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Combinatorial Targeting of HIV Transcription: Impact of Cocaine and Morphine on Latency Reactivation

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Cocaine and morphine have been shown to increase HIV activity. Our data suggests they directly affect immune cells. Recently, we found that combinatorial targeting of two stages of HIV transcription: elongation and premature termination synergistically block the reactivation of latent HIV. This was achieved by treating the latently infected cells with CDK9 inhibitors and PP2A activators. CDK9 stimulates HIV transcription elongation, and PP2A stimulates premature termination through the Integrator. Leveraging these two mechanisms not only blocks HIV reactivation, but the suppressive effect persists after removing the drugs for six days ("locking" effect). Epigenetically, we found that the combined treatment increased histone methylation and decreased histone acetylation on HIV LTR. Importantly, we found that, although cocaine and morphine only marginally increased the HIV latency reversal, they diminished the block and lock efficacy in HIV treatment. In latently infected cells treated with cocaine or morphine, the HIV activities are harder to be reduced by the combination of CDK9 inhibition and PP2A activation. A potential reason that cocaine and morphine reduce the block and lock effect could be due to their ability to activate HIV expression through the NF-κB and P-TEFb pathways, as reported previously. Our study reveals a direct cellular-level effect of drugs-of-abuse on HIV activity, warranting further investigation to elucidate the exact mechanism behind cocaine and morphine's effect on HIV reactivation so that we can reduce their prominence on inhibiting the block and lock effect.