Cocaine and HIV- Neuropathogenes: Epigenetic signature of DNA Methylation Role in Brain Energy Metabolism

Samikkannu Thangavel [1] and Madhavan P.N. Nair [2]

[1]Institute of NeuroImmune Pharmacology, Seton Hall University, South Orange, New Jersey 07079, USA; [2] Department of Immunology, College of Medicine, Florida International University, Miami, Florida 33199, USA

Previous studies have demonstrated that HIV infections and drugs of abuse such as cocaine have been identified as risk factors for triggering HIV-1disease progression and neuronal dysfunctions. Astrocytes are the major regulators for energy storage, utilization and metabolic function in the central nervous system (CNS). Cocaine abuse and HIV infections are significant risk factors for disrupting brain energy metabolism and have not been clearly elucidated. We hypothesize that HIV-1 Tat with cocaine activate energy sensor AMP-activated protein kinase (AMPK) synergistically dysregulate the glycolytic enzymes Hexokinase II, pyruvate kinase 1/2 (PKM1/2), monocarboxylate transports 1 & 4 (MCT-1and MCT-4) and mitochondrial biogenesis of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor AFTM leading to epigenetics modification of DNA Methylation (DNAMT1, DNMT3a and DNMT3b) mediated disease progression. Cell lysates were analyzed by western blotting to determine energy sensor AMPK, glycolytic protein expression in HK-I, HK-II, PKM ½, MCT1 & 4, mitochondrial PGC-1α, and AFTM and DNA Methyltransferase (DNMT1, DNMT3a and DNMT3b). Our results indicated that HIV-Tat significantly activated AMPKs and upregulated glycolytic enzymes HK-II, PKM ½, MCT1 & 4, and mitochondrial PGC-1α**,** and AFTM. Altered glycolytic profiles and mitochondrial biogenesis subsequently impact DNMT3a and DNMT3b, and these effects were accelerated by cocaine. These results suggest that cocaine synergistically accelerates glycolytic, mitochondrial biogenesis and DNMTs expression and subsequently impact astrocyte energy storage, utilization and energy transfer metabolism exacerbating neurodegeneration of HIV-positive cocaine user.

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