Cocaine-stimulated MSK1 promotes HIV transcription/replication both by augmenting the activity/recruitment of transcription factors and inducing euchromatin structures at HIV LTR

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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. Cocaine is one of the most widely abused drugs in the United States, which both impairs the normal functioning of brain cells and also activates HIV expression in central nervous system (CNS). Cocaine accelerates HIV replication by altering specific cell-signaling and epigenetic pathways. We have elucidated the underlying molecular mechanisms through which cocaine exerts its effect in myeloid cells, a major target of HIV in the CNS. We noted that cocaine strongly stimulates mitogen activated protein kinase (MAPK). MAPK stimulation later leads to the activation of mitogen- and stress-activated kinase 1 (MSK1). MSK1 subsequently catalyzes the phosphorylation of histone H3 at serine 10 (p-H3S10), and p65 subunit of NF-κB at 276^{th} serine residue (p-$p65^{276}$). We demonstrate that a short-term (acute) cocaine treatment promotes HIV-1 transcription by activating both nuclear factor-kappa B (NF-κB) and MSK1. However, during longer-term or chronic cocaine treatment MSK1 is the main facilitator of HIV1 transcription. These events enhance the interaction of NF-κB with histone acetyltransferases (HATs). Subsequently, acetylated core histones, along with p-H3S10, supports the development of an open/relaxed euchromatin structures at HIV LTR. MSK-1-induced p-H3S10 also facilitates the recruitment of positive transcription elongation factor b (P-TEFb) at LTR and thus, promotes the elongation phase of HIV transcription, a prerequisite to generate complete genomic transcript of HIV. Results are also confirmed in primary monocyte derived macrophages (MDM). Overall, our study provides detailed insights into cocaine-driven HIV-1 transcription and replication.