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Neurotoxic Profiles of HIV, Psychostimulant Drugs of Abuse, and their Concerted Effect on the Brain: Current Status of Dopamine System Vulnerability in NeuroAIDS

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Abstract

There are roughly 30 to 40 million HIV infected individuals in the world as of December 2007, and drug abuse directly contributes to one-third of all HIV-infections in the United States. Antiretroviral therapy has increased the lifespan of HIV-seropositives, but CNS function often remains diminished, effectively decreasing quality of life. A modest proportion may develop HIV-associated dementia, the severity and progression of which is increased with drug abuse. HIV and drugs of abuse in the CNS target subcortical brain structures and DA systems in particular. This toxicity is mediated by a number of neurotoxic mechanisms, including but not limited to, aberrant immune response and oxidative stress. Therefore, novel therapeutic strategies must be developed that can address a wide variety of disparate neurotoxic mechanisms and apoptotic cascades. This paper reviews the research pertaining to the *where*, *what*, and *how* of HIV and cocaine/methamphetamine toxicity in the CNS. Specifically, *where* these toxins most affect the brain, *what* aspects of the virus are neurotoxic, and *how* these toxins mediate neurotoxicity.

Keywords

HIV; AIDS; Cocaine; Methamphetamine; NeuroAIDS; Dopamine; DAT; Review; HAD; Psychostimulant; Tat; gp120

1. Introduction

The year 2007 saw the number of people infected with Human Immunodeficiency Virus (HIV) reach an all time high, as “the global prevalence of HIV infection is remaining at the same level, although the global number of persons living with HIV is increasing because of ongoing accumulation of new infections with longer survival times, measured over a continuously growing general population” (UNAIDS/WHO, 2007). As of December 2007, there are an estimated 30 to 40 million people infected with HIV worldwide, with little indication that HIV incidence rates are decreasing (UNAIDS/WHO, 2007). This figure represents roughly 1.0%

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of the world's adult population, but regional adult prevalence rates reach as high as 5.0% of the population, as in Sub-Saharan Africa for example (UNAIDS/WHO, 2007).

Multiple behavioral risk factors are responsible for the propagation of HIV; and in the United States, injection drug use is the second most risky behavior directly associated with the transmission of HIV, even exceeding heterosexual intercourse. Through the year 2002, injection drug use directly accounted for one-third of the total number of Acquired Immunodeficiency Syndrome (AIDS) cases in the United States (NIDA, 2004). HIV DNA has been positively identified on paraphernalia such as needles and syringes from drug "shooting galleries" (Shah et al., 1996). In a longitudinal study encompassing the early years (1978 – 1983) of the HIV/AIDS epidemic in the United States, parenteral cocaine (COC) and heroin drug-users in New York City were found to be "disproportionately HIV-infected" (Novick et al., 1989). Furthermore, The National Institute on Drug Abuse (NIDA) notes that drug abuse (injection or non-injection) can also indirectly lead to HIV transmission through interference with sound judgments in regard to sexual behavior, thereby increasing the likelihood of infection through homosexual or heterosexual intercourse. They note that crack smokers (i.e., non-injectors) in inner-city neighborhoods are three times more likely to contract HIV than those who do not smoke crack (NIDA, 2004). Clearly, drug abuse propagates HIV infection. Moreover, drugs of abuse such as COC and methamphetamine (METH), may act in concert with HIV to wreak havoc on glial systems in the brain, ultimately leading to glial and neuronal injury and/or death. This neurotoxicity is of a magnitude which exceeds the neurotoxicity of COC, METH, or HIV alone. A wealth of scientific research has substantiated HIV- and drug-induced concerted neurotoxicity and its precursory mechanism(s) of action. Thus, the current review of the extant literature of HIV and drug abuse is timely.

The general purpose of this paper is twofold; first, to review the research pertaining to dopamine (DA) neurotoxicity of HIV, as well as theories regarding the neurotoxic mechanism(s) of action. Reviews concerning the neurotoxicity of HIV are hardly lacking (Table 1), yet the utility of this review remains undiminished for two reasons. One, the comprehensiveness of the current paper incorporates and consolidates the broad range of reviews regarding HIV neurotoxicity and neurotoxic mechanisms of action. Two, reviewing the neurotoxic effects of HIV provides a springboard for the second general purpose of the paper; to review the relatively novel area of research on the concerted/synergistic, neurotoxic effects of COC or METH abuse plus (+) HIV. Possible mechanisms for this synergistic toxicity are covered as well as novel protective factors for the brain of HIV-infected, COC or METH abusers. Table 1 is included to direct interested readers to specific reviews of topics presented throughout this article, the purpose of which is to present the literature with both breadth and depth.

This review will be organized so as to mimic the general cellular/systemic pathology of HIV in the brain and to attempt to examine the *where*, *what*, and *how* of HIV neurotoxicity, beginning each major section with theories and research pertaining to HIV entrance into the CNS through the blood brain barrier (BBB). Breaching of the BBB occurs early in HIV infection (An et al., 1999; Toborek et al., 2005), and toxicity of BBB endothelial cells occurs throughout the infection in parallel with toxicity of neurons (Price et al., 2005). Therefore, theories and research pertaining to the kinetic aspects of HIV neurotoxicity, with a special emphasis placed on DA systems, will then be reviewed. This will provide an understanding of *where* HIV most affects the brain. HIV neurotoxicity and related mechanisms of action are mediated by a number of HIV structural and regulatory proteins. Therefore, a description of the most prominently studied HIV proteins (Tat and gp120) and their ability to mediate cell death will be reviewed, which will highlight *what* aspects of HIV are detrimental to brain parenchyma. Since evidence highlights the fact that DA neurons may succumb to HIV-induced oxidative stress (Aksenov et al., 2001, 2003; Pocernich et al., 2005), a review of this mechanism of neurotoxicity will be presented following the review of HIV proteins, giving one example

as to *how* HIV might induce neurotoxicity. A review of the individual effects of COC and METH, as well as the concerted toxicity of HIV+COC and/or METH, and their mechanisms of action will receive individual attention and will be incorporated in the context of the topics of *where*, *what*, and *how*.

2. Where are HIV and Cocaine/Methamphetamine Neurotoxic?

2.1. HIV Neurotoxicity

Perhaps the most accepted theory regarding HIV's entry into the CNS is the appropriately named Trojan Horse Theory, and so will receive sole attention in this section. That is, the virus infects peripheral leukocytes which will ultimately pass through the BBB, thereby allowing the virus access to CNS parenchyma. This is thought to happen very shortly after viral entry into the host as researchers have detected CNS viral load, HIV DNA, and HIV-induced cellular response and injury early in the course of infection (An et al., 1999; Gray et al., 1993a, 1996; Sinclair et al., 1994). It is important to note that while the "Trojan Horse" metaphor captures how HIV exploits normal migration of monocytes/macrophages across brain microvascular epithelial cells (BMEC), it should not be taken to imply that HIV remains idle in the CNS.

For example, matrix metalloproteinase (MMP) levels such as MMP-2, 7, and 9 have been found at higher levels in the cerebro-spinal fluid (CSF) of HIV-infected individuals (Conant et al., 1999; Sporer et al., 1998). MMP's are proteolytic enzymes that may break-down proteins in the extracellular space that support endothelial cell layers of the BBB. Therefore, it is likely that infected leukocytes possess an advantage not only in rolling and adhesion, but in diapedesis as well; that being the final step in infected leukocyte transmigration into the CNS (Nottet, 2005).

Proteins that mediate the transmigration of leukocytes across the BBB are not the only molecules to be up-regulated. In fact, endothelial cells have been shown to increase production of monocyte chemo-attractant protein (MCP) – 1 (Boven, 2000a). MCP is a protein which, as its name suggests, attracts increased numbers of leukocytes to the area in which the protein is released. Boven and colleagues (2000a) demonstrated that co-cultures of HIV-infected leukocytes and endothelial cells induce endothelial cell upregulation of MCP-1. Therefore, the increased transmigration of HIV-infected leukocytes across the BBB is further compounded by the increased number of infected leukocytes which are attracted to the brain. Thus, ever increasing numbers of infected leukocytes migrate across an ever more vulnerable BBB.

Post-mortem analysis of HIV-infected patients confirms this, and demonstrates BBB tight junction degradation in blood vessels which innervate subcortical white and gray matter, as well as cortical gray matter (Dallasta et al., 1999). Thus, a widespread area of the brain may be directly exposed to HIV and its virotoxins (e.g., Tat & gp120), and chemokines may continually recruit more and more infected leukocytes to these areas (Boven et al., 2000a; 2000b) in a positive feed-forward cycle. Additionally, it is likely that subcortical gray and white matter may be particularly vulnerable given their close proximity not only to a compromised BBB, but to the lateral and third ventricles (i.e., vulnerable choroid plexus) as well.

2.1.1. Behavioral Pathology and Clinical Definitions—The overwhelming majority of evidence at the behavioral, systemic, and molecular levels has labeled the neuropsychological manifestations of HIV a subcortical dementia. Behaviorally, 5% of HIV-associated dementia (HAD) patients from a prominent neuroAIDS clinic have Parkinsonism, and as much as 10% have Parkinsonian features (Berger and Nath, 1997). Furthermore, a case study reported HIV-induced chorea comparable to subcortical, Huntington's disease (Sporer et al., 2005). Indeed, behavioral manifestations of HAD include impairment on a number of motor abilities thought to stem from subcortical neurotoxicity which resembles Parkinson's disease. These include

fine motor skill impairment, resting tremor, loss of balance, bradykinesia, gait abnormalities, rigidity, and postural disturbances (Navia et al., 1986a). Furthermore, impairment on a number of cognitive tasks associated with subcortical dementia usually accompanies the impairment of motor abilities in HAD. These cognitive deficits include bradyphrenia, apathy, memory impairments, poor concentration and attention among others (Grant et al., 2002, 2005).

In most circumstances, to be clinically defined as HAD the patient must not have evidence of any etiology other than HIV/AIDS, and must have “marked acquired impairment in cognitive functioning involving at least two domains (e.g., memory, attention) ... [which] produces marked interference with day-to-day functioning ... for a period of at least one month” (Grant and Atkinson, 1995; McArthur and Grant, 1998). Note that this diagnosis usually manifests late in the disease, when CD4 cell counts are low. As a result, patients who do not meet these criteria may still exhibit some subtle impairment in one or more domains that is not severe enough to interfere with day-to-day functioning, and often sensitive measurements are needed to perceive the subtlety. These patients are often labeled asymptomatic HIV seropositives (e.g., Grant, 2002), and in many published investigations this group of individuals are generally not statistically different from HIV seronegative controls on a number of dependent variables; nevertheless, a trend towards impairment is often apparent.

The gray area between asymptomatics and those patients with HAD is often referred to as minor cognitive motor disorder (MCMD). This group generally incorporates HIV seropositive patients with impairment in at least two domains, which is indexed by a variety of standardized test scores. Impairment is noted for patients that score one standard deviation lower than matched controls in two of any given domain, and these impairments are not large enough to negatively influence day-to-day function (Grant, 2002).

Clearly, sensitive tests are needed to differentiate between HIV seronegatives, HIV asymptomatics, and patients with MCMD. Furthermore, it may be possible to confuse the level of impairment when distinguishing groups for research purposes, which may be one reason for the variability in estimates of percentage of patients with HAD (c.f., McArthur et al., 2003 vs. Navia, 1990). Another variable in HAD is that researchers may not all subscribe to the aforementioned criteria, as it may not be necessary for their purpose(s). For example, many researchers collapse patients into two groups, asymptomatic and symptomatic, thereby potentially splitting patients who may be considered by some researchers as possessing MCMD. Furthermore, given the difference in progression between the morphological degradation associated with HIV infection and behavioral manifestations of HIV dementia, the term “symptomatic” may take on divergent connotations for disciplines that investigate the disease from different levels. While it is true that a biochemist may never technically diagnose a patient with HAD, it is likely that the biochemist contributes to the literature in which the clinician references, making an understanding of divergent interpretations of disease state important.

2.1.2. Molecular Pathology—It is likely that HIV produces widespread damage to the brain; however, multiple lines of research have indicated that DA systems stemming from and located throughout extrapyramidal areas of the brain are especially vulnerable to neuronal injury and/or loss associated with HIV infection. To understand the extent and mechanisms of damage in a particular area, researchers may determine viral load in or around the region of interest, and must accurately characterize the extent and nature of the damage. Results with respect to these main goals are the product of studies employing multiple methodological techniques which are repeated in the context of various brain regions. Most of the studies reviewed in all of Section 2 are from human subjects, as this data gives the most accurate kinetic dimension to HIV which helps elucidate where HIV most affects the brain Figure 1 provides a schematic analogue to the remainder of Section 2.

2.1.2.1. Subcortical Degradation: Studies utilizing quantitative PCR have detected HIV DNA in the basal ganglia, and often times in higher quantities when compared to cortical gray matter and white matter (Achim et al., 1994). Commonly, studies utilizing techniques to determine viral load in various brain regions are performed on cadavers so that a snapshot of viral load is available only after full blown HAD or encephalitis has developed. Nevertheless, Glass et al. (1993) demonstrated the existence of the HIV envelope glycoprotein 41 in the basal ganglia of patients with HAD, as well as in HIV asymptomatics. Furthermore, HIV-infected microglial cells and aberrant cellular formations (e.g., multinucleated giant cells) are most heavily concentrated in the caudate and putamen of the basal ganglia (Navia et al., 1986b).

