HIV Tat and morphine-mediated activation of astrocytes: Epigenetic involvement of NLRP6 inflammasome in HAND

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Background: CDC describes HIV infection and drug abuse as intertwined epidemics, leading to compromised cART adherence and exacerbation of HIV-associated neurocognitive disorders (HAND) pathogenesis. Opiate use/abuse is highly prevalent in HIV-infected individuals. The interplay of HIV and opiates thus raises concerns regarding the effects of both on HAND pathogenesis. Rationale/significance: Chronic low-level inflammation (mediated by viral proteins, antiretrovirals, and abused drugs) has been implicated as a significant underlying factor in the HAND pathogenesis. Inflammation has been identified as an essential correlate of HAND. Hypothesis: Herein, we hypothesized that exposure of astrocytes to HIV Tat and morphine exacerbates astrocyte activation involving a) activation of the NLRP6 inflammasome via promoter DNA hypomethylation and, b) downregulation of miR-152, which in turn, targets NLRP6, leading to cleavage and release of IL1β and IL18. Ultimately, this culminates into increased neuroinflammation. Results: Whole-genome bisulfite sequencing in the frontal cortices of SIV-infected macaques demonstrated increased DNA hypomethylation of NLRP6 promoter with a concomitant upregulation of NLRP6 inflammasome. miRNA array analysis of HIV Tat and morphine exposed primary astrocytes showed decreased levels of miR-152 with a concomitant upregulation of NLRP6 inflammasome signaling and astrocyte activation. Pharmacological inhibition/gene silencing approaches further validated HIV Tat and morphine-mediated activation of NLRP6, cleavage of caspase1 and IL1β, and IL18 in primary astrocytes. Cell culture findings were also validated in the brains of Tat transgenic mice administered morphine. Discussion: These findings underpin the epigenetic involvement of NLRP6 inflammasome signaling in the activation of astrocytes in the context of HIV Tat and morphine.