of HIV infection on the reinforcing properties of opioids was investigated using the intravenous oxycodone self-administration procedure in EcoHIV/mock-inoculated mice. Oxycodone consumption was higher in HIV-infected mice relative to uninfected controls, which suggests that HIV infection enhanced the motivational properties of opioids. This effect of HIV infection was accompanied by dysregulated gene expression in addiction-related brain regions, including the prefrontal cortex, habenula, nucleus accumbens, and was abolished by ART treatment. This suggests that HIV infection enhanced the motivational properties of opioids. Combined, our findings suggest that HIV infection and opioid drugs interact in a reciprocal manner to increase vulnerability to HIV-NCI and opioid use disorder.

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