In the early 90's, ventricular enlargement had been noted in brains of HIV-infected patients (Dal Pan et al., 1992; Gelman and Guinto, 1992), likely as a result of a reduced volume of the basal ganglia (Aylward et al., 1993). Indeed, more recent MRI data has demonstrated caudate volume reductions, along with hippocampal and cortical (viz. frontal and temporal) reductions (Jernigan et al., 2005). Of note are significant correlations between central/caudate atrophy and impairment on a number of neuropsychological tests (Dal Pan et al., 1992; Hestad et al., 1993; Jakobsen et al., 1989). Furthermore, volume reductions in the nucleus accumbens are strongly negatively correlated with level of apathy ($r = -.59$) (Paul et al., 2005). These correlations converge to show the prominent subcortical nature of HIV neuropsychological impairment (see Paul et al., 2002 for review). Furthermore, researchers have reported a case study in which chorea developed and was associated with basal ganglia dysregulation (Sporer et al., 2005). Indeed, despite even the late onset of many behavioral and imaging abnormalities associated with HAD, subcortical degradation has been reported early in the disease.

Electrophysiological techniques have proven to be sensitive enough to detect early onset basal ganglia degeneration prior to the majority of imaging and behavioral measures, when most patients would be considered asymptomatic. For example, Arendt et al. (1990) collected electrophysiological data during a rapid, alternating finger-tapping task to show that early-onset HIV patient's finger contractions resemble finger contractions of patients with other subcortical degenerative diseases such as Huntington's disease and Parkinson's disease. In fact, early electrophysiological motor tasks not only predict basal ganglia vulnerability, but can predict fatal clinical outcome (Arendt et al., 1994; Berger and Arendt, 2000).

Magnetic resonance spectroscopy (MRS) is a commonly utilized imaging technique when studying HAD and converges with other imaging techniques by highlighting basal ganglia vulnerability (Von Giessen et al., 2001). Studies have shown decreased levels of metabolites such as N-acetyl-aspartate (NAA), as well as decreased levels of creatine in the basal ganglia of HIV infected individuals (Ernst and Chang, 2004). Decreases in NAA is reliable, but not the only marker for neuronal loss (see Section 2.1.2.4.).

The majority of published research on the subcortical molecular profile of HIV neurotoxicity has concentrated on the structures of the basal ganglia, which may stem in part from the lack of evidence for microglia and multinucleated giant cells in other subcortical structures like the substantia nigra (SN) (e.g., Reyes et al., 1991). Nevertheless, Reyes et al. (1991) reported shrunken cells, substantial cell loss on the order of 25%, extracellular melanin, and astrocytosis in the SN. Morphometric data has replicated the findings of Reyes and colleagues (1991) by demonstrating significant density and size reductions of pigmented cells in the SN pars compacta (Itoh et al., 2000). Recent immunoreactivity data from human nigral tissue demonstrated significant reductions in tyrosine hydroxylase (TH) from 7 HIV-infected brains relative to 8 age-matched controls (Silvers et al., 2006). These data, in combination with evidence of *early* reductions of DA in the striatum, along with *late* reductions of DA in the SN in monkeys (i.e., Simian Immunodeficiency Virus - SIV) have led some researchers to hypothesize the possibility of a "retrograde degeneration of dopaminergic

projections” (Koutsilieri et al., 2002b; pg 770); although it is unclear if the degeneration is truly retrograde, or whether direct damage to SN neurons occurs.

2.1.2.2. Cortical Degradation: Despite overwhelming evidence of the subcortical nature of HAD, multiple studies show that structural degradation can extend beyond the basal ganglia and into the cortex (Ketzler et al., 1990; Wiley et al., 1991). The extent to which various cortical structures affected by HIV also involve DA projections is not always clarified in research. Thus, it is possible for some cortical degradations noted in the literature to be DAergic in nature. Indeed, pre- and post-mortem studies have demonstrated the presence of HIV, HIV proteins, and DNA in the cortical areas throughout the brain, especially the frontal lobe (Glass et al., 1993; Wiley and Achim, 1995). Furthermore, some of the highest levels of HIV DNA have been located in the hippocampus (Fujimura and Bockstahler, 1995). Aylward and colleagues (1995) followed their investigation of the basal ganglia (1993) with a demonstration of decreased white matter volume and decreased volume of the parietal cortex in HAD patients. This degradation was not apparent in HIV non-demented and HIV seronegatives. Furthermore, functional MRI data have demonstrated increased activation within HIV infected patient’s prefrontal (Ernst et al., 2002), frontal, and parietal (Chang et al., 2001) areas of the brain during working memory and attention tasks, lending evidence for increased blood perfusion and tissue atrophy.

Given the complexity of neuronal circuitry with the cortex, it is plausible that specific neuronal populations, including those that make up DAergic circuitry, may be particularly vulnerable to HIV. Loss or damage to these neurons may account for the functional abnormalities and volume reductions noted in this section. Researchers have demonstrated loss of pyramidal neurons and a 20% reduction in cortical width in the temporal, parietal, and orbito-frontal lobes of the human brain (Ketzler et al., 1990; Masliah et al., 1992a, 1992b; Wiley et al., 1991). Using laser confocal microscopy and Golgi analysis of pyramidal neurons in the frontal cortex from severe HIV encephalitis brains, Masliah et al. (1992a) noted a 40% to 60% loss of spine density on apical dendrites, and a 40% loss of whole dendrites. Masliah and colleagues (1992b) continued their work identifying the specific neuronal populations that are particularly vulnerable to HIV by investigating pyramidal cells and interneurons in the frontal cortex and the hippocampus. Using antibodies against parvalbumin (PV), a protein detectable in interneurons, and neurofilament (NF), a protein detectable in the large pyramidal neurons, Masliah et al. (1992b) found that interneurons in the frontal cortex were fragmented; however this finding did not correlate with severity of HIV encephalitis. A novel finding, however, was that density of interneurons in the hippocampus was decreased; especially in layer CA3 where there was a 50–90% decrease in interneurons. Furthermore, this decrease in interneuron density in the hippocampus was more highly correlated with severity of HIV encephalitis.

While many researchers have noted neuronal loss throughout the cortex and hippocampus, many investigators maintain that HAD and neuropsychological impairment stems from subcortical degeneration. This is likely due to the behavioral manifestations of HAD most closely resembling behavioral manifestations of Parkinson’s disease and Huntington’s disease, as supported directly when HAD is compared to these subcortical dementias relative to other cortical dementias in investigations using discriminant function analyses (Peavy et al., 1994).

2.1.2.3. White Matter Degradation: Thus far, the focus of this section has been on both subcortical and cortical gray matter structures. However, more recently developed technologies such as diffusion tensor imaging (DTI) have enabled researchers to look more closely at white matter fiber tracts that interconnect multiple gray matter structures, which may correspond to DAergic projections. This technique may be a reliable diagnostic tool for deteriorating white matter even before clinical signs and overt lesions/volume reductions appear (Hall et al., 2004; Filippi et al., 2001). Thus, while early work is promising, more research needs to be

completed to gauge the overall contribution of this technique to the field. Nevertheless, fractional anisotropy (FA) has been shown to be decreased in HIV seropositives with dementia, as well as HIV seropositive asymptomatics (Hall et al., 2004). Decreased FA in white matter has been shown to be variably located, from diffuse and general enough to be clinically relevant for white matter disease (Hall et al., 2004; Tucker et al. 2004), to specifically confined to areas such as the frontal lobe (Cloak et al., 2004a; Pomara et al., 2001). For example, researchers have also noted decreases in creatine and choline in white matter of FIV-infected cats (Cloak et al., 2004b). Researchers have shown that FA decreased in the splenium and genu of the corpus callosum, and this was negatively related to viral load (Filippi et al., 2001) and neuropsychological impairments (Wu et al., 2006). Furthermore, increased diffusivity has been noted in the corpus callosum (Wu et al., 2006).

2.1.2.4. Dopamine System Vulnerability: Treating HIV seropositives with neuroleptics has been shown to greatly increase, often acutely, extrapyramidal dysfunction (Edelstein and Knight, 1987; Hollander et al., 1985; Hriso et al., 1991) leaving some patients with severe dystonia and rigidity; similar to what is observed in Parkinsonian patients (Factor et al., 1994). Both extrapyramidal vulnerability and DA susceptibility may explain these HAD behavioral manifestations that resemble Parkinson's and other subcortical dementias.

In fact, concentrations of homovanilic acid (HA) in CSF are decreased in HIV infected individuals, and this decline was shown to be correlated with impairment of neuropsychological function (Di Rocco et al., 2000). Specifically, the positive correlations between decline in HA levels and motor speed ($r = .59$) as well as for tests of attention and executive control ($r = .54$) were noteworthy. Berger and colleagues (1994) not only found decreased levels of HA in HIV-seropositives (42% decrease relative to HIV-seronegatives) which correlated with neuropsychological function, but also decreased levels of DA in CSF. Furthermore, new evidence suggests decreased levels of tyrosine hydroxylase (TH), the rate-limiting enzyme of DA synthesis, in the SN of human brains infected with HIV (Silvers et al., 2006). This is consistent with earlier *in vitro* work showing reduced expression of TH and DA in rat PC12 cell cultures after administration of Tat, presumably mediated by reduction in TH gene expression in these cells (Zauli et al., 2000). Furthermore, these authors demonstrated reduced TH expression in the SN one week post-intrastratial injection in rats.

Data on DAergic vulnerability from rhesus monkeys infected with SIV are similar to data from humans with HIV. Levels of DA, as well as the metabolites HA and 3,4-dihydroxyphenylacetic acid (DOPAC) are reduced in the basal ganglia; specifically, the nucleus accumbens (NAcc) and corpus amygdaloideum (Jenuwein et al., 2004). Furthermore, this study demonstrated decreases in the second-messenger cAMP in the NAcc and transcription factor CREB in both the NAcc and corpus amygdaloideum. These studies provide evidence for alterations in DA system function. The fact that these monkeys were asymptomatic lends credence to the notion that DA systems are vulnerable early in infection, prior to the emergence of overt behavioral symptomatology, and show that this vulnerability may be a major contributor to the progression of HAD.

The synaptosomal transmembrane DA transporter protein (DAT) has been investigated in the context of HIV-infection, especially in DA rich areas such as the basal ganglia structures. A case study of an HAD patient was reported in which SPECT revealed a bilateral reduction of DAT in the posterior striatum (Sporer et al., 2005). Wang et al. (2004) showed using positron emission tomography (PET) that viral load negatively correlated with levels of DAT in the putamen ($r = -.69$) and the striatum ($r = -.70$), as DAT levels were decreased by about 14% – 20% in both structures. They showed no concomitant decrease in D2 receptors, suggesting that decreases in DAT play a pivotal role in the molecular profile of HAD (however, see Sporer et al., 2005). Work in our laboratory and among collaborators have supported and extended

findings noted by Wang et al. (2004). Using midbrain cell cultures from rat fetuses, researchers have replicated decreases in DAT binding after administration of Tat, using the ligand [3H] WIN 35428 (Aksenova et al., 2006) or [¹²⁵I]RTI-121 (Theodore et al., 2006a). Perhaps even more interestingly, Aksenova et al. (2006) extended this research to show that antibodies specific for the C-end epitope of DAT did not show changes in DAT immunoreactivity upon administration of Tat. The combination of these findings indicate that DAT may not down-regulate *per se*, but that a functional change of the DAT protein occurs, rendering the transporter functionally inactive during the course of HIV-infection. Furthermore, Wallace et al. (2006a) demonstrated that not only does the regulatory HIV protein Tat decrease DA uptake, but the HIV structural protein gp120 also decreases the V_{max} of DAT, and that 17 β -Estradiol may therapeutically prevent this loss of DAT function.

2.2. Psychostimulant Neurotoxicity

One of the main purposes of this paper is to review evidence for the concerted neurotoxicity of HIV and psychostimulant drugs of abuse, specifically COC and METH. A review of HIV neurotoxicity is presented, and the current section is included as a brief highlight of research on the neurotoxic effects of COC and METH. This section is important in order to provide background for the concerted neurotoxicity of COC or METH + HIV.

2.2.1. Cocaine—To date, COC's hallmark affect on the brain resides in its capacity as a powerful reinforcing drug of abuse as well as its ensuing ability to induce neuroplasticity in the course of repeated administration. This neuroplasticity has been studied most extensively, although not exclusively, in mesocorticolimbic and nigral circuits thought to underlie neural reward and motivation circuitry, particularly in the context of DAergic transmission. Structural imaging research is relatively sparse while functional measures of neuroplasticity are more common. One of the most cited structural studies has demonstrated increases in lateral ventricular enlargement and cerebral atrophy (Pascual-Leone et al., 1991), while other data demonstrates reduced temporal lobe gray matter volume in COC-abusers (Bartzogis et al., 2000). Bartzogis et al. (2000) suggest an accelerated age related decline in temporal lobe volume among COC-abusers. A recently published comprehensive structural imaging study (i.e., voxel-based morphometry) of COC abusers demonstrates a number of bilateral and unilateral gray and white matter volume reductions; including regions such as the cerebellum, thalamic nuclei, and both the frontal and temporal cortical nuclei (Sim et al., 2007). Interestingly, the authors argue for continued work on COC-related cerebellar dysfunction, as cerebellar volume reductions were negatively correlated with duration of use and positively correlated with motor and neuropsychological impairment (Sim et al., 2007). Nevertheless, one problem that exists in interpreting structural alterations is polydrug abuse, to the extent that it is difficult to tease out the individual contributions for each substance. For example, researchers have demonstrated decreases in frontal white matter but not ventricular enlargement in COC abusers who also abuse heroin and cannabis (Schlaepfer et al., 2006). Another problem is teasing out direct COC-induced structural alterations from those involving indirect COC-induced alterations via cerebrovascular trauma.

