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Cocaine and HIV-1 Interplay in CNS: Cellular and Molecular Mechanisms

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Abstract

Although antiretrovirals are the mainstay of therapy against HIV infection, neurological complications associated with the virus continue to hamper quality of life of the infected individuals. Drugs of abuse in the infected individuals further fuel the epidemic. Epidemiological studies have demonstrated that abuse of cocaine resulted in acceleration of HIV infection and the progression of NeuroAIDS. Cocaine has not only been shown to play a crucial role in promoting virus replication, but also has diverse but often deleterious effects on various cell types of the CNS. In the neuronal system, cocaine exposure results in neuronal toxicity and also potentiates gp120-induced neurotoxicity. In the astroglia and microglia, cocaine exposure leads to up-regulation of pro-inflammatory mediators such as cytokines and chemokines. These in turn, can lead to neuroinflammation and transmission of toxic responses to the neurons. Additionally, cocaine exposure can also lead to leakiness of the blood-brain barrier that manifests as enhanced transmigration of leukocytes/monocytes into the CNS. Both *in vitro* and *in vivo* studies have provided valuable tools in exploring the role of cocaine in mediating HIV-associated neuropathogenesis. This review summarizes previous studies on the mechanism(s) underlying the interplay of cocaine and HIV as it relates to the CNS.

Keywords

HIV; AIDS; cocaine; Glial cell; neuron; HIV-1-associated neurocognitive disorders

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

INTRODUCTION

It is estimated that almost 25% of untreated HIV-1 infected individuals and ~7% of HIV-1 infected patients treated with combined antiretroviral therapy (cART) develop HIV-associated dementia (HAD) [1-4], a neurodegenerative syndrome that is clinically characterized by progressive cognitive, motor and behavioral abnormalities [5, 6]. HIV encephalitis (HIVE), the pathological correlate of HAD, is often accompanied by prominent microglial activation, formation of microglial nodules, perivascular accumulations of mononuclear cells, presence of multi-nucleated giant cells, and neuronal damage and loss [5, 7, 8].

HIV-infection is often associated with the co-morbid condition of illicit drug abuse. Since most of these abused drugs, similar to HIV, also target the CNS, understanding the interplay of drugs of abuse and HIV-1 infection is of paramount importance. Both intravenous drug use (IVDU) and HIV infections are interlinked epidemics. About 33% of the newly reported drug users are IV injection users in the United States. It has been reported that HIV-1 infection is one of the major causes of mortality among Americans. Several earlier reports point to the use of cocaine as a risk for HIV-infection as well as it being independently linked with progression to AIDS [9-11]. It is becoming increasingly clear that the number of HIV-infected patients that are also cocaine-abusers is constantly on a rise [12]. Intriguingly, HIV-infected individuals with concomitant cocaine abuse also display increased severity and progression to NeuroAIDS. It can thus be envisioned that concurrent use of cocaine by HIV-infected individuals contributes to progression of clinically diagnosed AIDS.

cART usage has resulted in augmented longevity of HIV-infected individuals, however, there is a paradoxical accompaniment of increased prevalence of HAND (HIV-1-associated neurocognitive disorders) in these individuals. Symptoms of HAND range from the undetectable neurocognitive impairment to more severe form of encephalitis/dementia affecting about 8% of infected individuals. Similar to the therapy naïve individuals, even in the cART treated group, interaction of HIV with abuse of illicit drugs continues to remain problematic. Making matters worse is the inability of various cART regimens to penetrate the CNS, thus making the brain a viral sanctuary.

Brain is one of the major targets for cocaine. Cocaine has been shown to impair the functions of macrophages and lymphocytes [13-17] and can also enhance the expression of HIV-1 in these cells [18-22]. It has been postulated that cocaine could serve as a co-factor in the vulnerability and development of HAND [9-11]. Epidemiological studies on drug abusers with NeuroAIDS associated abuse of cocaine (by any route of administration) to enhanced incidence of HIV seroprevalence and progression to AIDS [23-27]. Both *in vitro* and *in vivo* studies have demonstrated the synergistic interactions of HIV-1 and cocaine abuse in the progression of HAND. This review aims to unravel interplay of cocaine and HIV-1 infection.

