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Cocaine and HIV-1 Interplay: Molecular Mechanisms of Action and Addiction

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Abstract

Human immunodeficiency virus (HIV) infection is now being driven by drug-abusing populations. Epidemiological studies on drug abusers with AIDS link abuse of cocaine, even more than other drugs, to increased incidence of HIV seroprevalence and progression to AIDS. Both cell culture and animal studies demonstrate that cocaine can both potentiate HIV replication and can potentiate HIV proteins to cause enhanced glial cell activation, neurotoxicity, and breakdown of the blood-brain barrier. Based on the ability of both HIV proteins and cocaine to modulate NMDA receptor on neurons, NMDA R has been suggested as a common link underlying the crosstalk between drug addiction and HIV infection. While the role of dopamine system as a major target of cocaine cannot be overlooked, recent studies on the role of sigma receptors in mediating the effects of cocaine in both cell and organ systems warrants a deeper understanding of their functional role in the field. In this review, recent findings on the interplay of HIV infection and cocaine abuse and their possible implications in mode of action and/or addiction will be discussed.

Introduction

Drug users represent a significant proportion of the HIV-1 infected and at risk population. The influences of concurrent drug abuse in HIV-1 pathogenesis are also quite significant. In fact, intravenous drug use (IVDU) and HIV infections have become two linked global health crises. HIV-1 infection is one of the leading causes of death among Americans 25–44 years of age, and injection drug use accounts for one-third of all new cases of AIDS in the United States. It has been demonstrated earlier that use of crack cocaine is a risk factor for acquisition of HIV-infection and is also independently associated with progression to AIDS (Larrat and Zierler, 1993; Fiala et al., 1998; Webber et al., 1999). In recent years emergence of a cohort of HIV-infected individuals that are cocaine-abusers is becoming increasingly evident. It is thus likely that interplay of HIV-1 and cocaine in HIV-infected cocaine abusers might be involved in progression of clinical AIDS.

The CNS is a major target for HIV-1 infection. Within days following infection, HIV-1 enters the CNS where various brain resident cells can serve as reservoirs for HIV-1 (Brack-

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Werner, 1999; Canki et al., 2001; Clarke et al., 2006). In humans, HIV-1-associated neurocognitive disorders (HAND) occur in approximately one-third of infected patients. These symptoms can range from minor cognitive motor disorders that affect almost 50% of HIV+ individuals on antiretroviral therapy (ART), to severe encephalitis/dementia affecting almost 15 to 20% of those with AIDS that are treatment naïve. Although ART has led to a decreased incidence of HAND, and has significantly increased longevity of HIV-infected individuals, there is a paradoxical accompaniment of increased prevalence of HAND in these people. Into this mix, and often elusive, is the interaction of HIV with other co-morbid factor(s), such as abuse of illicit drugs, a condition that is prevalent both in HIV-infected cohorts, and, in those with increased risk of contracting the virus. Adding another level of complexity to this mix is also the ability of the brain to function as a potential viral sanctuary due to the inability of most of the ARTs to effectively penetrate the blood-brain barrier (BBB).

The brain is also a target organ for cocaine. Cocaine impairs the functions of macrophages and lymphocytes (Klein et al., 1993; Mao et al., 1996; Baldwin et al., 1997; Eisenstein and Hilburger, 1998; Friedman et al., 2003) and enhances HIV-1 expression in these cells (Peterson et al., 1990; Bagasra and Pomerantz, 1993; Nair et al., 2000; Roth et al., 2002; Steele et al., 2003). It has been postulated that cocaine may serve as a co-factor in the susceptibility and progression of HAND (Larrat and Zierler, 1993; Fiala et al., 1998; Webber et al., 1999). Epidemiological studies on drug abusers with AIDS link abuse of cocaine (by different routes), even more than other drugs, to increased incidence of HIV seroprevalence and progression to AIDS (Chaisson et al., 1989; Anthony et al., 1991; Chaisson et al., 1991; Baldwin et al., 1998; Doherty et al., 2000). Cell culture and murine animal models have provided valuable tools to explore the synergistic interactions of HIV-1 and cocaine in the pathogenesis of HAND. This review summarizes these studies and the current understanding of the interplay of HIV infection and cocaine abuse.

Effect of Cocaine on HIV-1 Replication

Cell culture studies

Despite the advent of ART to combat AIDS, cocaine abusers with HIV-1 infection are becoming a newly emerging cohort of HIV-positive individuals. It is therefore critical to understand how the two agents interact to increase the disease severity. Various studies have focused on exploring how cocaine can enhance virus replication in the *in vitro* cell culture systems. Peterson *et al.* addressed this question very elegantly using the peripheral blood mononuclear cell (PBMC) co-culture system (Peterson et al., 1991; Peterson et al., 1992). Briefly, the system comprised of PBMCs from healthy donors incubated in the absence or presence of cocaine prior to activation with a plant lectin, phytohemagglutinin (PHA), and, subsequently these cells were reconstituted with PBMCs that had been infected with a clinical isolate of HIV-1. The authors found that HIV replication, measured by the release of HIV p24 antigen in cell culture fluids was significantly enhanced in activated cells that had been exposed to cocaine (Peterson et al., 1991). Our previous study demonstrated that cocaine enhanced HIV virus replication in macrophages (Dhillon et al., 2007). It was further demonstrated that this effect of cocaine was mediated via the multifunctional cytokine, TGF- β . Since immune activation is considered critical for pathogenesis of HIV infection (Levy, 1989; Rosenberg and Fauci, 1989; Gallo, 1990), these *in vitro* studies suggest a clinical relevance of cocaine in disease pathogenesis (Peterson et al., 1991; Peterson et al., 1992; Peterson et al., 1993).

