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## HIV-1 gp120 and Methamphetamine-Mediated toxicity in the brain

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HIV associated neurocognitive disorder (HAND) remains a major concern for patients infected with HIV. The viral envelope protein, gp120 has been extensively studied and some of its neurotoxic effects are due to the increased expression of various proinflammatory cytokines. Additionally, it has been well documented that various drugs of abuse can exacerbate HAND, but the mechanism by which this occurs is still poorly understood. The present study was based on the central hypothesis that HIV-1 gp120 and methamphetamine (MA) interact with each other to increase the cytotoxicity in the astrocytes, which is mediated via induction of various pro-inflammatory cytokines/chemokines and oxidative stress. In order to test these hypothesis four different studies were designed. We also investigated the mechanism(s) and pathways involved in the functional interaction between gp120 and MA. Furthermore, in order to understand the functional implications of the interaction between MA and gp120, we examined the combined effect of MA and gp120 to produce oxidative stress and apoptotic cell death. We also studies the involvement of ER stress in the HIV-1 gp120-mediated cell death in the astrocytes. We investigated the role of gp120 in the cytokine production in astrocytes. SVGA astrocytes and human fetal astrocytes were either transfected with a plasmid coding gp120 or treated with recombinant gp120 protein and the expression levels of various cytokines at RNA and protein levels were measured. In order to better explain the role of gp120 in the induction of proinflammatory cytokines/chemokines, 3 major and highly induced cytokines/chemokines were screened and further mechanistic studies were aimed with these 3 cytokines/chemokines. We investigated the role of NF- $\kappa$ B pathway in the transcriptional regulation followed by studies to identify molecular mechanisms.

In conclusion, we have shown that both MA and gp120 independently and in combination increased the production of pro-inflammatory cytokine/chemokines via different pathways. The functional consequences for the interaction between gp120 and MA led to oxidative stress and ER stress, which resulted in apoptotic cell death in astrocytes. Thus, our current studies provide the evidence and underlying mechanisms for the neurotoxic potential of HIV protein, gp120 and substance of abuse, methamphetamine.

### Biography

Anil Kumar completed his education in Kanpur University, Kanpur, India, 1987. He is currently working as an Chair and Professor, University of Missouri-Kansas City School of Pharmacy Division of Pharmacology. He is current Research Interests on Effect of drug and alcohol abuse on pathogenesis of AIDS, Identification of target of immune responses in HIV-1 during natural infection, Compartmentalization of HIV during natural infection, Vaccine approaches in monkey model of AIDS.

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