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Cocaine and HIV- Tat Impact Brain Energy Metabolism: Role in Mitochondrial Epigenetic Signature of DNA Methylation

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HIV infections and drugs of abuse such as cocaine have been identified as risk factors for triggering HIV-1 disease progression and neuronal dysfunction. Astrocytes are the major regulators of energy metabolism in the central nervous system and mitochondria, the main producers of cellular energy by oxidative phosphorylation play an important role. Cocaine abuse and HIV infections are known to utilize brain energy reserves, and could possibly affect mitochondrial DNA (mtDNA) in which DNA methylation, an important epigenetic modification has not been elucidated yet. We hypothesize that HIV-1 Tat with cocaine impact epigenetic modification of global DNA methylation, activate mitochondrial DNA methyltransferases (mtDNMT1, mtDNMT3a and mtDNMT3b) which affect the displacement loop (D-loop) region and NADH dehydrogenase 1–6 [ND1-ND6] complex 1 thereby mediating disease progression. To study this, human astrocytes were treated with HIV-Tat and cocaine, individually or in combination, and DNA methylation was studied in both nuclear and mitochondrial DNA. Methylation of mtDNA was analyzed by bisulfite pyrosequencing and targeted next-gen sequencing. We observed significant decrease in DNMTs in nuclear extracts of astrocytes treated with HIV-Tat or cocaine, which correlated to global methylation of nuclear DNA. Bisulfite pyrosequencing analysis of the mtDNA D-loop (+121 to +62) region revealed an overall decrease in methylation in both Tat or cocaine exposed astrocytes, specifically in GRCh38/hg38 ChrM:121, 106, 97, 92, 81 and 79 positions. Our data provides evidence that cocaine and HIV-Tat impact astrocyte energy metabolism by altering DNMT expression, which might be a contributing factor towards neurodegeneration, observed in HIV-positive cocaine users.