Indeed, *direct* neurotoxic effects of COC on DA systems are controversial, and are significantly less characterized than METH- and HIV-induced DAergic neurotoxicity. For instance, much of the literature on COC-induced cytotoxicity stems from studies utilizing cells from other organ systems such as the hepatocytes (e.g., Zaragoza et al., 2000) or myocytes (e.g., Lattanzio et al., 2005). Some *in vitro* work has demonstrated COC-induced neurotoxicity to human neuronal progenitor cells (Poon et al., 2007), rat cortical cell cultures (Nassogne et al., 1997), and rat fetal locus coeruleus (LC) neurons and corresponding upregulation of apoptotic caspases-3 and -9 (Dey et al., 2007). Nevertheless, concurrent investigations using DAergic neurons from the SN failed to demonstrate COC-induced neurotoxicity or induction of caspase

activity (Dey et al., 2007). These results (Dey et al., 2006, 2007; Nassogne et al., 1997; Poon et al., 2007) and the lack of evidence for COC-induced DAergic neurotoxicity in particular suggest a degree of cell and/or age related specificity for COC-induced neurotoxicity, whereby COC may not be directly toxic to DA neurons, and/or selectively toxic to developing LC neurons.

With respect to DA neurons in fact, a plethora of research on COC abuse has directly demonstrated evidence for a lack of COC-induced DA neurotoxicity (Bennett et al., 1993; Goodman and Sloviter, 1993) often times by using COC administration as a control group in the context of other neurotoxic substances (e.g., Aksenov et al., 2006; Turchan et al., 2001), or even implicitly demonstrating lack of neurotoxicity by demonstrating upregulation of various molecules known to be present in or on DA nerve terminals, such as TH and DAT (Daws et al., 2002). Despite the lack of evidence for a direct COC-induced toxic effect on DA neurons, the overwhelming evidence for COC-induced neuroplasticity and cerebrovascular trauma makes COC abuse a cause of concern for public health. Furthermore, given our goal of understanding HIV-infection in the context of COC abuse, the lack of evidence for COC-induced DA neurotoxicity does not mitigate the importance in understanding their interaction (discussed in Section 2.3. and 4.1.4.1.), nor does it mitigate the importance of understanding the state of the COC-abusers brain at the time of HIV-infection.

Regardless of a lack of evidence for direct DAergic toxicity, COC possesses a well documented ability to incite indirect brain trauma, such that the vast majority of evidence for COC-induced brain damage and cell death is the drug's ability to induce a variety of cerebrovascular complications (Büttner et al., 2003). Acute COC administration has been shown to increase blood pressure and heart rate (Ambrosio et al., 1996), and functional alterations in brainstem noradrenergic nuclei responsible for autonomic function has been noted (Beveridge et al., 2004). COC-induced vasoconstriction can ultimately lead to stroke, hemorrhages, blood clots, and/or cerebral ischemia in abusers (Büttner et al., 2003; Peterson et al., 1991), including populations considered young for vascular impairments (Levine et al., 1991). For example, a recent 4 year epidemiological study concluded that COC use was associated with both hemorrhagic and ischemic stroke (Westover et al., 2007). A COC-induced reduction in cerebral blood flow or hemorrhaging of cerebral blood vessels may damage and lesion brain tissue. For example, MRI has demonstrated a COC-induced increased risk of white matter lesioning, mediated by vasospasm and stroke (Bartzokis et al., 1999). Indeed, imaging studies should consider cerebrovascular abnormalities as a cofactor to control for when discussing COC-induced structural abnormalities.

Therefore, since there may be little to no direct neurotoxic effect of COC on DAergic systems in the brain, mental deficits that have been associated with COC abuse, such as poor attention, learning, memory, concentration, and information processing speed (Goodkin et al., 1998), as well as paranoia and delusions may be related more to COC-induced DAergic neuroplasticity and/or indirect neurotoxicity via vasculopathies. Indeed, DA depletion theories and neuroplasticity, independent of neurotoxicity, have been hypothesized to account for craving and the above-named neuropsychological complications (Bolla et al., 1998) to such an extent that the idea of chronic COC related plasticity as a syndrome in-and-of-itself has been entertained (Cadet and Bolla, 1996).

Porrino, Nader, and colleagues have more recently outlined neuroplasticity that follows acute to chronic self-administration in nonhuman primates, and have demonstrated that neuroplasticity, although not exclusively relegated to the striatum, is most evident in this area (for review, see Porrino et al., 2004). Metabolic assays have demonstrated COC-induced utilization of areas of the striatum associated with limbic function upon acute self-administration of COC (Porrino et al., 2002), which then extends upon chronic self-

administration to include a vast portion of the striatum responsible for limbic, cognitive, and sensorimotor function (Nader et al., 2002). In COC-abusing humans, global increases in brain glucose metabolism, especially for DA rich areas of the brain (e.g., basal ganglia), have been noted within 1-week of COC cessation; a likely consequence of alterations in DA activity (Volkow et al., 1991). Furthermore, administration of COC has been associated with alterations in D1 and D2 receptors (Nader et al., 2002), and individual differences in the expression or activation of these receptors have been shown to predict vulnerability to COC addiction, as well as COC seeking, extinction, and reward responses (Edwards et al., 2007; Nader and Czoty, 2005). Chronic COC administration has been associated with significant downregulation of D2 receptors (Moore et al., 1998; Nader and Czoty, 2005), which has been shown to persist months after cessation and be associated with decreased brain metabolism in the frontal cortex (Volkow et al., 1993). Significant upregulation of DAT is repeatedly noted in both subcortical and cortical areas of interest (Daws et al., 2002; Fang and Ronnekleiv, 1999; Kalivas and Duffy, 1993; Letchworth et al., 2001; however see Hitri et al., 1994). This fact may be particularly important in the context of HIV-infection given evidence for the direct interaction of HIV-proteins with DAT (Aksenova et al., 2006; Wallace et al., 2006a).

2.2.2. Methamphetamine Neurotoxicity—Similar to COC, METH is a powerfully reinforcing psychostimulant drug of abuse which can induce neuroplasticity upon repeated administration. Unlike COC however, METH induced neurotoxicity has been convincingly demonstrated at various doses. Bartzokis et al. (2000) report reductions in temporal lobe volume for amphetamine and COC abusers relative to non-abusing controls, and Thompson et al. (2004) report loss of volume to limbic gray matter such as the cingulate gyrus and the hippocampus, as well as hypertrophy of cerebral white matter. The losses were correlated with impairment of memory on neuropsychological tests. As with many drugs however, it is misleading to describe a blanket effect of METH abuse, as exogenous factors such as the dose, frequency and duration of use, and route of administration often interact with each other and with endogenous factors to determine the level of toxicity. Differences in these factors may account for divergent, and sometimes conflicting, results found in the literature. For instance, Jernigan et al. (2005) noted volume *increases* in caudate nucleus, lenticular nuclei, nucleus accumbens, and parietal lobe for METH abusers. It is important to note that while the structures from these three studies are mutually exclusive, Jernigan et al. (2005) failed to replicate the earlier studies in the relevant brain regions, noting small increases in temporal lobe volume (c.f., Bartzokis et al., 2000), and no change to small increases in limbic structures such as the hippocampus, thalamus, and amygdala (c.f., Thompson et al., 2004). Nevertheless, Jernigan et al. (2005) explain increased brain volume in humans, and results from animal studies which show neuron growth, as compensatory processes to METH-induced damage to DA systems.

With respect to specific molecular alterations, PET imaging has demonstrated reduced DAT binding in METH abusers in prefrontal cortex and basal ganglia nuclei. Specifically, reductions in nucleus accumbens and caudate/putamen DAT were negatively correlated with duration of METH abuse, but not related to abstinence; while both DAT reduction and increased duration of METH were associated with increased neuropsychological complications (Sekine et al., 2001). Other studies using doses relevant for human intake have shown decreased DAT binding, and reduced DA and DOPAC in non-human primate striatal tissue, administered as 4 injections over an 8 hr period. Further, these reductions were negatively related to increases in dose, from 0.5 mg/kg to 2.0 mg/kg (Villemagne et al., 1998).

A plethora of research has been performed on animal and *in vitro* models of METH-induced neurological impairment and toxicity, and these models overwhelmingly demonstrated METH induced DAergic neurotoxicity, especially at higher doses. Interestingly, METH has been shown to damage DAergic neurons (Cadet et al., 1998), specifically in nigrostriatal pathways (Hanson et al., 2004), and activate glial cells (Sonsalla et al., 1992). However, there have been

exceptions in certain cases, usually contingent on level of dose. For example, low-dose amphetamine induces lengthening of dendrites and increased density and number of spines in the nucleus accumbens (Robinson and Kolb, 1997, 1999). These studies support the Jernigan et al. (2005) imaging study described earlier, and so low-dose METH may result in the increased brain volume described therein, perhaps acting as a compensatory mechanism to acute METH-induced brain damage.

2.3. HIV + Cocaine and/or Methamphetamine Neurotoxicity

Research on HIV's interaction with COC or METH in the brain is a relatively novel investigation and certainly less studied, and the lack of understanding regarding HIV neurotoxicity is compounded when additional factors such as drug abuse are added. Unfortunately, drug abusers make up a significant percent of the HIV seropositive population. There is some debate as to whether HIV interacts with either of these drugs to increase neurotoxicity above and beyond what these substances induce alone; and those who support the idea of a concerted effect, may be further divided as to whether a concerted toxicity is additive or interactive/synergistic. Furthermore, a detailed account of HIV's concerted effect with one psychostimulant drug will not sufficiently address HIV's concerted effect with a different psychostimulant. This is due to the fact that psychostimulants can be further subdivided according to their primary mechanism of action (i.e., DA blocker vs. DA releaser; see Sections 4.1.2. and 4.1.3. on mechanisms). Thus, the field may ultimately discover some psychostimulant as particularly damaging in combination with HIV, while other psychostimulants may have no effect, or even be therapeutic (Hinkin et al., 2001; van Dyck et al., 1997). These permutations become increasingly complicated when one factors in duration of drug use and HIV-infection, route of drug administration, poly-drug use, etc. Despite all caveats, prior to an investigation involving HIV+COC, or HIV+METH, most investigators will ultimately hypothesize a concerted effect of the virus and drug. This may be due to demonstrations that neurotoxicity of *in vivo* and *in vitro* HIV+METH, as well as *in vitro* HIV+COC, have generally been shown to be of a magnitude which exceeds the neurotoxicity of COC, METH, or HIV alone. In keeping with the caveat, there are examples of a lack of concerted neurotoxicity with these substances (e.g., see Griffin et al., 2007 for HIV+COC; see Jernigan et al., 2005 for HIV+METH).

In the HIV+COC field, due to the lack of evidence for the neurotoxic effects on DA systems of COC alone, one may speculate that any concerted effect of HIV and COC must be synergistic, as an additive effect of HIV+COC on DAergic systems would result in no concerted effect above and beyond HIV alone. On the other hand, METH has been repeatedly demonstrated as having neurotoxic effects, indicating the potential for additive effects when paired with HIV. Taking all these factors into account, the extant theory in the field to date is that HIV+COC is either not concertedly neurotoxic, or is synergistically so; while HIV+METH is either not concertedly neurotoxic, additively neurotoxic, or synergistically so; the later of the corresponding possibilities being the most supported in the literature (i.e., synergism for both drugs of abuse with HIV). The lack of understanding with respect to concerted effects is consequent to the lack of human research and data in these fields.

What is becoming clear from some data is that the probability of infected leukocyte transmigration across the BBB may be even greater for COC and/or METH abusers than non-drug abusers; as COC and METH have been shown to up-regulate molecules that facilitate transmigration of HIV across the BBB such as MMPs and DC-SIGN (Conant et al., 2004; Nair et al., 2004). Furthermore, research has shown that COC binds to and enters brain microvascular endothelial cells (BMEC), and up-regulates gene transcription important for normal physiological functioning and maintenance of BMECs, thereby disrupting tight junctions and increasing permeability to HIV among other things (Fiala et al., 2005). Indeed,

researchers have shown that COC can increase monocyte transmigration of the BBB (Fiala et al., 1998). The demonstration of increased BBB permeability in the COC and METH abusing populations demonstrates one way which psychostimulant drug-abuse may interact with HIV virotoxins to produce high viral burden in the CNS, and possibly increase neurotoxicity.

One common outcome regarding neurotoxicity of HIV+COC or METH, confirmed in research, is that increased breaching of the BBB may facilitate degradation of DA systems and their respective neuronal/brain substrates due to the proximity of these structures to a compromised BBB. This is not surprising given the convergence of the individual, detrimental effect of HIV, COC, and METH abuse on DA systems in the brain. For example, Nath and colleagues (2001) reported a 44-year old patient with rapidly accelerating HAD who abused COC and METH for 10 years, and at least 4 years after testing positive for HIV. They noted multiple behavioral and morphological alterations associated with HAD and aberrant DA system function in particular. Involvement of the DA system was further confirmed as treatment with L-Dopa improved motor dysfunction in this patient. It is important to note however that data from this single case report may not represent the HIV-infected COC and/or METH abusing population, and may be an extreme example from possibly any number of HIV-infected patients who abuse these drugs and do not experience CNS complications. In fact, some researchers underscore the variability and lack of clarity with regard to the deleterious combined effect of HIV+COC or METH (Goodkin et al., 1998).

