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Cocaine-stimulated signaling pathways enhance HIV gene expression by inducing the establishment of euchromatin structure via modulating the recruitment of different epigenetic enzymes at HIV LTR.

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Background: Illicit drug users are a high risk population for infection with the Human Immunodeficiency Virus (HIV). A strong correlation exists between prohibited drugs use and an increase rate of HIV transmission.

Rationale/significance: Cocaine is one of the most widely abused drugs in the United States, which both impairs the normal functioning of brain cells and also augments HIV expression in central nervous system (CNS), even in the presence of effective antiretroviral therapy (ART).

Hypothesis: Based on our previous findings that cocaine stimulates specific epigenetic changes, we hypothesize that cocaine induces specific epigenetic changes at HIV LTR by modulating the recruitment kinetics of selective epigenetic enzymes at LTR.

Results and discussion: We found that cocaine enhances HIV gene expression primarily by stimulating mitogen- and stress-activated kinase 1 (MSK1) in myeloid cells. MSK1-catalyzed phosphorylation events subsequently facilitate both the initiation and elongation phases of HIV transcription, a necessity to generate complete genomic transcript of HIV and enhance HIV replication. Here, we demonstrate that cocaine accelerates HIV replication by altering specific cell-signaling and epigenetic pathways. We found that cocaine modulates a large number of signaling pathways. We assessed the epigenetic changes at LTR that are known to modulate HIV transcription. Later, we characterized the recruitment kinetics of relevant epigenetic enzymes at HIV LTR, which regulate the extent of histone phosphorylation, acetylation and methylation. We noted that certain reversible pathways are activated following cocaine exposure, which counter each other's effect, but during this tango, the activated transcription factors enhance HIV transcription.