Based on the premise that cocaine up-regulated virus replication in activated PBMCs, the authors subsequently extended their earlier studies by asking the question whether cocaine could also enhance virus replication in PBMCs that had been activated with CMV, a known

enhancer of HIV replication in certain lymphocytic lines (Skolnik et al., 1988; Clouse et al., 1989). Using the similar co-culture system as described earlier, PBMCs from CMV positive or CMV-negative donors were pre-treated with cocaine followed by culturing in the presence of HIV-infected PBMCs (Peterson et al., 1992). These studies demonstrated that while cocaine by itself was not able to trigger HIV-1 replication, in the presence of other activation signals of clinical relevance, such as CMV (Drew, 1988; Jacobson and Mills, 1988; Skolnik et al., 1988; Schooley, 1990), it was able to synergistically enhance virus replication. Furthermore, similar to the mitogen-stimulated PBMCs, the mechanism of cocaine-mediated up-regulation of virus replication in CMV-stimulated PBMCs also occurred via TGF- β with a possible involvement of another cytokine such as TNF- α (Peterson et al., 1991; Peterson et al., 1992; Peterson et al., 1993).

Additional studies aimed at unraveling the role of cocaine have been carried out by Bagasra *et al.*, wherein instead of using the co-culture system described earlier, which the authors argued, could have inherent potential allogenic effects that could confound the data, PBMCs without any stimulation were used to assess the effects of cocaine on modulation of HIV-1 replication. It was found that cocaine-treated, un-stimulated PBMCs when infected with HIV-1, were also capable of responding with enhanced virus replication as evidenced by increased HIV-1p24 antigen levels, syncytium formation and increased viral RNA compared to cells not treated with cocaine (Bagasra and Pomerantz, 1993).

***In vivo* studies**

Interaction of cocaine and HIV-1 has also been evaluated *in vivo* under more physiologic conditions using a hybrid-mouse model (huPBL SCID mouse) infected with HIV-1 in the presence and absence of cocaine. In this model, systemic cocaine administration was accompanied with accelerated HIV-1 infection of human peripheral blood leukocytes (PBL), decreased CD4⁺ cells and a dramatic rise in circulating virus load (Roth et al., 2002). HIV-1 infection is known to depress the hypothalamic-pituitary-adrenal axis (Kumar et al., 2002). Intriguingly, cocaine exposure to uninfected huPBL-SCID mice resulted in increased corticosterone production but, in concert with HIV-1 infection, resulted in depressed corticosterone production compared with the hu-PBL-SCID mice infected with HIV-1 alone (Roth et al., 2005). These authors also showed that cocaine induced an up-regulation of CCR5 expression in peritoneal cells from HIV-infected, cocaine-treated huPBL-SCID mice, which preceded the increase in number of virally infected cells. Since cocaine binds to sigma-1 receptor (σ -1R), using its antagonist, Roth *et al.* demonstrated that cocaine acted via σ -1R since blocking this receptor abolished the effects of cocaine on HIV-1 replication (Roth et al., 2005).

The σ -1R is a non-opioid receptor that resides specifically at the endoplasmic reticulum (ER) interface referred to as the mitochondrion-associated ER membrane or the MAM where σ -1R is known to act as a molecular chaperone maintaining the functionality of IP3 receptor (Hayashi and Su, 2007). Interestingly, the σ -1R can translocate to the other parts of cells when stimulated by an agonist like cocaine (Hayashi and Su, 2003; Su et al., 2010). Perhaps as a result of the translocation, σ -1R is known to regulate receptors or ion channels on the plasma membrane (Aydar et al., 2002; Navarro et al., 2010; Su et al., 2010). Cocaine is known to interact with σ -1R (Sharkey et al., 1988; Hayashi and Su, 2007). The actions of cocaine mediated by σ -1R will be mentioned in the following sections.

Effect of Cocaine on Glia

Microglia

Further extension of these studies has also been carried out in a more relevant cell type, the microglia, which are the resident macrophages of the brain and are the target cells for virus

replication in HIV-associated dementia (Reynolds et al., 2006). Microglia play a critical role in defense as well in the neuropathogenic effects of HIV-1. Similar to the effects of cocaine seen in HIV-infected PBMCs, cocaine also enhanced virus replication in microglial cells (Peterson et al., 1992; Bagasra and Pomerantz, 1993; Nair et al., 2000; Roth et al., 2002). Assessment of p24 antigen levels in culture supernatants from the HIV-infected human microglial cells treated with cocaine showed a concentration-dependent increase in viral expression. Extension of these studies using κ -opioid receptor ligands further demonstrated suppression of cocaine-induced potentiation of HIV-1 replication in microglial cells. This effect was mediated by down-modulation of CCR5, a coreceptor of HIV-1, involving the extracellular signal-regulated kinase1/2 (Gekker et al., 2004). More recently, it has been found that cocaine-induced HIV-1 expression in these cells also involved the σ -1R and the cytokine, TGF- β 1, since the inhibitors specific for both σ -1R and TGF- β 1 effectively blocked cocaine-mediated enhancement of virus replication (Gekker et al., 2006).