Addressing this issue, Nath et al. (2001) theorize that drugs of abuse may not affect incidence of HAD, but that drugs of abuse may initiate a rapid and severe decline in brain function once HAD does occur. They reference research that shows 56% of brains from HIV-infected drug abusers demonstrated HIV encephalitis while only 17% HIV-infected non-drug abusers demonstrated encephalitis (Bell et al., 1998), and the fact that HIV-infected drug abusers generally have more prominent macrophage activation and psychomotor slowing (Bouwman et al., 1998). It is noteworthy that Bell's research population in the United Kingdom is opiate preferring, with little to no contact with COC or METH (Bell et al., 1998). Whether compounded encephalitis occurs in HIV-infected COC and/or METH abusing populations is arguable and more research needs to be performed. For example, encephalitis was mitigated in an HIV-infected METH abusing population relative to HIV-infected non-abusers (Langford et al., 2003). Nevertheless, encephalitis is only one sign of brain injury as these authors demonstrated increased levels of ischemia, altered neuronal sprouting, and increased microglial response in METH abusing HIV-infected populations (Langford et al., 2003). Thus, Nath et al.'s (2001) original assertion of a more rapid, drug + HIV-induced decrease in brain function is not mitigated in the context of potential drug-specific differences in encephalitic expression. Nevertheless, given the divergent mechanisms of psychostimulant DA blockers (COC) versus DA releasers (METH) (see Section 4.1.2. and 4.1.3. on mechanisms), one cannot assume the same result would be demonstrated in HIV+COC abusers.

Unfortunately to date, virtually no *in vivo* research has been published with respect to the neurotoxic effect of HIV+COC in human HIV-infected, or SIV-infected non-human primates. To reiterate our goals, the purpose of this section is to provide information regarding *where* HIV+COC (or METH) affects the brain. The lack of research in this area relegates areas most affected by HIV+COC as only speculative. Nevertheless, Kidwell and Blank (1996) provided interesting data on mortality rates of HIV-infected COC users compared to HIV-infected non-users. They found that male HIV-infected COC users had a 13% higher mortality rate than male HIV-infected non-users, while female HIV-infected COC user's mortality rate was 22% higher than female HIV-infected non-users. Other research has shown that COC use significantly accounts for variability in mortality rates for women with HIV, above and beyond the virus alone, and is negatively related to CD4 cell count and positively related to viral load (Goodkin et al., 1998; Shapshak et al., 1997). Fiala and colleagues have published a number

of *in vitro* investigations demonstrating a concerted breakdown of the BBB, and breaching of the virus in HIV+COC relative to HIV alone. This evidence, in combination with evidence for the individual effects of HIV and COC on the BBB, leads some in the field to speculate a possible synergistic viral load and ensuing neurotoxicity in HIV+COC abusers, especially in areas close to a compromised BBB (i.e., subcortical DA systems). Furthermore, COC has been shown to increase HIV replication *in vitro* (e.g., Gekker et al., 2004), including a recent demonstration in human astrocytes (Reynolds et al., 2006), also suggesting an HIV+COC synergistic viral load in the brain. Nevertheless, Griffin et al. (2007) demonstrated no concerted effect of HIV+COC on neurobehavioral and neuropathological assays.

With respect to HIV+METH, relatively more work has been accomplished, but research is still lacking. Chang and colleagues (2005) recently discovered a concerted effect of METH abuse and HIV on the amount of brain metabolites and cellular byproducts, specifically the neuronal marker NAA. NAA is a reliable neuronal marker as it has been shown to be detectable almost exclusively in neurons (Moffet et al., 1991; Simmons et al., 1991), and reductions in NAA often correlate with neuronal loss (for review, see Schuff et al., 2006). Chang et al (2005) found the lowest amount of NAA in frontal gray matter (-5.7%), frontal white matter (-6.1%), and the basal ganglia (-9%) relative to HIV seropositive non-drug abusers and HIV seronegative METH abusers. Furthermore, levels of creatine were lowest in the HIV-infected METH abusers in the basal ganglia (-7.4%) indicating possible alterations in cellular metabolism, while levels of the glial marker myo-inositol were increased in frontal white matter. This study demonstrates not only neuronal damage in the frontal lobe and basal ganglia for HIV-infected patients and for METH abusers, but also the concerted effect (i.e., additive) of HIV infection and METH abuse on these brain structures. Furthermore, DA nuclei in the SN, a critical area of the mesolimbic DA pathway due to its DA productive capacity and efferent projections, may be more vulnerable to the effects of HIV+METH or COC abuse than HIV alone (Reyes et al., 1991).

It should be noted, however, studies that show increased cognitive impairment in HIV-infected drug abusers (e.g., Grassi et al., 1997) are in stark contrast to studies that show no difference in HAD incidence between drug abusers and non-abusers (e.g., Selnes et al., 1997). Jernigan et al. (2005) recently demonstrated no differences in brain volume between HIV-infected/METH abusers and non-infected/non-METH abusers using MRI scans of a multiple areas including the thalamus, basal ganglia structures including the nucleus accumbens and caudate nucleus, hippocampus, amygdala, and the four outer lobes of the cerebral cortex. Both of these groups have increased brain volumes relative to HIV-infected/non-METH abusers, with greatest effect sizes in the caudate nucleus, hippocampus, and frontal and temporal lobes. As reviewed earlier, perhaps the most interesting finding from this study is increased brain volume for non-infected/METH abusers relative to non-infected/non-METH abusers, specifically in the caudate nucleus, lenticular nucleus, nucleus accumbens, and parietal cortex. In fact, effect sizes for increased brain volume for this group is comparable to effect sizes for decreased brain volume for HIV-infected/non-METH abusers relative to controls. The authors note that perhaps the merging of two opposing groups with respect to brain volume, as represented by the HIV-infected/METH abusers, offsets brain volume changes and this explains why no change is noted for HIV-infected/METH abusers relative to controls. This explanation needs more support in research, and a replication of this study would certainly be warranted given the unexpected findings in human participants. Further, the apparent lack of effect in the context of human data supporting concerted toxicity raises an important point; namely, that more research on HIV-infected COC and/or METH abusers, in conjunction with SIV-infected, contingent drug administering non-human primates, needs to be performed in order to fully assess the concerted effects of these drugs with HIV on a structural/systems level.

2.4. Section Summary and Conclusions

The potential for widespread damage and cell death in the CNS has been established in the HAD literature. Research has made apparent that a variety of HIV infected and non-infected cells (e.g., brain endothelial, neurons, glia) are vulnerable to a farrago of neurotoxic mechanisms brought on by several HIV virotoxins and infected immunotrophic cells, most of which occur in parallel. Hence, exact temporal sequencing of HIV mediated neurotoxicity is difficult, if not impossible at this point in time. Nevertheless, imaging studies of both humans and animals have demonstrated vulnerability to subcortical brain structures, and DA systems in particular. Clinical observation supports many of these studies by demonstrating the similarity between symptoms of HAD and symptoms of other subcortical dementias like Parkinson's disease and Huntington's disease. Furthermore, the effects on DA systems within the CNS may be more severe for the one-third of the HIV population who are also abusing drugs. However, more research with this population need to be performed as the limited data is inconclusive as to HIV's interaction with COC or METH. Figure 1 provides a schematic summary of major, consistent findings in the HIV and the HIV+COC or METH abuse literatures, while Table 1 directs interested readers to specific reviews of some of the relevant topics covered in this section. Note that most of the research presented in this section was selected from studies using human subjects, the purpose of which was to provide evidence for *where* the virus most affects the CNS. Using data from this population, researchers can now use human and animal models to investigate *what* aspects of the virion are most detrimental to brain parenchyma.

3. What Makes HIV and Cocaine/Methamphetamine Neurotoxic?

3.1. HIV Proteins

HIV neurotoxicity and related mechanisms of action are mediated by a number of HIV structural and regulatory proteins (Di Stefano et al., 2005). The purpose of this section is to provide evidence as to *what* aspects of HIV make the CNS vulnerable. Therefore, evidence for the location of a few of the proteins in CNS parenchyma, as well as evidence that they mediate both entrance into the BBB and neurotoxicity, is reviewed below. Specifically, a description and review of neurotoxicity of two of the most heavily studied proteins, gp120 and Tat, is provided.

Briefly, with respect to breaching of the BBB, several studies have shown that Tat and gp120 mediate upregulation of several endogenous proteins involved in BMEC/leukocyte adhesion and diapedesis, and can cross the BBB independent of the virus (Banks et al., 2005). For example, under normal conditions peripheral leukocytes utilize endogenous adhesion proteins to first roll along endothelial cells in order to subsequently slow their velocity and adhere. HIV infection of leukocytes have been shown to increase expression of adhesion molecules on the surface of BMEC, such as E-selectin and vascular cell adhesion molecule (VCAM) -1 (Nottet et al., 1996); a process which may be mediated by the Tat protein (Hofman et al., 1993). Adhesion molecule upregulation is not restricted to BMEC. Tat has been shown to up-regulate adhesion molecules, such as β -integrins, on the surface of leukocytes as well (Lafrenie et al., 1996). This upregulation of adhesion molecules on both BMEC and infected leukocytes slows leukocyte rolling and enhances leukocyte/BMEC binding, thereby giving HIV infected leukocytes an enhanced adhesion to BMEC (Nottet, 2005). This Tat and/or gp120 induced enhancement in rolling and adhesion to the BMEC increases the likelihood of HIV breaching the BBB. Whether Tat actively breaching the BBB, independent of the virus (Banks et al., 2005), induces additional neurotoxicity is not known, but given evidence for a monotonic dose-neurotoxic response to Tat (Bansal et al., 2000), one can speculate a scenario of increased neurotoxicity and weakening of the BBB. The rest of this section will review evidence for the mediation of Tat and gp120 in HIV-induced neurotoxicity. Figure 2 provides a schematic analogue to the rest of Section 3.

3.1.1. Glycoprotein 120 (gp120)—Gp120 is a structural protein located exteriorly, part of the envelope of HIV. It provides a means for HIV to bind to target cells in order to ultimately infect the host. Gp120 has been shown to bind to CD4 receptors and chemokine co-receptors, and is essential for infection of the host. Perhaps more importantly for neuroAIDS research is the fact that a substantial amount of gp120 is shed from the viral envelop surface into the CNS milieu once the virus has successfully bound and/or fused to the target cell (Moore and Klasse, 1992). Gp120 has been shown to be a mediator of neurotoxicity independent of HIV and other viral proteins. Despite this, location or isolation of gp120 in the CNS of HIV positive patients has been a daunting task (Kandaneeratchi, 2005). Jones et al. (2000) successfully immunolocalized gp120 in brain parenchyma using an anti-gp120 antibody. Injection of gp120 into rat brains has been shown not only to cause DNA fragmentation (Bagetta et al., 1995), but *in-vivo* and *in-vitro* application of gp120 has been shown to be neurotoxic with varying amounts, as small as 1 pM concentration (Brenneman et al., 1998) and 100 ng (Barks et al., 1995). Furthermore, gp120 is toxic across multiple species and cells including human neurons (Lannuzel et al., 1995), human astrocytes (Pulliam et al., 1993), and rat neurons (Diop et al., 1994) (for more complete list, see Nath and Geiger, 1998). An *in vivo* dose-response study demonstrated no toxicity at 100 ng of gp120, significantly greater level of toxicity at 250 ng of gp120, and the greatest level of toxicity at 400 ng of gp120, indicating a dose-response in the striatum of the rat (Bansal et al., 2000). This toxicity was not present when given injections of immunoabsorbed gp120, indicating gp120 is a likely mediator of neurotoxicity (see also, Turchan et al., 2001). Functionally, injection of gp120 in rats has impaired development of motor abilities resembling HAD in humans (Hill et al., 1993). Impairment on water maze tasks has also been noted (Glowa et al., 1992), as well as gp120-induced impairment in sensory-motor function (Fitting et al., 2006a), and long-term alterations in DA-based inhibition of the startle response (Fitting et al., 2006b). This shows that molecular impairment from even a single HIV protein can result in clinical HAD symptoms in an animal model.

3.1.2. Transactivator of Transcription (Tat)—Tat is a regulatory protein that facilitates but is not limited to HIV gene transcription and HIV RNA processing, so it is of “pivotal importance” for HIV gene expression (Di Stefano et al., 2005). Hudson and colleagues (2000) detected Tat mRNA in brain tissue from a number of HIV-positive human brains and the Tat protein from rhesus monkeys infected with SIV. Tat is the only HIV protein actively released by HIV infected cells (Ensoli et al. 1993), and can influence areas of the CNS far from the infected area (Bruce-Keller et al., 2003; Chauhan et al., 2003). In fact, recent evidence shows that Tat can be released extracellularly and transported axonally (Chauhan et al., 2003) across multiple brain regions including transport from striatum to the SN (Bruce-Keller et al., 2003). This transported Tat was also associated with reductions in motor performance, neurotoxicity, and glial response in the SN; this being the first demonstration of Tat immunolocalizing, inciting neurotoxic and glial response, and altering motor performance at a site distal, yet anatomically connected, to the infected brain area (Bruce-Keller et al., 2003).

