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Cocaine Enhances HIV Infection, Gene Expression, and Replication by Stimulating Cell Metabolism and DNA-PK

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Background: Illicit drug users are at significant risk of contracting the Human Immunodeficiency Virus (HIV). A strong correlation exists between substance abuse and an increased rate of HIV infection and 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 augments HIV gene expression in the central nervous system (CNS), even in the presence of effective antiretroviral therapy (ART).

Hypothesis: HIV replication depends primarily on the metabolic state of the host cell. Higher cell metabolisms allow the availability of required building blocks for viral progeny. We hypothesized that cocaine-induced signaling pathways lead to the stimulation of different basal transcription factors, and DNA-PK, which augments both overall cellular gene expression and metabolism, thus helping HIV gene expression and replication.

Results and discussion: We discovered that cocaine enhances overall cell metabolism by costimulating various transcription factors, especially DNA-PK, which enhance transcription by supporting different phases of HIV transcription, including initiation, pause release, and elongation. Given that HIV transcription governs both replication and latency-reactivation, the stimulation of DNA-PK and cell metabolism greatly augment overall viral load and contribute to the expansion of reservoirs even in the presence of effective ART. The enhanced HIV and cellular transcription were also confirmed by increased recruitment of RNA polymerase via ChIP-Seq analysis following cocaine treatment. The obtained knowledge could be beneficial in designing novel, highly specific therapies to counter cocaine and HIV effects in the illicit drug-using population.

Relevant publications:

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- Zicari S, Sharma AL, Sahu G, Dubrovsky L, Sun L, Yue H, Jada T, Ochem A, Simon G, Bukrinsky M, Tyagi M. DNA dependent protein kinase (DNA-PK) enhances HIV transcription by promoting RNA polymerase II activity and recruitment of transcription machinery at HIV LTR. Oncotarget. 2020;11(7):699-726. Epub 2020/03/07. doi: 10.18632/oncotarget.27487. PubMed PMID: 32133046; PMCID: PMC7041937.