INTERPLAY OF HIV AND COCAINE IN MEDIATING ASTROCYTE APOPTOSIS

Mounting evidence from clinical studies suggest that astrocytosis, microglial activation, and CD8 lymphocytic infiltration are typical characteristics of neuroinflammation observed in drug abusers [28, 29]. Astrocytes, the most abundant cells in the CNS, play critical roles in maintenance of normal brain development and functioning. However, in the course of HIV infection, astrocytes can get both infected as well as activated leading to the release of neurotoxic mediators such as cytokines, chemokines and growth factors that are toxic for not only for neurons but also their neighboring cells. This cascade of inflammation in turn, leads

to the ensuing neuropathogenesis associated with HIV-1. As a result normally neuroprotective astrocytes get functionally transformed into deleterious cells, ultimately leading to disrupted CNS homeostasis. While earlier it was believed that activation of astrocytes played important role in the progress of HAND, it is now becoming clear that astrocyte viability is also critical for acceleration of HAND.

HIV-1 infection and co-morbidities have been reviewed by many researchers in the recent years [30, 31]. Our previous study has reported that cocaine potentiated HIV viral envelope protein gp120-mediated decrease of astrocyte viability, which was ameliorated by sigma receptor-1 (σ -1R) antagonist. Furthermore, the detailed molecular mechanisms underlying cocaine-mediated potentiation of reduced cell viability in the presence of gp120 was mediated by increased intracellular reactive oxygen species (ROS) and imbalance in mitochondrial membrane potential [32]. The subsequent signaling pathways in this process involved extracellular signal-regulated kinase, c-jun N-terminal kinase and p38 and its downstream nuclear factor (NF- κ B) [32]. Similar to cocaine, Tat can also synergize with morphine, the active metabolite of heroin, to induced the activation of astrocytes as evidenced by the fact that persistent exposure of astrocyte to both morphine and Tat results in cellular apoptosis mediated by mu-opioid receptors (MORs) [33]. It has been reported that opiate and Tat exposure synergistically destabilizes levels of intracellular calcium, increases ROS, and causes increased release of proinflammatory chemokines in cultured striatal astroglia [34]. Taken together, these findings demonstrate cooperative effects of drugs of abuse and HIV-1 Tat on astrocyte apoptosis and induction of neurotoxic mediators resulting in exacerbation of HIV-associated neuropathogenesis.

COCAINE ENHANCES INFLAMMATORY RESPONSES IN MICROGLIA

Numbers of both activated microglia/macrophages as well as infiltrating macrophages are significantly increased among cocaine users. It can thus be envisioned that both microglial activation and macrophage infiltration in the brain could be critical players in cocaine-induced neuroinflammation leading to ensuing neurotoxicity. Despite the recognized impact of the abuse of cocaine on the brain reward system, mechanisms underlying the ability of cocaine to enhance the neuroinflammation comprising microglial activation and monocyte migration into the brain remain elusive. Microglia that are resident macrophages of the CNS, serve not only as productive virus hosts, but also elicit a plethora of cytokines, chemokines and neurotoxic factors in response to stimulation. Among the known chemokines that are key players in HIV-associated CNS disease is MCP-1, which correlated positively with cocaine exposure. In our earlier study we demonstrated that cocaine *via* binding to its cognate σ -1R, resulted in induction of the chemokine MCP-1. This chemokine in turn, has been shown to exert robust chemotactic properties and, in this capacity, could recruit peripheral monocytes across the blood-brain barrier (BBB) into the CNS. Transmigration of the monocytes results in differentiation of these cells into macrophages, which being virus factories, release a plethora of neurotoxic factors culminating ultimately into an exacerbated inflammatory and pathogenic cascade within the CNS [35]. Consistent with our finding on the role of σ -1R in chemokine expression, other reports have also implicated the role of this receptor in cocaine-induced replication of HIV-1 since σ -1R inhibitor-BD1047 effectively inhibited cocaine-mediated virus replication in microglia [36].