Tat not only serves in HIV gene expression; a number of *in vivo* and *in vitro* studies have shown that it is neurotoxic. Maragos and colleagues (2003) showed both *in vivo* and *in vitro* neurotoxicity to areas within the rat and human hippocampus, respectively. They noted destruction of neurons in CA3, while neurons in CA1/CA2 were relatively spared for both human (*in vitro*) and rat (*in vivo* injections) hippocampal slices. Interestingly, this is a similar finding to the Masliah et al. (1992b) observation of a 50% to 90% decrease in the number of CA3 interneurons in HAD patients, with relative sparing of CA1 and CA2 interneurons (see Section 2.1.2.2.).

Apropos to the apparent neuronal subtype selectivity illustrated by Tat neurotoxicity in this investigation, some researchers point out that Tat toxicity may be cell/neuron specific and even species specific (Nath and Geiger, 1998). They point to mixed results with respect to Tat

neurotoxicity. On one hand extracellular Tat, but not the Tat gene, has been shown to be toxic to neuroblastoma cells (Zauli et al., 1993). On the other hand, they note that a different neuroblastoma cell line was not damaged when exposed to Tat (Kolson et al., 1994); hence, their suggestion of cell specific interactions with the Tat protein. Of further example is how studies using rat neuronal cell cultures did not show Tat mediated toxicity (e.g., Kolson et al., 1993), but that human neurons are susceptible to Tat toxicity (e.g., Nath et al., 1996); hence, their suggestion of species specific interactions with the Tat protein. However, it is important to highlight that other investigations have found Tat to be neurotoxic to rat brains (e.g., Hayman et al., 1993) and rat brain cells in culture. For example, an *in vivo* dose-response study demonstrated no toxicity at 1 µg of Tat, significantly greater level of toxicity at 5 µg of Tat, and the greatest level of toxicity at 50 µg of Tat, indicating a dose-response in the striatum of the rat (Bansal et al., 2000). Furthermore, this toxicity is not present when given injections of immunoabsorbed Tat, heat-inactivated Tat, or mutant Tat (δ 31-61) (Aksenov et al., 2003, 2006; see Turchan et al., 2001 for direct manipulation); indicating activated Tat is a mediator of neurotoxicity.

3.1.3. Tat+gp120 Concerted Neurotoxicity—The distinct contribution of each HIV protein to the neurotoxicity associated with neuronal injury as described above is an important consideration when attempting to understand disease pathology. Nevertheless, it is obvious that viral proteins are rarely isolated from the rest of the virion. Thus, in order to get a complete understanding of the neurotoxicity of HIV, one must decipher the toxicity of viral proteins in concert. Research into this and related issues are relatively new, but some seminal investigations have surfaced in regard to combined neurotoxicity of Tat and gp120.

Bansal et al. (2000) demonstrated the distinct, isolated toxicity of Tat and gp120. This same investigation also underscores the toxicity of Tat and gp120 acting in concert; a scenario which is more likely to manifest in the course of infection with HIV. They demonstrated that Tat + gp120 injected into the rat striatum induced a greater degree of neurotoxicity and reactive astrogliosis than either one of the proteins injected alone. This *in vivo* study was a follow-up to support a seminal *in vitro* study which demonstrated greater toxicity of Tat + gp120 to cultured neurons, relative to toxicity of either viral protein alone (Nath et al., 2000a).

Given the evidence for combined neurotoxicity of Tat + gp120, as well as evidence for sole neuroalterations of COC or METH (see Section 2.2.), particularly with respect to DA systems, it is likely that any combination of Tat, gp120, COC, and/or METH produces a concerted, and likely synergistic neurotoxicity that is of a magnitude which exceeds any of the aforementioned alone.

3.2. Tat, gp120 + Cocaine and/or Methamphetamine Concerted Neurotoxicity

In vitro studies show neuronal damage and death when exposed to COC or METH + Tat or gp120. Often times, data from these studies is what drives the theoretical notion of a synergistic neurotoxicity associated with HIV(-proteins) + COC or METH. For example, cultured neurons have died when exposed to HIV-infected cell supernatants in combination with COC or METH (Koutsilieri et al., 1997). Another study showed a dramatic increase in percent of cell death of Tat or gp120 when combined with either METH or COC; on the order of 500 µM and 16 µM of METH and COC, respectively (Turchan et al., 2001). The synergistic neurotoxicity was dose dependent, decreasing with lower levels of METH or COC, while both Tat and gp120 were kept to subthreshold levels of toxicity. Therefore, it is likely that subthreshold levels of HIV proteins synergize with COC or METH to reach neurotoxic levels. Other researchers have shown synergistically higher levels of cell death with Tat+COC as well (Aksenov et al., 2006; Kendall et al., 2005), a synergism that was abrogated through pretreatment with D1 receptor antagonist, SCH23390 (Aksenov et al., 2006).

To date, there have been no published *in vivo* investigations on the effects of Tat or gp120 +COC. However, studies of the synergistic neurotoxicity of Tat or gp120+METH have supported findings from *in vitro* cell culture systems. Using HPLC, researchers found that the combination of METH + Tat produced over a 60% reduction in DA levels in the rat striatum (Maragos et al., 2002). This percentage stands out relative to only a 7% reduction in the METH-only group and an 8% reduction in the Tat-only group. Maragos et al. (2002) also found a greater than 50% reduction in DAT binding. This finding was replicated recently with the demonstration of a 61% reduction of DA, and a 54% reduction of DOPAC, in the striatum of Tat+METH treated rats using HPLC, as well as significantly increased silver staining in the Tat+METH treated animals (Theodore et al., 2006a). These authors theorize the degeneration of DAergic nerve terminals as a result of these reductions in combination with increased silver staining (Theodore et al., 2006a). Brain microdialysis, when used to analyze the levels of HA, DOPAC, and DA following intrastriatal injections of Tat, METH, or Tat+METH, supports other research in highlighting DA system vulnerabilities (Cass et al., 2003). Most notably, injections of Tat+METH was comparable to multiple-fold reductions in striatal DA, DOPAC, and HA relative to injections of either Tat or METH alone (Cass et al., 2003; Nath et al., 2002).

3.3. Section Summary and Conclusions

In vivo and *in vitro* studies indicate that multiple HIV proteins are responsible for cell damage and death in the CNS, and this paper reviewed the two most commonly investigated: Tat and gp120. When Tat and gp120 are combined with COC or METH abuse an even greater level of toxicity is induced relative to either agent alone. Research from literature investigating single HIV-proteins converges with data from human HIV-infected patients demonstrating toxicity to DA neurons in the hippocampus, and in subcortical areas like the striatum and SN. Furthermore, transport of individual proteins (i.e., Tat) has been demonstrated in subcortical structures in an animal model (Bruce-Keller et al., 2003). Figure 2 provides a schematic summary of major, consistent findings with Tat and gp120-induced neurotoxicity, and Tat/gp120+COC and/or METH synergistic neurotoxicity, while Table 1 directs interested readers to specific reviews of some of the relevant topics covered in this section. Note that most of the research presented in this section was selected from studies using either animal subjects *in vivo*, or *in vitro* culture systems, the purpose of which was to provide evidence for *what* aspect (s) of the virus most affects the CNS. These models allow researchers to partition the virion, to more precisely investigate individual and concerted effects of individual HIV-proteins in a selected region of interest, thus establishing *what* aspects of the virion are neurotoxic. Using data from *where* HIV most affects the brain as demonstrated by data from human participants, as well as *what* aspects of the virion induce neurotoxicity as demonstrated by animal and cell culture systems, researchers can now use human and animal models to investigate *how* HIV induces neurotoxicity.

4. How is HIV and Cocaine/Methamphetamine Neurotoxic?

4.1. Mechanisms of HIV and Cocaine/Methamphetamine Neurotoxicity

Over the last two decades, multiple different, but likely interrelated mechanisms of neurotoxicity have emerged from the NeuroAIDS literature. These mechanisms can be broadly defined as neurotoxicity from *direct* influences of HIV(-proteins) on neuronal integrity and survival, and neurotoxicity from *indirect* influences of HIV(-proteins) on neuronal survival via HIV-induced aberrant functioning of glial cells in the brain. Note that mechanisms such as calcium imbalance, apoptotic cascades, mitochondrial dysfunction, and excitotoxicity exceed the limits of this review, or are included as part of these two broadly defined mechanisms and will be discussed in context. For example, neuronal mitochondrial dysfunction is often considered a means for HIV to directly induce oxidative stress in the neuron without the indirect

influence of cytokine and chemokine upregulation. Thus, mitochondrial dysfunction and cytokine expression are discussed in the context of direct and indirect mechanisms. Regardless, these broad mechanisms are interrelated in that they may form a positive feedback cycle in which HIV first either directly or indirectly induces oxidative stress, which then initiates aberrant responses from the endogenous immune system, thereby inducing more stress through oxidative processes. Thus at a more advanced stage of the HIV-infection, oxidative stress may be increased both by the virus itself, and by reactivity of the immune system. Evidence for this cycle resides in years of evidence supporting both direct and indirect mechanisms individually as *the* major contributor of neuronal injury/death, to the extent that a multitude of evidence has gathered to support *both* mechanisms as major contributors. It is also apparent that both mechanisms may arise independently of one another. Thus, one of the many debates that remain is whether a direct or indirect mechanism initiates neuronal injury; that is, which mechanism *triggers* HIV-induced neurotoxicity? This question may seem trivial, however it has massive implications in developing effective CNS directed therapy. If, in fact, HIV and/or HIV virtoxins initiate both direct and indirect neurotoxicity, then therapy is completely relevant only when both mechanisms can be extinguished.

The following sections will review the oxidative stress mechanism of neurotoxicity first in terms of how it may be induced indirectly through aberrant immune activation, and second in terms of a direct contribution of HIV and/or its proteins to neurotoxicity.

4.1.1. HIV Infection—Oxidative stress is the alteration and damage of molecules and cells by increased accumulation of free radicals/reactive oxygen species (ROS) relative to antioxidants in the body. Researchers are discovering oxidative stress and accumulation of ROS may be a forerunner in mediating neuronal and glial injury/death, as the balance of oxidant and anti-oxidant substrates has repeatedly demonstrated a tilt favoring oxidation even early after exposure to HIV-proteins (see Pocernich et al., 2005; Steiner et al., 2006). Demonstrations of oxidative stress in the CNS of HAD patients exist (Turchan et al., 2003). Further, oxidative stress may be correlated with HIV-induced neuropsychological impairment (Turchan et al., 2003). This is partly due not only to the fact that HIV proteins and aberrant immune activation mediates the accumulation of ROS, but also to the fact that some antiretroviral therapy based on nucleoside reverse transcriptase inhibitors (NRTI) has been shown to increase oxidative stress (Hulgan et al., 2003) and may be toxic to mitochondria (Lewis et al., 2003). Valcour and Shiramizu (2004) highlight the fact that factors which may accompany HIV infected individuals such as tobacco use, illicit drug use, antiretroviral medication, and the normal aging process will inevitably contribute to additional amounts of oxidative stress. An aging, HIV-infected, drug abuser on antiretroviral medication represents a large proportion of the human population to be concerned, so increasing prevalence of neuropsychological impairment mediated by oxidative stress is conceivable, and expected by some researchers.

The following scenario is one example of how HIV, or HIV+COC, and/or METH may incite increased production of ROS or reactive nitrogen species (RNS) by facilitating the increase of a host of catalysts or precursors, such as superoxide ion (O_2^-) and nitric oxide (NO). Indeed, perhaps one of the most studied free radicals known to increase during HIV infection and METH abuse is NO. Inducible-NO synthase (iNOS) is an enzyme that converts L-arginine to ultimately lead to production of NO, which is released endogenously from cells even in non-infected individuals. HIV+COC or METH has been shown to “tip the oxidant scale” by increasing production of this free radical and iNOS (Boven et al., 2000a). NO may be a weak direct neurotoxic free radical, but it is also thought to be associated with NMDA receptor/ glutamate initiated neurotoxicity (Snyder, 1992). Further, the level of neurotoxicity can be enhanced when superoxide ion interacts with NO to form peroxynitrite ($ONOO^-$). Increased production of superoxide ion is countered by increased production of the scavenger, superoxide dismutase (SOD), in order to keep levels of O_2^- low (Coyle et al., 1993; Mollace et al.,

2001). Unfortunately, NO outcompetes SOD for O_2^- when present in large amounts (Beckman et al., 1996), as in HAD patients and METH abusers; so that ONOO⁻ production is not withheld. SOD's counteraction is "paradoxical", as Mollace and others have pointed out (2001); because, while SOD acts to protect from O_2^- , it can catalyze the neurotoxic mechanism of ONOO⁻. ONOO⁻ is thought to target structural proteins of neurons, especially neurofilament protein that provides stability to the neuronal structure (Beckman et al., 1996; Coyle et al., 1993). The oxidative stress scenario described above not exclusive, but is commonplace, as a mediator of neurotoxicity in HIV infection, COC or METH abuse, and the combination of any of the two.

