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Role of Complement Activation in HIV Neuropathogenesis Associated with Methamphetamine (METH) Abuse

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Background: Methamphetamine (METH) abuse significantly influences HIV-1 transmission, viral replication, immune function, and adherence to antiretroviral therapy (ART), while also playing a key role in the development of HIV-associated neurological disorders (HAND). The complement system, a critical component of innate immunity, has been shown to have diverse roles in the neuropatho-genesis of HIV-1 infection. In particular, complement levels are elevated in the brains of HIV-1-infected individuals, suggesting that HIV-induced complement activation may be a crucial mechanism in the progression of neurological damage.

Rationale/Significance: Our previous research has demonstrated increased gene expression of complement receptors C5aR, C3aR, and the complement protein C9 in brain tissue from HIV-1-infected patients with HAND who also abused opiates. Furthermore, we observed significant upregulation of complement proteins, including C9, C5L2, C5aR, and C3aR, in microglia derived from HIV-1-infected individuals treated with opiates. These findings suggest that complement activation plays a role in the neuropathogenesis of HIV, a process further exacerbated by drug abuse. Recent studies have also reported an upregulation of complement factor H (CFH) in the serum of METH-addicted individuals.

Results & Discussion: We obtained postmortem brain tissue samples from HIV-1-infected individuals who abused METH, provided by the National Disease Research Interchange (NDRI, Philadelphia, PA). We examined the expression of CFH, C9, C5L2, C5aR, and C3aR in these samples and assessed microglial activation and levels of pro-inflammatory cytokines and reactive oxygen species (ROS) released by activated microglia. We hypothesize that these factors contribute to neuroinflammation, leading to neuronal damage, cell death, and the cognitive impairments observed in METH-abusing HIV-1 patients. Our study aims to elucidate the role of complement activation in the context of METH-related neuropathogenesis in HIV-infected individuals. We anticipate that our findings will not only enhance our understanding of the underlying mechanisms of neuroinflammation in this population but also highlight the potential therapeutic and biomarker value of C3 and CFH in METH-abusing HIV patients.