Furthermore, we have recently demonstrated that cocaine induces the chemokine MCP-1 in rodent microglia through translocation of the σ -1R to the lipid raft microdomains of the plasma membrane. Sequential activation of Src, mitogen-activated protein kinases (MAPKs) and phosphatidylinositol-3' kinase (PI3K)/Akt and nuclear factor kappa B (NF- κ B) pathways resulted in increased MCP-1 expression. Furthermore, conditioned media from cocaine-exposed microglia increased monocyte transmigration, and this was blocked by antagonists for CCR2 or σ -1R. These findings were corroborated by demonstrating increased monocyte transmigration in mice exposed to cocaine, which was attenuated by pretreatment of mice with the σ -1R antagonist. Interestingly, cocaine-mediated trans migratory effects were not observed in CCR2 knockout mice. These findings led to the conclusion that cocaine-mediated induction of MCP-1 accelerates monocyte extravasation across the endothelium; this could have a plausible role in increased neuroinflammation observed in HIV-infected cocaine abusers. Understanding the regulation of MCP-1 expression and functional changes by cocaine/ σ -1R axis may provide insights into the development of potential therapeutic targets for HIV-1 associated neurocognitive disorders (Yao et al., 2010a).

Astroglia

Although macrophages and microglial cells are the primary sources of HIV-1 replication in the CNS (Minagar et al., 2002; Gonzalez-Scarano and Martin-Garcia, 2005), it is becoming increasingly clear that astrocytes are also susceptible to HIV-1 infection in the presence of relevant cytokines (Conant et al., 1994; Brack-Werner, 1999; Canki et al., 2001; Carroll-Anzinger and Al-Harhi, 2006; Carroll-Anzinger et al., 2007; Churchill et al., 2009). Astrocytes are integral components of the CNS since they maintain a homeostatic environment and actively participate in bi-directional communication with neurons (Brack-Werner, 1999; Dong and Benveniste, 2001; Hansson and Ronnback, 2003). Following initial infection with HIV-1, astrocytes exhibit a transient surge of viral replication that subsequently diminishes to low levels and often persists (Conant et al., 1994; Brack-Werner, 1999; Canki et al., 2001). It has been estimated that up to twenty percent of astrocytes can be infected with the virus in HIV-infected patients and remain as reservoirs for latent virus (Canki et al., 2001). Effect of cocaine on astrocytes in the context of HIV-1 infection has recently been reported by Nair *et al* (Reynolds et al., 2006). Since astrocytes constitute a major proportion of cells in the brain and, since significant numbers of astrocytes can be infected with HIV-1, and cocaine is known to act as a cofactor in HAND, these authors hypothesized that cocaine-induced HIV-1 susceptibility and progression to HIV-encephalitis, is mediated via dysregulation of specific proteins critical for fostering neuropathogenesis of HIV-1 infection in these cells. These authors investigated the effect of cocaine on HIV-1 infectivity in normal human astrocytes and demonstrated that pre-

treatment with cocaine prior to HIV-1 infection significantly up-regulated viral replication as monitored by a significant increase in LTR-R/U5 gene expression (Reynolds et al., 2006), representing early stages of reverse transcription of HIV-1. Using the p24 antigen assay, it was demonstrated that culture supernatants from astrocytes treated with cocaine exhibited increased virus replication at day fifteen post-infection. Proteomic analysis of cocaine-treated human astrocytes using difference gel electrophoresis (DIGE) combined with protein identification through HPLC-MS/MS identified twenty-two proteins that were differentially regulated compared with astrocytes not treated with cocaine. Specifically, these proteins comprised the intracellular signaling molecules, translation elongation factor and molecular chaperones (Reynolds et al., 2006). These proteins were found to be critical in the neuropathogenesis of HIV-1 infection. These findings have clinical implications for HIV encephalitis (HIV-E) since astrocytes make up a significant population of cells in the brain, and their responsiveness to cocaine and/or HIV-1 can lead to increased viral load and subsequent toxicity in the CNS. In addition to enhancing virus replication in astroglial cells *in vitro*, cocaine administration in mice also resulted in increased proliferation and expression of glial fibrillar acidic protein (GFAP) in the dentate gyrus (Fattore et al., 2002).