Apropos to indirect HIV influence over neurons, HIV infection of (or gp120 and Tat exposure to) microglia and astrocytes leads to increased production of O_2^- , leading then to increased ROS and RNS such as NO, further leading to other harmful toxins such as ONOO⁻, as well as other catalysts necessary for many of the reactions describe above, like iNOS for example (Floyd et al., 1999; Mollace et al., 1995). ROS can also be released from BMEC as well as macrophages from the periphery, which not only induces neuronal death, but breakdown of the BBB itself. For example, HIV-exposed macrophages have been shown to produce iNOS (Boven et al., 1999, 2000a) and superoxide ion (Boven et al., 1999), and BMECs have been shown to produce iNOS (Boven et al., 2000a). The culmination of ROS and inducible enzymes may lead to up-regulation of peroxynitrite in proximity to the BBB, perhaps acting as a mechanism for increased breakdown of the BBB. This increased ROS production has also been demonstrated with cortical astrocytoma cells (Mollace et al., 1993) and neurons (Dawson et al., 1993) exposed to gp120. Researchers have also shown that proinflammatory cytokines such as tumor necrosis factor alpha (TNF α) and interleukin-1 beta (IL-1b) up-regulate iNOS (Mollace et al., 2001). IL-1b has also been shown to invoke oxidative stress on cultured glial cells. The fact that HIV proteins have been shown to up-regulate cytokine release (e.g., Floyd et al., 1999) and induce oxidative stress through glial cells provides evidence for an indirect, glial-dependent route of neurotoxicity.

However, there is some debate in the field as to whether or not direct or indirect influence of HIV on neurons is a "trigger" for the handful of other neurotoxic mediators in HIV-infection. Recent studies helped lay the foundation in favor of a direct influence of HIV as the trigger mechanism (Aksenov et al., 2001, 2003, 2006). These investigators found that the HIV Tat protein induces oxidative damage in the rat brain and they highlighted the temporal characteristics of the neurotoxicity. In one study, injections of 5 μ g, 15 μ g, or 50 μ g of Tat were administered unilaterally into the striatum of the rat (Aksenov et al., 2001). Of note is the discovery that protein carbonyls (indicator of oxidative stress damage) and levels of Glial Fibrillary Acidic Protein (GFAP) are significantly increased seven days post-Tat injection. Another study demonstrated that oxidative stress, and not reactive astrocytosis occurs within two hours of Tat-administration (Aksenov et al., 2006). These authors theorize that oxidative stress occurs early after the injection of Tat and continues for multiple days, whereas reactive astrocytosis occurs later and is noticeable only after seven days post-injection. Since a single acute injection of Tat would likely clear from the extracellular milieu by day seven, then it is possible that the initial and lingering oxidative damage "triggered" reactive astrocytosis at a later time-point.

Until 2003, this hypothesis was almost purely theoretical as a more detailed replication of the temporal characteristics of HIV neurotoxicity needed to be established. Therefore, Aksenov and colleagues (2003) followed their previous study with such an investigation. Following a single microinjection of Tat₁₋₇₂ into the rat striatum, they stained for protein carbonyl levels, OX-42 positive microglia, and GFAP levels at times of two hours, twenty-four hours, seven days, and thirty days post-injection. They replicated earlier studies by observing a significant increase in protein carbonyl levels as early as two-hours post injection and continuing through seven days, while OX-42 immunoreactivity was increased only after twenty-four hours, and

GFAP levels increased only after seven days. This study demonstrates that oxidative stress is an initial mechanism in HIV-associated neuronal injury; present as early as two hours after exposure to Tat, followed by immune response by microglia, and finally reactive astrocytosis. This demonstration has since been replicated and extended to show a Tat-induced depolarization of the mitochondrial membrane potential very early (2 hr.) after Tat administration (Aksenov et al., 2006; Maragos et al., 2002). Mitochondrial membrane depolarization, in conjunction with evidence for mitochondrial toxicity (Turchan et al., 2001) suggests that the mitochondria may be “leaking” ROS prior to reaction from glial cells. Accumulation of ROS not only facilitates oxidative stress (i.e., degeneration of cellular components and cellular function), but also acts as a signal for the initiation of pro-apoptotic cascades (Oh and Lim, 2005). Studies have demonstrated Tat-induced initiation of apoptotic cascades, possibly mediated to accumulation of ROS (Kruman et al., 1998). In at least one study, Tat induced apoptosis was prevented by inhibiting iNOS (Kruman et al., 1998), and other studies have demonstrated antioxidant-induced prevention of ROS-induced apoptosis (Oh and Lim, 2005).

Given evidence for a direct Tat/neuron interaction, interest in neuronal membrane- and cytosolic-protein/Tat interactions has been increasing. Most of the research in this area has focused on NMDA receptor (NMDAR)/Tat interactions (see King et al., 2006) mediating apoptotic cascades, calcium imbalance and excitotoxicity. Complete review of glutamatergic NMDAR exceeds the purpose of the review (see King et al., 2006). Nevertheless, Tat/NMDAR mediated toxicity likely effects DA systems; and research in our laboratory (Silvers et al., 2007) has recently demonstrated a D1 receptor/Tat interaction, whereby Tat-induced neurotoxicity to rat fetal midbrain cell cultures was abrogated by a D1 receptor antagonist (SCH23390) where D1 receptor binding was abundant. Interestingly, this study demonstrated a lack of SCH23390-mediated attenuation of Tat-induced neurotoxicity to fetal hippocampal culture, where D1 receptor binding is low. The correlation between D1 receptor binding and SCH23390 protection from Tat-toxicity demonstrates a possible role for D1 receptors in the neurotoxic mechanism of Tat (Silvers et al., 2007). Furthermore, based on evidence for NMDAR/D1 regulatory and structural heteromeric interactions (Cepeda and Levine, 2006; Missale et al., 2006), Silvers et al. (in press) speculate a possible NMDAR/D1 reciprocal regulation of pro-apoptotic cascades, mediated by Tat and/or Tat-induced ROS. Taken together, these studies (Aksenov et al., 2001, 2003, 2006) provide evidence that HIV proteins may directly increase oxidative stress to neurons by inducing mitochondrial dysfunction and through interactions with membrane or cytosolic bound proteins; thus, they may play an initial, “upstream” role in neuronal injury/death, while immune response may occur later “downstream.” It may also be the case that HIV-induced ROS interacts with these proteins to trigger pro-apoptotic signaling cascades, or additional oxidative stress in neurons (King et al., 2006; Kruman et al., 1998; Silvers et al., 2007). Table 2 provides representative research performed on DA systems within the last few years which demonstrate a possible time-course of effects following an acute injection or administration of Tat and/or gp120. Of note is the early effect of HIV on the mitochondria and DAT, and an increase in oxidative stress, followed then by immune response mechanisms.

In summary, there is a debate as to whether a direct HIV-protein/neuron interaction is the trigger for neurotoxic mechanisms in the grand scheme of HIV neurotoxicity, as suitable counter-arguments to such a theory exists. Research on indirect mechanisms of HIV-induced neurotoxicity have demonstrated that an HIV-infected immune system can degrade the BBB and incite increased production of neurotoxic cytokines and chemokines which generate free radicals; thereby switching which mechanism should be considered “upstream.” Indeed, peripheral CD4⁺ immune cells are the first to be infected with the virus, which ultimately transport the virus into the CNS. Nevertheless, more direct mediators of neurotoxicity such as mitochondrial dysfunction and oxidative stress has been noted much earlier than microglial

and astrocyte response, as well as alterations in neuronal transmembrane proteins (Aksenova et al., 2006; Wallace et al., 2006a). Answering which mechanism comes first is currently beyond the scope of this review. Further, it is useful to consider not multiple distinct mechanisms of toxicity, but one large mechanism of oxidative stress, mitochondrial dysfunction, aberrant immune response, and apoptotic cascades in which a positive feedback cycle develops, gaining momentum as more areas of the brain and BBB succumb to the virus.

4.1.2. Cocaine Mechanisms—Given the overall lack of evidence for direct COC-induced DAergic neurotoxicity, mechanisms of COC-induced DAergic neurotoxicity are difficult to elucidate. If COC does induce toxicity of DAergic neurons, it is possible to speculate that it would share similar mechanisms of toxicity observed in other non-DAergic neurons or cells in other organ systems. To date, mechanisms associated with COC-induced cytotoxicity overlap with those demonstrated in HIV-induced neurotoxicity and include oxidative stress, mitochondrial dysfunction, and calcium imbalance. Nevertheless, research with respect to mechanisms of DA system toxicity is rare. Given the overall lack of evidence for COC-induced DAergic toxicity, COC's mechanisms at the presynaptic terminal and consequent mechanisms/descriptions of neuroplasticity is reviewed below. COC-induced neuroplasticity may have serious implications for chronic COC-abusers who contract HIV in the course of addiction (See section 4.1.5.1.).

COC is generally considered a “dirty drug.” This term is attributed COC's non-specific mechanism of action in the CNS, as it binds and blocks noradrenergic (NET), dopaminergic (DAT), and serotonergic (SERT) transporters. Extracellular DA concentrations under normal conditions are the net result of release (exocytosis) and clearance (uptake) from the extracellular space. Re-uptake through the plasma membrane DAT is the primary mechanism for the regulation of extracellular DA concentrations, and thus, the most effective means of terminating DA actions at postsynaptic and presynaptic receptors (Gainetdinov and Caron, 2003). COC-induced blocking of DAT thereby prevents reuptake and leads to overflow of DA in the synaptic space. The ensuing extracellular increase in DA is generally accepted as the primary rewarding/reinforcing property underlying COC's efficacy at multiple transporter sites, also increasing locomotor activity and inducing stereotypical behavior. (Johanson and Fischman, 1989). Consequent to increases in extracellular DA level, especially in the course of repeated administration, neuroalterations in surface/cytosolic proteins among other molecules ensue. This up- or down-regulation of molecules is understood to be the initiating events in the cascade of COC-induced neuroplasticity leading to craving and dependence. For example, the ensuing, transient rise in extracellular levels of DA are thought to immediately precede and perhaps trigger trafficking of DAT to the plasmalemmal surface of pre-synaptic nerve terminals, as the dynamic regulation of DA clearance involves modulation of cell surface transporter expression (Loder and Melikian, 2003; Melikian and Buckley, 1999; Sorkina et al., 2005), especially in the context of increased DA overflow. Representative COC-induced alteration of the DAT in humans was reviewed in Section 2.2.1. Animal and cell culture models support findings reported in humans. For example, DAT transport activity, plasma membrane expression, and phosphorylation level are acutely modulated by exogenous kinase and phosphatase treatments (Doolen and Zahniser, 2002; Vaughan et al., 2004), which in turn may be effected by chronic COC abuse. For example, evidence suggests COC may either down-regulate (Cowell et al., 2000), or have no affect on DAT phosphorylation. COC has been shown to prevent METH-induced phosphorylation increases, suggesting that COC may possess an independent effect on DAT phosphorylation (Cervinski et al., 2005). Furthermore, COC exposure increases the maximal rate of [³H]DA uptake and DAT cell surface expression in rat nucleus accumbens and human DAT-transfected N2A cells (Daws et al., 2002; Little et al., 2002). COC, when administered with amphetamine or METH, blocked the reduction in the maximal rate of [³H]DA uptake and the METH-induced down-regulation of DAT expression in the plasma membrane (Chi and Reith, 2003; Kahlig et al., 2004; Saunders et al., 2000;

Sorkina et al., 2003). It is becoming increasingly understood that vesicular monoamine transporters (VMAT), particularly VMAT2, are correspondingly up-regulated and increase cytosolic uptake of DA upon repeated COC administration as well (Brown et al., 2001; Riddle et al., 2005; however see Wilson and Kish, 1996). DA D2 autoreceptors have also been shown to be down-regulated in chronic COC abusers (Moore et al., 1998; Nader and Czoty, 2005), but this is not entirely clear as D2 increases (Sousa et al., 1999) and no change (Stanwood et al., 2000) has been noted in other model systems.

Additionally, post-synaptic alteration upon repeated or chronic COC administration is apparent, but the exact mechanism and characterization of the alterations are less clear (see Anderson and Pierce, 2005 for additional review). Specifically, D1 receptors have been demonstrated to down-regulate (Laurier et al., 1994) or remain unaltered (Sousa et al., 1999) in the context of repeated COC administration. This may be mediated by persistent COC-induced up-regulation of cAMP and CREB (see Anderson and Pierce, 2005). It follows then, that alterations in the molecules and their respective activity may be a compensatory process to the aberrant increase in extracellular DA cause by DA blockers (Riddle et al., 2005), which in turn have implications for HIV-infected COC abusers (See section 4.1.5.1.).

4.1.3. Methamphetamine Mechanisms—Just as in HIV infection, the exact mechanism (s) of METH neurotoxicity remains under investigation, however, there is a large overlap between mechanisms of METH-induced neurotoxicity and mechanisms of HIV (or Tat/gp120)-induced neurotoxicity. In other words, it is likely that generation of ROS leading to oxidative stress, mitochondrial dysfunction, excitotoxicity/calcium imbalance, and dysregulation of monoamine transporters are heavily involved in METH-induced neurotoxicity (Cadet and Brannock, 1998; Quinton and Yamamoto, 2006).