EFFECT OF COCAINE ON NEURONS

Although neurons are susceptible to the affects of HIV, the virus is unable to infect the neurons *per se*. It has been demonstrated that the viral protein products such as the transactivator protein (Tat) and the envelope (gp120), that can be released from the infected cells can lead to neurotoxicity both *in vitro* and *in vivo* [37-43]. Furthermore, increasing

evidence suggests that cocaine can amplify the neurotoxic responses of viral proteins Tat and gp120 [39, 44-46]. Using cell culture model systems it has been shown that HIV-1 and cocaine can modulate neurotoxicity through increased oxidative stress [47, 48], and caspase-3 mediated pathways. Furthermore, the downstream cell signaling pathways including MAPKs (ERK, JNK and p38) and also its downstream nuclear NF- κ B have also been implicated in cocaine and gp120 mediated neurotoxicity [49]. Consistent with these findings, cocaine potentiates Tat-mediated neurotoxicity in hippocampal neurons, an effect that was ameliorated by blocking of D1 dopamine receptor. These findings thus underpin the role of cocaine in potentiating Tat-mediated neurotoxicity *via* modulation of the D1 dopamine receptor-mediated signaling cascades [50]. *In vivo* evidence for cocaine-mediated potentiation of neurotoxicity induced by gp120 was validated [51]. This study demonstrated that injection of cocaine in combination with microinjection of recombinant HIV gp120 to ventricle in rats resulted in increased iNOS expression as well as neuronal apoptosis in the neocortex. Furthermore, this effect was ameliorated in animals pretreated with the iNOS inhibitor, thereby underpinning the role of iNOS in gp120 and cocaine-mediated neuronal apoptosis.

EFFECT OF COCAINE ON THE BBB INTEGRITY

BBB plays a central role in the development of HAND because it serves as the conduit by which free virus and infected immune cells enter the brain from the circulatory system [52-54]. Cocaine has been shown to augment HIV-1 neuroinvasion in HAND through its direct effect on human brain microvascular endothelial cells (HBMECs) and its indirect paracrine effects on BBB *via* release of cytokines [55-58]. Mounting evidence demonstrates that exposure of HBMECs to cocaine resulted in upregulation of the expression of endothelial adhesion molecules such as intracellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin, thereby leading to increased leukocyte migration across endothelial monolayers [56, 59]. Our previous study has shown that exposure of HBMECs to cocaine resulted in increased expression of ALCAM with trafficking of α 1R to the plasma membrane, causing subsequent phosphorylation of platelet-derived growth factor (PDGF)- β receptor. Furthermore, the downstream cell signaling pathway such as MAPKs, Akt, and NF- κ B pathways were involved in the subsequent induction of ALCAM. Intriguingly, ALCAM induced monocyte adhesion and migration, effects that were ameliorated by ALCAM-neutralizing antibody. In addition to the cell adhesion molecule, cocaine also increased the permeability of brain endothelial cells through upregulation of PDGF-BB- α a vascular permeant [60]. The underlying mechanisms in this process involved in activation of MAPKs and the transcription factor Egr-1. This was further confirmed in Egr-1 knock out mice, wherein cocaine failed to enhance endothelial permeability [61]. Understanding the regulation by cocaine of permeability of endothelial cells may thus be beneficial for the development of potential therapeutic targets for neuroinflammation associated with cocaine abuse in the context of HIV infection.

CONCLUDING REMARKS

Taken together, cocaine can be considered as a multifactorial agent that accelerates HIV-1 infection and its progression. Cocaine not only enhances cell toxicity in astrocytes, but also accelerates the inflammatory responses in microglia. Cocaine also potentiates neurotoxicity induced by viral proteins resulting in neuronal damage. Intriguingly, cocaine also exerts toxic effects on BBB permeability, resulting in recruitment of virus-infected inflammatory cells. In summary, cocaine abuse in HIV-1 infected individuals exerts deleterious effects on the CNS resulting in exacerbated neuropathogenesis *via* multiple pathways.

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