Cocaine Potentiates HIV Protein (Tat & Gp120)-Induced Neurotoxicity

Cell culture studies

It is widely accepted that while neurodegeneration is one of the hallmark features of HAND, the virus does not infect the neurons per se. It has been implicated that viral protein products, Tat and gp120, but not the virus, can exert neurotoxicity, both *in vitro* and *in vivo* (Lipton et al., 1991; Savio and Levi, 1993; New et al., 1997; Kaul and Lipton, 1999; Bansal et al., 2000; Gurwell et al., 2001; Kaul et al., 2001). Furthermore, emerging new cell culture data demonstrates that cocaine can amplify the neurotoxic responses of HIV-1 proteins, Tat and gp120 (Gurwell et al., 2001; Turchan et al., 2001; Maragos et al., 2002; Nath et al., 2002). Evidence for the interactions of HIV-1 and cocaine in modulating neurotoxicity has been demonstrated in cell culture studies wherein cocaine enhanced oxidative stress as well as dysfunction of neurons exposed to Tat and gp120 (Koutsilieri et al., 1997; Nath et al., 2000). Additional studies on the molecular mechanisms underlying the interaction between cocaine and gp120 have demonstrated that exposure of rat primary neurons to both cocaine and gp120 resulted in increased cell toxicity compared to cells treated with either factor alone. The combinatorial toxicity of cocaine and gp120 was accompanied by an increase in both caspase-3 activity and expression of the proapoptotic protein Bax. Furthermore, increased neurotoxicity in the presence of both the agents was associated with a concomitant increase in the production of intracellular reactive oxygen species and loss of mitochondrial membrane potential. Increased neurotoxicity mediated by cocaine and gp120 was ameliorated by NADPH oxidase inhibitor apocynin, thus underscoring the role of oxidative stress in this cooperation. Signaling pathways including c-jun N-terminal kinase (JNK), p38, extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinases (MAPK), and nuclear factor (NF)-kB were also identified to be critical in the neurotoxicity induced by cocaine and gp120 (Yao et al., 2009b).

Similar potentiation of cocaine-mediated neurotoxicity has also been reported with yet another HIV protein -Tat. In this study using primary rat hippocampal cultures, it was shown that physiologically relevant doses of cocaine augmented Tat-mediated mitochondrial depolarization and intracellular production of reactive oxygen species (ROS), leading to enhanced oxidative stress and neurotoxicity (Aksenov et al., 2006). Additionally, treatment of hippocampal cells with a specific D1 dopamine receptor antagonist blocked the potentiation of Tat toxicity by cocaine (Aksenov et al., 2006). These findings led to the speculation that cocaine enhances Tat-mediated neurotoxicity via modulation of the D1 dopamine receptor-controlled signaling cascades (Aksenov et al., 2006).

Neurologic impairment in patients with HAND is known to correlate with synaptodendritic injury. To investigate whether cocaine-mediated neurotoxicity could also involve a similar mechanism of injury, Yao *et al.* exposed hippocampal neurons to cocaine and observed increased neuronal beading in the presence of cocaine. Further investigation on the mechanisms underlying cocaine-mediated impairment of neuronal dendrites in primary hippocampal neurons involved down-regulation of the neuronal plasticity gene Arc. Additionally, exposure of neurons to HIV-1 envelope protein gp120 resulted in enhanced loss of neuronal dendrites of neurons exposed to cocaine (Yao et al., 2009a).

***In vivo* studies**

In vivo corroboration of cocaine-mediated potentiation of gp120 neurotoxicity was also carried out by Bagetta *et al* wherein it was demonstrated that subchronic intraperitoneal administration of cocaine to wild-type Wistar rats in combination with intracerebro-ventricular injection of recombinant HIV gp120 resulted in enhancement of both iNOS expression and neuronal apoptosis in the neocortex (Bagetta et al., 2004). Cocaine when administered alone, however, did not cause neuronal apoptosis. The addition of iNOS inhibitors minimized the neurotoxicity associated with gp120 and cocaine thus underpinning its role in gp120 and cocaine-mediated neuronal apoptosis.

In addition to the neurotoxicity, gp120 can also lead to decreased neural stem cell proliferation thereby suggesting that there are fewer progenitor cells available to differentiate into neurons, thus impairing neurogenesis (Kaul et al., 2005). Recent observations indicate that drugs of abuse, including alcohol and opiates, impair adult neurogenesis in the hippocampus. Using 5'-bromo-2-deoxyuridine (BrdU) it was also reported that that long-term cocaine exposure significantly reduced cell proliferation in the dentate gyrus (DG) of the hippocampus. By labeling astrocytes with GFAP, it was also determined that long-term cocaine exposure caused increased astrocyte activation.

Cocaine and the Blood-Brain Barrier (BBB)

BBB normally functions as an interface between the blood and brain parenchyma, acting as a watch guard to inhibit the entry of ions, molecules and infiltrating cells into the CNS. During progressive HIV-1 infection, however, there is a breach in this barrier (Nottet et al., 1996; Burger et al., 1997; Dallasta et al., 1999; Avison et al., 2004) leading to influx of inflammatory cells into the brain resulting in clinical and pathological abnormalities, ranging from mild cognitive impairment to frank dementia. Cocaine, through its direct effect on brain microvascular endothelial cells (BMVECs) and its paracrine effects on BBB via release of pro-inflammatory cytokines, augments HIV-1 neuroinvasion in HAD. Cocaine effects on the enhancement of viral neuroinvasion through the BBB have been studied in great detail (Fiala et al., 1998; Gan et al., 1999; Chang et al., 2000; Fiala et al., 2001; Lee et al., 2001).

