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Commentary on the Interactions of HIV and Alcohol in the Central Nervous System

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Abstract

This commentary is to highlight the relevance and public interest of the review published by Silverstein and Kumar (2013), which focuses on the mechanisms by which alcohol and HIV-1 – infection cause increased in CNS damage. The overall review is based on previous literature with cell culture systems and animal models that have demonstrated that exposure to alcohol and HIV infection or HIV viral proteins result in synergistic up-regulation of pro-inflammatory cytokines and oxidative stress. The authors discuss the effects of alcohol on cells in the CNS, followed by a brief discussion on the impact of HIV-1 and HIV proteins on the CNS and the final section focus on the combined effects of HIV and alcohol on the CNS as determined by in vitro, in vivo and clinical studies.

According to the World Health Organization (WHO) alcohol abuse and sexual behavior are risk factors for HIV infection (WHO, 2005). Among HIV-infected patients, alcohol abuse is highly prevalent, with reports of approximately 53% of HIV patients drinking alcohol and 8% classified as heavy drinkers (Galvan et al., 2002). In the new post-Antiretroviral therapy (ART) era, drug to drug interactions and substance abuse have been known to interfere with ART metabolism and adherence (de Olalla et al., 2002).

Due to the observations above, the combined effects of alcohol and HIV infection has been of public interest; therefore, the review highlighted in this commentary focuses on the effects of alcohol and HIV infection on the CNS (Silverstein and Kumar, 2013). Three main areas of discussion are highlighted: the effects of alcohol on cells in the CNS, the impact of HIV-1 and HIV proteins on the CNS, and the combined effects of HIV and alcohol on the CNS as determined by in vitro, in vivo and clinical studies.

Effects of alcohol on the CNS

The effects of alcohol on the CNS as shown by the activation of the NF- κ B pathway and other inflammatory pathways that induce the production of cytokines along with iNOS, the activation of IRAK, ERK, JNK and p38 and other activation pathways mediated by TLR4 and IL-1R (Blanco et al., 2005) were discussed in detail. Along with activation of pro-inflammatory cytokines and inflammatory pathways, alcohol induces oxidative stress. Cell culture studies with acute and chronic alcohol treatment, and animal models of chronic ethanol exposure were discussed and shown to demonstrate that oxidative stress is responsible for neuronal injury. Acute ethanol exposure has been shown to increase superoxide anion production in microglia (Colton et al., 1998) and astrocytes (Davis and Syapin, 2004); and activate NADPH oxidase and ROS in SH-SY5Y neuroblastoma cell line

(Wang et al., 2012). Another point of interest in this review article was the alcohol-induced neuronal damage mediated by NMDA receptor and NMDA-mediated excitotoxicity (Smothers et al., 1997) and these were highlighted as a key therapeutic target to reduce the effects of withdrawal and decreased in self-administration of ethanol. However, another report discussed in this review has attributed neuronal damage associated with binge drinking to oxidative stress and independent of NMDA receptor activity (Collins and Neafsey, 2012). The authors also highlight previous literature on the mechanisms through which ethanol affects the blood-brain barrier by increasing permeability and the involvement of myosin light chain kinase (MLCK), myosin light chain, claudin-5 and occludin (Persidsky et al., 2011).

The impact of HIV-1 and HIV proteins on the CNS

Studies over two decades ago reported the presence of neurological complications in patients with HIV as the first indication of the ability of the virus to induce neurotoxicity (Price et al., 1988). In this section Silverstein and Kumar discussed and reviewed literature pertaining to the induction of CNS toxicity by HIV in microglia and perivascular macrophages (Pumarola-Sune et al., 1987). Also, co-cultures of HIV- infected monocytes and astroglia were reported to result in the production of neurotoxins such as cytokines and leukotrienes (Genis et al., 1992). Overall, the review emphasizes that HIV-induced neuronal toxicity is attributed to the release of toxic factors by infected microglia, perivascular macrophages, and astrocytes as well as toxicity resulting from the exposure to HIV-proteins secreted by infected microglia (Kaul and Lipton, 2006). As in the case of alcohol, HIV infection or exposure to HIV viral proteins has been associated with increased levels of inflammatory cytokines, chemokines, as well as induction of markers of oxidative stress.

Combined effects of HIV and alcohol on the CNS

To summarize the review, the concomitant effects of HIV and alcohol on neuronal toxicity as determined by in vitro, in vivo and clinical studies were addressed. A section was dedicated to the relevance of non-human primate studies and current models of research such as the SIV and SHIV and their effects on the periphery, where alcohol was shown to contribute to muscle wasting in the later stages of SIV infection (Molina et al., 2008). Further, a macaque-SIV/SHIV model where alcohol-addicted animals were reported to have lower CD4 counts with higher viral loads in the CSF and plasma compared to the control group (Kumar et al., 2005) was presented. Ex vivo clinical studies that suggest significant associations between increased viral load and daily alcohol use (Wu et al., 2011) and alcohol use and non-adherence to ART (Hendershot et al., 2009) were also reviewed. Additionally, the review highlights other reports on magnetic resonance imaging (MRI) studies performed on HIV-infected patients who had AIDS and who were alcoholics showing greater severe effects on white matter than the control groups (Pfefferbaum et al., 2012). Overall, the literature reviewed in this section suggests that alcoholism exacerbates the neurological effects of HIV and AIDS.

As presented above, data from in vitro models, animal models, and clinical studies suggest that alcohol abuse along with HIV-infection may result in detrimental neuronal and peripheral effects inducing further HIV neuropathogenesis. Therefore, it is crucial to understand the interactions between HIV infection and alcohol abuse in the CNS.

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