With respect to oxidative stress mechanisms, researchers have noted increased free radicals/ROS upon administration of METH (e.g., Imam et al., 2001). A number of other researchers have noted oxidative stress *in vitro* (e.g., Cubells et al., 1994), as well as in transgenic mice (e.g., Cadet et al., 1994), to both DA and non-DA neurons. Cadet and Brannock (1998) point out the effects of oxidative stress extends beyond monoaminergic systems in METH abuse. Furthermore, administration of various antioxidants has been shown to mitigate METH-induced neurotoxicity (Fukami et al., 2004). Cadet and colleagues (1994, 1998) have noted that superoxide radicals are important in mediating neuronal toxicity. In transgenic mice with up-regulated SOD, METH-induced toxicity of DA neurons was less than 8%, while toxicity was at 58% or greater with wild-type litter mates. Since SOD is a scavenger of superoxide and toxicity was decreased upon upregulation of SOD, then superoxide must be a mediator of neuronal toxicity. Also, blocking the synthesis of NO using any one of a number of agents (e.g., Nitroarginine and Monomethyl-L-arginine in Kontur et al., 1991) attenuates a METH-induced, dose-dependent toxicity to neurons *in vitro*. Specifically, blocking NO attenuated a 1.5 mM and 3.5 mM METH dose that was associated with a 50% and almost 100% loss of neurons, respectively.

Furthermore, persistent DA overflow and DAT has been implicated as playing a significant role the course of METH-induced neurotoxicity. Researchers have pointed out that striatal DAergic neurons may be sensitive to METH induced toxicity as a result of the abundance of DAT in this area (Eisch et al., 1992; Hanson et al., 2004). This may be due to the fact that METH is a DAT substrate that raises extracellular transmitter levels by competing with endogenous DA for transport and inducing DA efflux through transport reversal (Eshleman et al., 1994; Sulzer et al., 1995). With this mechanism of regulation, acute application of METH would reduce DA uptake not only by direct competition for uptake, but also by reducing the available cell-surface DAT. This may also be true for intracellular VMAT2, leaving unsequestered DA in the cytosol.

Results from *in vivo* voltammetry studies show that COC and amphetamine decrease DAT function by reducing DA clearance (Cass et al., 1993; Zahniser et al., 1999). Moreover, phosphorylation of DAT was increased by *in vitro* treatment with METH in cell line and in rat striatal tissue by *in vitro* application or *in vivo* injection of METH (Cervinski, MA et al., 2005). Thus, acute treatment with amphetamine and METH reduce the maximal rate of [³H] DA uptake and results in DAT redistribution away from the plasma membrane (Chi and Reith, 2003; Kahlig et al., 2004; Sandoval et al., 2001; Saunders et al., 2000; Sorkina et al., 2003). Further, acute METH administration in animals with levels comparable to human intake has been shown to reduce DAT binding and reduce DA and its metabolites (Kuczenski et al., 1997; Segal et al., 2003). DAT function has been shown to decrease even upon a single administration of METH, although it is likely that loss of function in this scenario is recovered within 24 hrs. Multiple injections seem to down-regulate DAT function for an extended period of time (for review of single vs. multiple injections, see Fleckenstein et al., 2000). The loss of DAT function has been demonstrated to persist for up to one month after cessation (Eisch et al., 1996), and even after METH has been removed from the medium in synaptosomal preparations (Fleckenstein et al., 1999). Western blot analyses indicated that the decrease in DAT activity may not be attributed to loss of the transporter protein *per se* (Kokoshka et al., 1998), but to a modification of the protein or dysregulation of DAT function (Fleckenstein et al., 2000). To this end, researchers have demonstrated a METH-induced DAT oligomerization as a result of the interaction between reactive quinones and cysteine containing DAT. Extracellular DA overflow and unsequestered intracellular DA form reactive quinones which may further damage neuronal integrity, and further potentiate the inactivation of DAT (Baucum et al., 2004; Hanson et al., 2004; Fleckenstein et al., 2000; Quinton and Yamamoto, 2005).

4.1.4. HIV + Psychostimulant Mechanisms—The mechanism for the synergistic neurotoxicity of HIV+COC or METH is just as unclear, if not more unclear, than the neurotoxicity of HIV alone. There is considerable overlap between mechanisms of HIV neurotoxicity and mechanisms of METH neurotoxicity; and therefore, a prevailing theory on the mechanisms of the synergistic neurotoxicity is that of increased oxidative stress and increased cytokine and chemokine production in the CNS. In fact, the time-course of Tat/gp120-induced effects on DA systems in the brain is altered only in the sense that it makes each effect more severe, (i.e., it may not alter the temporal dynamics).

4.1.4.1. HIV + Cocaine Mechanisms: Kuljis et al. (2002) have demonstrated increases of iNOS in the temporal lobes of HIV-infected COC and heroine abusers. These increases were as high as 40-fold relative to controls. Turchan et al. (2001) also demonstrated an antioxidant-induced abrogation of Tat+COC synergistic toxicity, indicating the oxidative stress is a mediating factor. Other researchers have shown synergistically higher levels of protein carbonyls, a synergistically decreased mitochondrial membrane potential, and synergistic cell death with Tat+COC. Furthermore, this synergism was abrogated through pretreatment with a D1 receptor antagonist, SCH23390, as well as through an antioxidant (Aksenov et al., 2006). These results suggest a D1 receptor mediated increase in ROS, oxidative stress, and neuronal damage. Furthermore, to reiterate from Section 4.1.1., the increased accumulation of ROS may act as a signal for the initiation of pro-apoptotic cascades (Oh and Lim, 2005) that has been demonstrated in the literature on Tat alone (Kruman et al., 1998), and in the literature on COC administration (Aksenov et al., 2006; Fosnaugh et al., 1995). Furthermore, D1 receptors facilitate the release of DA, and DA has been shown to auto-oxidize (Flora et al., 2003; Wrona et al., 1997) to form ROS and reactive quinones. Thus, it is reasonable to expect consistently higher levels of oxidation in the Tat+COC exposed tissue.

While oxidative stress is a prevailing theory on HIV+COC or METH neurotoxicity, another likely contributor to the synergistic toxicity is a more compromised BBB. COC has been shown

to disrupt normal BBB function (Zhang et al., 1998), which can enhance infected macrophage migration (Fiala et al., 1998). Furthermore, researchers have repeatedly demonstrated a COC-induced increase in HIV expression in human microglia cultures of more than 50% (Gekker et al., 2004, 2006). In these studies, Kappa-opioid receptor agonists have been shown to decrease HIV expression, both with and without COC present (Gekker et al., 2004). Additionally, more recent data suggests that inhibiting sigma-1 receptors and transforming growth factor- β 1 attenuates a COC-induced increase in HIV expression in human microglial cultures and in the SCID mouse model (Roth et al., 2005), highlighting involvement of this receptor and cytokines in the potentiation process (Gekker et al., 2006). This attenuation is thought to occur in part by suppression of COC-induced kinase activity.

Currently, there is no published research on the effects of HIV+COC on many pre-synaptic DAergic nerve terminal proteins/molecules (e.g., DAT, TH, and VMAT2). These molecules may be particularly important in the mechanism of the concerted toxicity of HIV+COC. For example, it is possible that COC-induced upregulation of TH and HIV-induced downregulation of DAT may converge to augment extended DA overflow in the extracellular milieu; thus producing higher levels of ROS and reactive quinones, while further triggering D1 receptor apoptotic cascades. This may parallel the toxicity associated with METH alone, whereby DAT activity is down-regulated and DA is released, ultimately forming reactive quinones. Since COC does not inactivate DAT, HIV(-proteins) may fill this role, resulting in a similar mechanism to METH-induced neurotoxicity. Unfortunately to date, this theory is purely speculative, as no research has been done on HIV or HIV+COC's interaction with other proteins important to this process, like VMAT for example.

4.1.4.2. HIV + Methamphetamine Mechanisms: Flora et al. (2003) demonstrated dramatic increases in a number of ROS and cytokines to neurotoxic levels upon administration of Tat +METH; even extending beyond the temporal lobe and into other areas of the cortex, hippocampus, and striatum. Thus, it is reasonable to expect consistently higher levels of oxidation in the Tat+METH exposed tissue, abrogated by antioxidants (Turchan et al., 2001). Of further note is the fact that higher levels of gene expression of pro-inflammatory cytokines, such as TNF- α and IL-1 β , were observed in mice striatal tissue following injection of Tat +METH, relative to Tat and METH alone (Flora et al., 2003). Other researchers have noted the contribution of cytokines in Tat+METH synergistic toxicity (Theodore et al., 2006b). This may be indicative of immune response mechanisms reacting, perhaps in part, to increased oxidative stress.

Tat+METH has also been shown to synergistically increase mediators of BBB degradation, such as cell adhesion molecules (ICAM-1) (Flora et al., 2003). The relatively late onset of HAD corresponds to a late-onset, increased infiltration of the CNS through a compromised BBB (McArthur et al., 1997; Von Geisen et al., 2005). It is likely that since METH increases the permeability of the BBB, this may explain why some HIV-infected METH abusers have a more rapid progression and increased severity of HAD symptoms relative to non-drug abusing patients (Nath et al., 2001, Sporer et al., 2005). Furthermore, researchers have demonstrated that METH can increase HIV replication *in vitro*. Researchers using a Feline model (FIV) for HIV demonstrated as much as a 15-fold increase in replication upon administration of METH (Gavrilin et al., 2002). Increased breakdown of the BBB in combination with increased replication of the virus in an HIV-infected METH abuser may be indicative of saturation of the CNS with HIV, thus leading to the possibility of a more severe and earlier-onset neuropsychological impairment (Nath et al., 2001).

Currently, a few researchers (e.g., Maragos et al., 2002; Theodore et al., 2006a) have published potential mechanisms on the effects of HIV+METH on pre-synaptic DAergic nerve terminal proteins/molecules (e.g., DAT, TH, DA, etc.). They demonstrate a synergistic destruction of

nerve terminals and corresponding reduction in pre-synaptic proteins/molecules. Nevertheless, little research has been done on the contributions these pre-synaptic molecules may possess in the synergistic toxicity of HIV+COC, even before the destruction of nerve terminals. This is especially poignant when considering the role of VMAT2, DAT, and auto-oxidizing DA in the course of METH neurotoxicity (Hanson et al., 2004), and early down-regulation of DAT after Tat administration (Wallace et al., 2006a).

4.2. Therapeutic Strategies

“Where preventive measures fail, biological intervention prevails, hence it is imperative that therapeutic measures be developed that intervene in counteracting the effects of drugs of abuse and HIV infection” (Nath et al., 1999). However, such a task has proven to be daunting given that HIV virotoxins, COC, and METH induce neurotoxicity through a number of interrelated mechanisms such as aberrant immune response and oxidative stress, which may arise independent of each other and ultimately lead to more direct mediation of neurotoxicity via calcium imbalance, mitochondrial dysfunction, excitotoxicity, etc. Given the wide array of potential neurotoxic mediators, in order for biological intervention to prevail therapy needs to be general enough to address each of the potential mechanisms, yet specific enough to effectively root out the problem. Catching the infection early would be fruitful in order to “prevent” the spread of neurotoxic mechanisms and a neurotoxic positive feedback cycle. But again, this leads one back into preventive measures, and with an HIV-infected/drug abusing population, prevention of neurotoxic mechanisms once initiated is difficult. Therefore, the purpose of this section is to briefly review some of the “biological interventions” for HIV-infection that have shown promise to date. Note that this section will not provide an exhaustive account of all possible therapeutic avenues for an HIV-infected psychostimulant drug abuser. Given the co-morbidity of such a condition, one may hypothesize that therapy can extend beyond HIV therapy and include drug abuse treatment as well. Indeed, the extant literature on treatment for psychostimulant drug abuse is expansive, and includes cognitive/behavioral therapy (e.g., for reviews, see Knapp et al., 2007; Shearer, 2007) and pharmacotherapies (e.g., for reviews, see Bubar and Cunningham, 2006; Dwoskin et al., 2006; Lile, 2006; Tanda, 2007; Withers et al., 1995). The latter of which include antidepressants (Dwoskin et al., 2006), serotonin modulation (Bubar and Cunningham, 2006), and endocannabinoid modulation (Tanda, 2007), to name a few. One may theorize that cessation of psychostimulant drug abuse would be beneficial for the HIV-infected population; so in essence, may serve as an intervention in the progression of HIV-related symptomatology. Nevertheless, the current section focuses on more established interventions for HIV in particular, such as antiretroviral therapy, and then extends to more novel interventions such as antioxidant and hormonal therapy.

4.2.1. Antiretroviral Therapy (ART)—Antiretroviral regimens such as HAART have decreased the incidence of HIV/AIDS (Sacktor et al., 2001); nevertheless, the prevalence of HIV/AIDS is on the rise given the fact that HIV-infected individuals on ART are living longer (UNAIDS/WHO, 2007; Neuenburg et al., 2002). The CNS acts as a noteworthy reservoir for HIV and HIV replication (Nath and Sacktor, 2006), as some ART medications only weakly penetrate the BBB (Petito et al., 1999). Therefore, not only is prevalence of HIV/AIDS increasing, but prevalence of HAD and HIV sensory neuropathies are ever increasing (McArthur et al., 2003). Furthermore, strict adherence to ART is necessary since HIV replicates rapidly and if viral suppression is not achieved, then the virus will develop resistance to ART. The HIV-infected drug abuser may have considerable trouble in maintaining the strict adherence to ART (Avants et al., 2001; Malone and Osborne, 2000; Sorensen et al., 1998). Therefore, given the high probability of inconsistent self-medication in this population ART may not be the gold standard for all patients, especially considering that inconsistency would supply a means for viral-resistance. Perhaps even more problematic for those on ART is the

potential for mitochondrial toxicity (Peterhans, 1997). ART based on NRTI's inhibit normal DNA function and promotes oxidative stress which is toxic to mitochondria (Lewis et al., 2003) which lends to the notion that ART therapy does not fully alleviate potential HAD-inducing oxidative stress mechanisms. Researchers have observed high levels of neuroinflammation in HIV-infected, post-HAART treated patients; comparable to, and even exceeding, levels of inflammation in pre-HAART and asymptomatic patients. (Anthony et al., 2005).