Role of cell adhesion molecule

Exposure of brain endothelial cells to cocaine has been demonstrated to up-regulate the expression of endothelial adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, thus facilitating leukocyte migration across the endothelial monolayers (Gan et al., 1999). Recently it has been demonstrated that up-regulation of ALCAM in the brain endothelium in HIV+/cocaine drug abusers accompanied increased monocyte/macrophage immunostaining (CD68+) compared with HIV+ individuals with no drug abuse history or uninfected controls. These findings underpinned the role of ALCAM in promoting leukocyte infiltration across the BBB. In parallel, ALCAM expression was also increased in cocaine-treated mice with a concomitant increase in monocyte adhesion and transmigration *in vivo*, which was

ameliorated in mice pre-treated with the neutralizing antibody to ALCAM, lending further support to the role of ALCAM. This new concept was further confirmed by *in vitro* experiments wherein cocaine mediated induction of ALCAM in human brain microvascular endothelial cells (HBMECs) through the translocation of σ -1R to the plasma membrane, followed by phosphorylation of platelet-derived growth factor (PDGF)- β receptor. Downstream activation of mitogen-activated protein kinases, Akt, and NF- κ B pathways subsequently resulted in induced expression of ALCAM. Functional implication of up-regulated ALCAM was confirmed using cell adhesion and transmigration assays. Neutralizing antibody to ALCAM ameliorated this effect. Taken together, these findings implicate cocaine-mediated induction of ALCAM as a mediator of increased monocyte adhesion/transmigration into the CNS.

Role of PDGF-BB

Additionally, cocaine has also been shown to induce the cerebrovascular permeant PDGF-BB in HBMECs through the binding to its cognate σ -1R. This effect was mediated via activation of mitogen-activated protein kinases (MAPKs) and the transcription factor Egr-1, culminating ultimately into increased expression of PDGF-BB. Cocaine exposure resulted in increased permeability of the endothelial barrier and this effect was abrogated in mice exposed to PDGF-BB neutralizing antibody, thus underscoring its role as a vascular permeant. *In vivo* relevance of these findings was further corroborated in cocaine-treated mice that were administered neutralizing antibody specific for PDGF-BB as well as in Egr-1 knock out mice. Understanding the regulation of PDGF-BB expression may provide insights into the development of potential therapeutic targets for neuroinflammation associated with HIV infection and drug abuse.

Cocaine and Other mediators

Cocaine is also known to upregulate dendritic cell-specific C type ICAM-3 grabbing nonintegrin (DC-SIGN) and matrix metalloproteinases (MMPs) in bovine endothelial cells (Nair et al., 2005). Chronic cocaine treatment has also been reported to potentiate chemotactic agent-induced leukocyte-endothelial cell adhesion (LEA) in rats (Chang et al., 2000). In addition, cocaine has been reported to decrease cellular glutathione levels, enhance DNA-binding activity of redox-regulated transcription factors (NF- κ B and AP-1) and increased expression of TNF- α in human brain endothelial cells, thereby contributing to BBB dysfunction and enhanced leukocyte migration across the cerebral vessel (Lee et al., 2001). More recently cocaine has also been shown to remodel bovine endothelial cells by up-regulating transcription of genes critical in cytoskeleton organization, signal transduction, cell swelling and vesicular trafficking (Fiala et al., 2005).

NMDARs as an interplayer between cocaine abuse and HIV infection

Impact of HIV infection on NMDAR function

Given the fact that neurons themselves are not directly infected by HIV-1, how these viruses induce neurotoxicity has been a central topic during the past decades (Kraft-Terry et al., 2009). To this end, the NMDAR represents the most interesting and important subtype among all glutamate receptors based on the fact that it has been most thoroughly investigated in this regard and is one of the common pathways causing HIV neurotoxicity disorders (Kaul and Lipton, 2006). Generally, HIV- or immune-associated neurotoxins lead to neuronal injury via complex network interactions between macrophages (or microglia), astrocytes, and neurons. HIV-infected monocytoid cells (i.e., microglia or macrophages) or activated astrocytes secrete a variety of neurotoxins, including quinolinate, cytokines, free radicals, etc. Some of these substances can either increase glutamate release or decrease glutamate reuptake. Secreted substances and/or glutamate activate the final NMDAR-

sensitive pathway to produce neurotoxicity (Xiong et al., 2003; Kaul and Lipton, 2006; Zhu et al., 2009). Both the HIV-1 envelope glycoprotein, gp120, and the HIV-1 transactivator protein, Tat, are well-documented to induce NMDAR-dependent neuronal death (Pattarini et al., 1998; Schroder et al., 1998; Wang et al., 1999; Haughey et al., 2001). Of note, recombinant gp120 directly binds to NMDAR subunits expressed in a baculovirus system (Xin et al., 1999) (Xin et al., 1999). Tat also directly binds to GluN1 subunits subunits (Li et al., 2008) (Li et al., 2008) or a polyamine-sensitive site on NMDARs (Prendergast et al., 2002; Self et al., 2004). In rat hippocampal neurons, Tat seems to directly activate NMDARs at an allosteric Zn^{2+} -sensitive site (Song et al., 2003). These direct protein-protein interactions regulate NMDAR function and in part, mediate the neurotoxic effects of these proteins. In addition, both gp120 and Tat increase tyrosine phosphorylation of NMDARs (Viviani et al., 2006; King et al., 2010). This could augment synaptic delivery of NMDARs, leading to sensitized receptor activity and neurotoxicity.

Memory deficits are another cognitive disorder resulting from HIV-1 infection. The physiological basis for this is also linked to NMDARs. The NMDAR-dependent synaptic plasticity in the form of long-term potentiation (LTP), a cellular model of learning and memory, in hippocampal neurons was attenuated following intracerebroventricular injections of Tat (Li et al., 2004). This electrophysiological change was accompanied by suppression of spatial learning behavior (Li et al., 2004). These data provide evidence that the Tat pathway underlies the memory dysfunction via a mechanism involving NMDARs.

