Methamphetamine promotes in macrophages stimulated with LTR mimic ssRNA40 expression of HIV-regulating IncRNA HEAL and pro-inflammatory factors but suppresses the interferon response

Marcus Kaul¹, Jeffrey Koury¹, Ricky, Maung¹, Nina Y. Yuan¹

¹School of Medicine, Div. Biomedical Sciences, University of California, Riverside, CA 92521

Methamphetamine (METH) is frequently used by people living with human immunodeficiency virus-1 (PWH/HIV-1) and apparently compromises the anti-viral immune response. However, the underlying mechanisms are incompletely understood. We have recently identified the IncRNA HEAL as a promoter of HIV-1 infection (Chao et al. mBio 2019). Transfecting monocytic THP-1 cells with different concentrations of ssRNA40, a mimic of the HIV-1 long terminal repeat (LTR), recapitulating infection and using a scrambled ssRNA as control, we investigated the effects of METH (100 uM) on IncRNA HEAL and immune factors, including several implicated in HIV neurotoxicity. After 24 hours incubation the cells were collected for RNA analysis using quantitative RT-PCR. The ssRNA40 induced in a concentration-dependent fashion IncRNA HEAL and mRNA for IFNb and several pro-inflammatory factors at 2.5 and 5, but not at 1 ug/ml. METH alone triggered no significant changes of these RNAs. However, in combination with ssRNA40 at 1 ug/ml METH significantly increased expression of IncRNA HEAL and a subset of inflammatory factors. These METH effects were less pronounced or even reversed at ssRNA40 concentrations of 2.5 and 5 ug/ml. However, METH consistently down-regulated IFNb in combination with all ssRNA40 concentrations. In summary, METH appears to exert its strongest effect in promoting HIV via IncRNA HEAL at the lowest concentration of the LTR mimic while also inducing components of the pro-inflammatory arachidonic acid cascade and suppressing anti-viral IFNb. Therefore, METH apparently promotes HIV propagation, persistence and inflammatory factors implicated in macrophage-driven HIV neurotoxicity. (Supported by NIH R01 DA052209 to M.K.)