NMDARs in psychostimulant addiction

NMDARs are densely expressed in key structures of the reward circuitry, including the ventral tegmental area (VTA), the dorsal striatum/caudate putamen (CPu), the ventral striatum/nucleus accumbens (NAc), and the prefrontal cortex (PFC). In the striatum, GluN1, GluN2A, and GluN2B are observed at high levels in both the striatonigral and striatopallidal medium spiny output neurons (Landwehrmeyer et al., 1995; Chen and Reiner, 1996; Standaert et al., 1999), while GluN2C and GluN2D are barely present (Wenzel et al., 1997) (Wenzel et al., 1997). GluN2A-, GluN2B-, or GluN2A/B-containing NMDARs are thus the principal subtypes in this region. The existence of abundant NMDARs in striatal neurons implies their potential involvement in drug action. Indeed, in a rodent behavioral sensitization model, the NMDAR selective antagonist MK-801 prevented the sensitized motor response to repeated cocaine administration (Karler et al., 1989). Thus, NMDARs are important for behavioral sensitization to stimulants. NMDARs may exert their roles via a transcription-dependent manner. As a Ca^{2+} -permeable channel, NMDARs can trigger and organize a Ca^{2+} -sensitive signaling pathway that couples drug stimulation to nuclear gene expression, which subsequently transcriptionally controls morphological, synaptic, and behavioral plasticity. In support of this, NMDAR/ Ca^{2+} signals directly regulated gene expression in striatal neurons via several Ca^{2+} -sensitive pathways involving cAMP response element-binding protein (CREB) and ERK (Konradi et al., 1996; Wang et al., 2007). Intriguingly, MK-801 blocked cocaine or D1 receptor agonist induced expression of immediate early gene and other genes (Wang et al., 1994; Keefe and Ganguly, 1998; Sun et al., 2008). Similarly, the NMDAR antagonist CPP attenuated cocaine-induced and ERK-dependent changes in dendritic branching and spine density in the striatum (Ren et al., 2010).

In a conditioned place preference (CPP) model testing the reward property of stimulants, NMDARs have been demonstrated to be important. A conditional NMDAR knockout mouse whose NMDAR gene was deleted by Cre expression restricted to striatal neurons failed to develop cocaine CPP (Agatsuma et al., 2010). Pharmacological blockade of NMDARs with MK-801 extinguished cocaine CPP or reduced cocaine-primed reinstatement (Brown et al., 2008; Itzhak, 2008). In an operant drug self-administration model in which drug seeking

behavior is directly assessed, the NMDAR antagonist MK-801 or APV reduced cocaine self-administration in rats (Pulvirenti et al., 1992; Schenk et al., 1993). Another NMDAR antagonist LY235959 either reduced or facilitated rat cocaine self-administration, depending upon the dose and access duration of self-administered cocaine (Allen, Carelli et al. 2005; Allen, Dykstra et al. 2007). MK-801 was also reported to have no impact on cocaine-associated memory in cocaine self-administering animals (Brown, Lee et al. 2008). These data underscore the complexity of NMDARs in stimulant seeking behavior.

Since cocaine abuse and HIV infection often go hand-in-hand, it can be envisioned that they are interactive and interdependent to reinforce and endure their damages to multiple organ systems such as the brain. Indeed, consistent data support the notion that drug addicts are at a much higher risk for HIV-1 infection than the general population and that drugs of abuse potentiate neuroimmune effects of HIV-1 (Nath 2010; Bokhari, Hegde et al. 2011; Yao, Duan et al. 2011). The reciprocal relationship is also true; HIV-positive individuals are more prone to addictive effects of psychostimulants than HIV-negative normal subjects (Molitor, Truax et al. 1998). The fact that HIV-1 infection increases the use of psychostimulants raises an interesting and important question as to whether HIV infection provides a needed incubation for increased predisposition to drug addiction. While this possibility represents a fundamental and priority topic linking HIV to addiction, little is known about its basic properties, underlying mechanism(s), and implications in pathogenesis.

Glutamate, as aforementioned, is the most abundant and important transmitter in the CNS. Glutamatergic afferents and glutamate receptors such as NMDARs are densely distributed in the reward circuitry. In response to drug exposure, NMDARs undergo plastic changes which constitute an essential component in the metaplastic basis for persistent addictive properties of stimulants. As a critical receptor mediating drug action, the NMDAR is also a sensitive neuroimmune target of HIV. As such, the NMDAR may act as a previously unrecognized interplayer mediating the crosstalk between drug addiction and HIV infection. It is possible that HIV infection regulates NMDARs to predispose and/or reinforce drug abuse and vice versa. In sum, drug abuse and HIV infection are tightly-associated events. An increasing need to study their crosstalk calls for more cross-cultural collaborations among researchers in the two fields. As a common target of psychostimulants and HIV, NMDARs could be a promising interface linking the two. Studies in this new field will facilitate the development of novel pharmacotherapies, by targeting glutamate receptors, for the treatment and prevention of what's called HIV/AIDS-addiction vicious cycle.

Role of σ -1R in cocaine exposure: two component action of cocaine

Although the dopamine system has been recognized as a major target of cocaine, new evidence demonstrates the role of σ -1R in cocaine-mediated effects in cell and organ systems. σ -1R was initially considered as a member of the opioid receptors (Martin et al., 1976). Recently, Hayashi and Su (Hayashi and Su, 2007) demonstrated that σ -1R is mainly localized at the endoplasmic reticulum (ER), especially mitochondrion-associated ER membrane (MAM) domain, and is a ligand-operated ER-chaperone protein that regulates ER stress by promoting the proper folding of newly synthesized protein. Chaperone activity of σ -1R is regulated by protein-protein interaction between σ -1R and immunoglobulin heavy chain binding protein (BiP). Under normal conditions, the σ -1R forms a heterodimer with BiP. However, σ -1R agonists like cocaine can induce the dissociation of σ -1R from BiP. The σ -1R antagonist like progesterone or haloperidol on the other hand blocks the BiP- σ -1R dissociation caused by the agonist (Hayashi and Su, 2007). Interestingly, it was reported that external stress in retinal neurons caused the phosphorylation of σ -1Rs in the σ -1R-BiP complex whereas the σ -1R agonist (+)pentazocine, in addition to causing the dissociation of σ -1R from BiP, concomitantly decreased the phosphorylation of σ -1R (Ha et al., 2011). Those actions of the σ -1R agonist (+) pentazocine correlate with the neuroprotective action

of the drug in retinal neurons. Findings as aforementioned may provide new insights into the unresolved pharmacological effects of σ -1R ligands.

Although psychostimulants, such as cocaine, amphetamine and methamphetamine have many effects on a variety of physiological functions [e.g., general CNS activity, body temperature, and blood pressure], these drugs when abused induce feelings of euphoria and subjective effects in humans. On the other hand, the immediate effects of cocaine are an extremely intense pleasurable sensation ("high"), magnification of normal pleasures, release of social inhibitions, talkativeness, and an unrealistic feeling of cleverness, great competence, and power. It is well known that psychostimulants induce several behavioral effects in rodents, that are believed to be mediated by the activation of (especially mesolimbic) dopaminergic system (Di Chiara and Imperato, 1988).

The involvement of σ -1R in the behavioral effects of psychostimulants has been well studied. Cocaine can bind σ -1R at physiologically relevant concentrations (Matsumoto et al., 2002; Matsumoto et al., 2003). σ -1R antagonists as well as antisense oligonucleotides for σ -1R can reduce the hyperlocomotion-induced by cocaine (Matsumoto et al., 2002; Matsumoto et al., 2003). On the other hand, σ -1R agonist SA4503 can attenuate hyperlocomotion-induced by cocaine in mice. The analysis of drug effects on locomotor activity or exploratory behavior has been central to the field of behavioral pharmacology. Although the investigation of these behaviors is sometimes considered simplistic or uninformative, alternation of these behaviors can have important implications for paradigms that aim to study more specific process, such as memory function and reinforcing effects, and provide the explanation for underlying mechanism of drug effects. The excess dopaminergic activation can differentially regulate the psychostimulants-induced increase in locomotor activity in mice through the activation of mesolimbic and nigrostriatum dopaminergic systems (Mori et al., 2004). Since acute and repeated administration of cocaine upregulates σ -1R in the mouse brain, upregulation of the σ -1R may regulate the functions of the dopaminergic system (Liu et al., 2005; Liu and Matsumoto, 2008).

Most important determinant of abuse potential is the nature of the subjective effects that the drug produces. Psychostimulants produce a syndrome that includes feelings referred to as "euphoria". In view of the apparent relationship between subjective effects of abused drugs and abuse potential, it is clearly desirable to develop animal models for studying the mechanism(s) of abused drugs that bear on their subjective effects in human. A methodology having considerable potential in this regard is drug discrimination procedures. Thus, it is believed that subjective effects of abused drugs may be related to their discriminative stimulus effects. On the other hand, self-administration procedure as well as conditioned place preference procedure has provided a animal model for studying factors that influence the reinforcing effects, which are thought to be linked to the psychic dependence, of drugs (Houdi et al., 1989). SA4503 partially generalized to the discriminative stimulus effects of cocaine, and potentiated the cocaine-like discriminative stimulus effects of methamphetamine. It is likely however that σ -1R agonists themselves do not affect the release of dopamine from nucleus accumbens (Garces-Ramirez et al., 2011). These results indicate that σ -1R agonist exert subjective or discriminative stimulus effects even though the agonist does not directly mediated by activation of dopaminergic system. Further, while σ -1Rs in the ventral tegmental area and substantia nigra, in the cell bodies of dopaminergic system, are upregulated by self-administration of methamphetamine in rats (Hayashi et al., 2010), σ -1R agonist itself does not induced the reinforcing effects (Romieu et al., 2004). However, the σ -1R agonist reactivates the reinforcing effects in rats previously conditioned to cocaine as measured by the relapse model (Romieu et al., 2004). In addition, self-administration was maintained by σ -1R agonists in rats previously trained to self-administer cocaine whereas σ -1 R antagonists did not affect self-administration of cocaine

(Hiranita et al., 2010). Those behavioral data suggest that the activation of σ -1Rs serve as “silent” players in the overall addictive property of cocaine, having been primed by cocaine at first but called into action only when triggered by signals related to other actions of cocaine. More specifically, the behavioral data suggest a two components action of cocaine: one intracellularly by activating σ -1Rs inside of neurons and the other extracellularly through neuronal networks that provide neurotransmitters to the neuron. The intracellular action of cocaine on σ -1Rs may thus cause σ -1Rs to translocate to the plasma membrane where σ -1Rs may bind receptors or ion channels that are “silent” for now but might be activated when external neurotransmitters evoked by cocaine begin to act on the receptors or channels. Certainly, more experiments are warranted to further clarify the involvement of σ -1Rs in the addictive processes evoked by cocaine.

Recently, Fontanilla et al. (2009) showed that hallucinogen (N,Ndimethyltryptamine) might be an endogenous σ -1R regulator (Fontanilla et al., 2009). σ -1R agonists exert psychotimimetic-like discriminative stimulus effects in rats (Mori et al., 2011). Therefore, psychotimimetic-like discriminative stimulus effects by σ -1R agonist might affect its reinforcing effects-like behaviors.

Underlying mechanism(s) of how σ -1R agonists or σ -1R chaperone itself can regulate any behavioral effect remains elusive. As mentioned above, σ -1R agonist can induce the dissociation from BiP at the MAM domain (Hayashi and Su, 2007). Cocaine causes translocation of σ -1R from the MAM to the lipid rafts on the plasma membrane (Yao et al., 2010b). It was also shown recently that σ -1R-D1 receptor heteromers are required to activate the dopamine D1-receptor-mediated adenylyl cyclase in the cell line (Navarro et al., 2010). Some of these effects were also demonstrated in murine striatal slices and were absent in the σ -1R KO mice, providing evidence for the existence of σ -1R-D1 receptor heteromers in the brain (Navarro et al., 2010). These results provide a molecular explanation by which D1 receptor plays a more significant role in the behavioral effects of cocaine, perhaps through the σ -1R-D1 receptor heteromerization, and suggest thus a unique perspective toward understanding the molecular basis of cocaine addiction. In fact, the above-mentioned two components action of cocaine may utilize the σ -1RD1 receptor complex as the primed “silent” intracellular component to wait for the “arrival” of increased dopamine caused by the presynaptic action of cocaine thereby consummating the overall action of cocaine in executing its addictive action.

How would the two component action of cocaine fit into the neuroimmune action of cocaine within the context of HAND is certainly a challenging question. However, when taking our most recent data together in which cocaine “hijacking” σ -1Rs from inside of the cell to the plasma membrane to “meet” the activated kinases or receptors is a common mechanism of action (Yao et al., 2009, 2010, 2011), it is not unreasonable to conclude that the two component action of cocaine may apply to the HAND-related action of cocaine as well.

Concluding Remarks

In summary, cocaine is a multifactorial agent that mediates its effects on several pathways in cells infected with HIV-1. The drug not only promotes virus replication in PBMCs, macrophages, microglia and astrocytes, but it can also shift the cytokine balance towards a Th2 response via its modulation of IL-10 (Stanulis et al., 1997; Gardner et al., 2004). Such a shift has been shown to promote enhancement of CXCR4-utilizing viruses (Buch et al., 2001; Buch et al., 2002; Dhillon et al., 2005). Alternatively, cocaine can also upregulate the CCR5 coreceptor, and reciprocally inhibit its ligands, thereby increasing virus infectivity. Cocaine can also modulate astroglial function and activation. Cocaine also causes interactive neurotoxicity with viral proteins, Tat and gp120, thereby exacerbating neuronal apoptosis.

Additionally, cocaine also exerts potent effects on microvascular permeability, thereby impacting the influx of virus-infected inflammatory cells in brain parenchyma.

By direct or indirect modulations of NMDARs, HIV viral proteins and neurotoxins secreted as a result of HIV infection can modulate neuronal injury and cognitive dysfunction. NMDAR may thus act as a molecular switch linking crosstalk between drug addiction and HIV-1 infection. Although the dopamine system has been recognized as a major target of cocaine, there is accumulating evidence that σ -1R is also a major player in cocaine-mediated adjunctive effects on cell and organ systems. By amplifying the toxic responses that characterize HAND, cocaine skews the balance in favor of the virus leading to accelerated progression and severity of disease.

Drug addiction and human immunodeficiency virus (HIV) infection potentiate each other's impact on neural activity and brain function, although detailed mechanisms underlying their neuroimmune crosstalk are poorly understood. The *N*-methyl-D-aspartate receptor (NMDAR) densely expressed in the reward circuitry is a sensitive target of psychostimulants (cocaine and amphetamine). In response to chronic exposure to these drugs, NMDARs undergo plastic changes essential for the remodeling of excitatory synapses and drug seeking behavior. In addition, the NMDAR is a central target of HIV in acquired immunodeficiency syndrome (AIDS). By direct or indirect modulations of NMDARs, HIV viral proteins and neurotoxic substances secreted as a result of HIV infection causes neuron injury and cognitive dysfunction. Thus, the NMDAR may act as an interplayer underlying crosstalk between drug addiction and HIV infection. It is possible that HIV infection regulates NMDARs to predispose or reinforce drug abuse and vice versa. This review summarizes available data to project the NMDAR as a common target of drug addiction and HIV infection and a potential interface linking the two. Given the importance of neuroimmune linkage between two diseases, in-depth collaborations between addiction and HIV researchers are increasingly demanded to unravel underlying mechanisms for the HIV/AIDS-addiction vicious cycle.

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