Regardless of these downsides, the fact that ART has decreased incidence of HIV and HAD is certainly a step in the positive direction, and one could argue that HIV and HAD prevalence are simply the byproduct of a beneficial effect of the drugs (i.e., longer lifespan). However, this increased prevalence is an importance consideration for HAD therapy. Now more than ever, patients are in need of therapy in combination with ART in order to alleviate the potentially greater neuropsychological decline over a longer lifespan. The following two sections will review additional therapeutic approaches that could potentially improve the longer lifespan of HIV-infected individuals.

4.2.2. Antioxidant and Hormone Therapy—Antioxidants serve to counteract oxidative stress and reduce ROS. Endogenous antioxidants may be administered or supplemented exogenously, and so serve as a potential therapeutic tool to counteract neurotoxicity mediated by oxidative stress. This section will briefly focus on only a few antioxidants that are easily accessible and show promise as a therapeutic agent. Note that while endogenous antioxidants can be protective, they can also catalyze neurotoxic cascades and alteration of some endogenous antioxidant levels (i.e., SOD, glutathione, catalase) can serve as a marker for oxidative stress (Mollace et al., 2001).

Epigallocatechin gallate (EGCG) and a variety of vitamins are popular antioxidants because of their accessibility and variety of therapeutic effects (Nance et al., 2003). EGCG has been shown to interact with the envelope/membrane of HIV and other cells to protect from infection. It can destroy the virion by binding to the envelope of HIV (Yamaguchi et al., 2002) and can compete for CD4 receptors on target cells, thereby preventing gp120 binding and HIV infection (Kwong et al., 1998). Multivitamin regimen has been shown to be beneficial for HIV-infected individuals (Fawzi et al., 2004). For example, vitamins E and C have been shown to reduce viral load and markers of oxidative stress (Allard et al., 1998; Pocernich et al., 2005), as vitamin C reduces viral replication (Harakeh et al., 1990) and vitamin E inhibits activation of NF- κ B (Isreal et al., 1992).

Other endogenous factors that can be utilized as exogenous antioxidants are gonadal hormones. Research demonstrates that these hormones may partially act through mechanisms other than anti-oxidation. The therapeutic benefit of gonadal hormones such as estrogen, testosterone, and progesterone on the neurotoxic effects of HIV proteins, METH, and COC has only recently been investigated. In fact, only two published investigations on gonadal hormones as a neuroprotective factor for HIV+COC and/or METH exist to date, and from many of the same investigators (i.e., Kendall et al., 2005; Turchan et al., 2001). In fact, only a handful of published investigations exist on gonadal hormones as a neuroprotective factor for any of the aforementioned neurotoxins alone, much less the conjunction of any two.

The neurotoxic effects of the HIV proteins Tat and gp120 have been shown to be abrogated by estrogen, specifically the subtype 17 β -estradiol (Corasaniti et al., 2005; Kendall et al., 2005; Russo et al., 2005; Turchan et al., 2001; Wallace et al., 2006a). Russo et al. (2005) demonstrate the fact that estrogen protects against gp120 neurotoxicity through a receptor-mediated mechanism *in vitro*. Interestingly, 17 β -estradiol did reduce ROS accumulated after administration of gp120, which does indicate the potential for estrogen as an antioxidant.

However, they showed that the estrogen antagonist ICI 182,780 prevented the neuroprotective characteristic of 17β -estradiol, but did not alter the amount of ROS reduced by 17β -estradiol. Since cell death occurred despite the reduction of ROS, 17β -estradiol protection may be receptor mediated. Wallace et al. (2006a) also demonstrated increased oxidative stress by increased dichlorofluorescein fluorescence levels after administration of Tat and/or gp120, which is attenuated by 17β -estradiol. However, they note that ICI 182,780 prevented the reduction in oxidative stress found upon administration of 17β -estradiol, indicating the possibility of a non-receptor-mediated mechanism. It is likely that both a receptor-mediated and a non-receptor-mediated mechanism are responsible for the protective effects of estrogen. It is apparent from these studies that 17β -estradiol reduces ROS and oxidative stress, and protects mitochondria (Turchan et al., 2001), making the extracellular milieu more conducive to cell survival. Toxicity may occur despite these reductions, without the receptor mediated protective effects of 17β -estradiol. Perhaps even more interesting is Wallace et al.'s (2006a) demonstration of the protective effects of 17β -estradiol on DAT. They measured uptake of [3 H] DA and demonstrated a significant decrease in DAT binding (v_{max}) following administration of Tat and gp120, while affinity (k_m) for the receptor remained unchanged. The deleterious effect on DAT binding sites was attenuated with co-incubation of 17β -estradiol. This finding not only further demonstrates the neurotoxic effect of HIV on DA systems, specifically DAT (see Section 2.1.2.4.), but highlights estrogen as a promising therapy even in the range of pM concentrations (Turchan et al., 2001; Wallace et al., 2006a). Carasanti et al. (2005) provide evidence for the neuroprotective effects of 17β -estradiol *in vivo*, as the subtype successfully attenuated neuronal death that ensues following administration of gp120, specifically in the neocortex of the rat.

As mentioned before, two studies have examined the role of estrogen and other gonadal hormones on the synergistic neurotoxicity of HIV proteins + COC or METH (i.e., Kendall et al., 2005; Turchan et al., 2001). Turchan et al. (2001) demonstrated a dose dependent attenuation of the neurotoxic effects of Tat and gp120, with and without COC or METH, by 17β -estradiol. Furthermore, they demonstrated that 17β -estradiol prevented mitochondrial dysfunction caused by HIV proteins even in the presence of the estrogen receptor antagonists ICI 182,780 and tamoxifen, thereby indicating a non-receptor-mediated mechanism of protection in conjunction with the receptor-mediated effects. Lastly, they found that neuroprotection of estrogen is subtype specific, as 17α -estradiol did not provide protection from neurotoxic factors from HIV, COC, or METH.

Kendall et al. (2005) successfully replicated Turchan and colleagues by demonstrating the neuroprotective effects of 17β -estradiol on HIV and COC neurotoxins and by demonstrating the lack of protection with respect to 17α -estradiol. They extended the replication to demonstrate a neuroprotective effect of 5α -testosterone which is comparable to the effect and mechanism of 17β -estradiol. That is, 5α -testosterone protection was mitigated with estrogen receptor antagonist ICI 182,780, indicating the testosterone works via estrogen receptors to protect from HIV and COC neurotoxins. This study, as well as Wallace et al. (2006a), demonstrated the limited neuroprotective capabilities of progesterone, and the potent actions of 17β -estradiol.

4.3. Section Summary and Conclusions

The purpose of this section was to provide evidence for *how* HIV induces neurotoxicity, and Table 1 directs interested readers to more specific reviews of some of the relevant topics covered in this section. Neurotoxicity is mediated by a number of mechanisms, and the two most generally considered are aberrant immune response and oxidative stress. These two mechanisms become more of a threat when synergistically induced by HIV+COC or METH abuse, to form a positive feedback loop inducing multiple, more direct mediators of toxicity

like mitochondrial toxicity, calcium imbalance, excitotoxicity, and apoptotic cascades. Using data from *where* HIV most affects the brain, as well as *what* aspects of the virion induce neurotoxicity and *how*, researchers have begun to understand avenues for research on promising therapeutic interventions. Novel therapeutic strategies like hormonal therapy must be developed that can handle a wide variety of disparate neurotoxic mechanisms and apoptotic cascades, as these neurotoxic mechanisms may be able to arise independent of one another.

5. General Conclusions, Implications, and Future Directions

Since the discovery of the HIV over two decades ago, an entire neuroAIDS literature was not only developed, but significant and rapid advances have been made with respect to characterizing the HIV-induced dementia from molecular and behavioral levels; specifically *where* HIV is neurotoxic, *what* aspects of the virion are neurotoxic, and *how* these act to mediate neurotoxicity. Nevertheless, there remains a tremendous amount of work to be done.

Researcher must utilize past discoveries presented in this review in order move forward to a sound and ecologically valid therapy for HIV-induced neuropsychological impairment. To attain this goal, additional models need to be developed and/or employed; both *in vitro* and *in vivo*. For example, it is apparent in the HIV, and the HIV+COC or METH abuse literature *in vitro* assays abound. The utility of *in vitro* investigations is made apparent when assessing how far this field has progressed using these techniques since the 1980's (see Aksenova et al., 2005 for review).

Currently, there are not enough investigations utilizing imaging techniques to understand the structural and functional alterations in brains of HIV-infected COC and/or METH abusers. Imaging the brains of human COC and METH abusers as well as contingent animal models of COC administration (e.g., self-administration) provide excellent platforms for understanding neural plasticity and toxicity associated with nearly all aspects of COC and METH abuse within the continuum of acute to chronic effects, and in the context of withdrawal and/or reinstatement. Research has demonstrated behavioral differences in animals receiving COC contingently vs. non-contingently (e.g., Markou et al., 1999). Imaging of chronic COC or METH abusers and research using contingent self-administration models of chronic COC or METH administration provides the most ecologically valid representation of the COC and METH abusing population, including the HIV-infected subset. Indeed, the rate of transmission for intravenous drug injection with infected needles ranges from .63% to 2.4% (Baggaley et al., 2006; Hudgens et al., 2002; Kaplan and Heimer, 1992), indicating that while HIV transmission after acute drug administration is possible, it is far more likely for chronic abusers to contract the disease. Thus, neural plasticity and toxicity associated with chronic COC or METH administration provides the most ecologically valid representation of the brain at the time of and throughout the course of HIV-infection, an argument which has implications for the most appropriate animal models of HIV-infection plus drug abuse.

5.1. Animal Models

Nevertheless, *in vivo* animal studies are becoming more common, and have certainly proven to be more than helpful in elucidating what HIV-proteins are detrimental and the mechanism associated with this in the modeled brains of HIV-infected COC and/or METH abusers. There are numerous, solid investigations of SIV-infected monkeys and FIV-infected cats. These two models are particularly advantageous because they provide human analogs to HIV, while allowing for more invasive techniques to study CNS vulnerability to the immunodeficiency virus. Unfortunately, there is no human analog to HIV in wild-type rodents; the difficulty with such a model residing in the fact that rodents lack the surface receptors necessary for the binding and infection of the virus. Nevertheless, there are efforts to overcome this paramount problem. For example, two related lines of research have emerged with slightly different theoretical

notions of how to infect rodents with HIV. One line of work transgenetically alters the rodent so that target cells express the proteins (e.g., CD4, CCR5) necessary for HIV-infection (e.g., Sawada et al., 1998). The other line of work involves creating a chimeric form of HIV (termed EcoHIV and EcoNDK) that expresses proteins on the viral membrane which would facilitate infection of wild-type rodents, thereby replacing gp120 (e.g., Potash et al., 2005). As with any model, there are advantages and disadvantages to both. Non-exhaustively, the advantage of the transgenic rodents expressing cell surface receptors would be the ecological validity in studying the intact HIV in a live organism, especially since the chimeric model lacks the neurotoxic protein gp120. The advantage if the chimeric HIV resides in ease of infecting across rodent species in combination with decreased risk associated with the chimeric virus' inability to infect human cells. Other rodent models include one that was developed just over a decade ago which approaches the ecological validity of SIV and FIV models; called the severe combined immunodeficiency (SCID) mouse model. This model is characterized by inoculation of HIV-1 infected cell xenografts into a predetermined area of the brain of a mouse infected with SCID (see Masliah, 1996; Persidsky et al., 1996). The brain pathology of SCID mice infected with HIV-monocytes has been demonstrated to be similar to that of humans infected with HIV, including prominent characteristics of encephalitis (e.g., multinucleated giant cells, astrogliosis, and neuronal toxicity) (Persidsky et al., 1996), cytokine and chemokine upregulation (Persidsky et al., 1996, 1997), and even behavioral abnormalities (Avgeropoulos et al., 1998). To date, researchers continue to use the SCID model not only for characterization of HIV pathology, but for studying therapeutic interventions of HIV (Cook-Easterwood et al., 2007; Spitzenberger et al., 2007). Even before the use of the SCID mouse model, transgenic mice which express various HIV-proteins have been used to study HIV related syndromes (Klotman et al., 1995), and the effect of HIV-proteins on the CNS (Keswani et al., 2006; Toneatto et al., 1999) (see Persidsky et al., 2005 for review of rodent HIV models). Since the development of this model, the use of HIV-1 transgenic rats that express one or more HIV-proteins, including Tat and gp120, has been developed (Mazzucchelli et al., 2004; Ray et al., 2003; Reid et al., 2004; Yadav et al., 2006). However, published investigations of CNS function in rats expressing HIV-protein(s) are almost nonexistent (however, see Vigorito et al., 2007; Reid et al., 2001), and the extent to which Tat and/or gp120 is expressed in the brain is not known. Thus, this model is currently relegated to developmental stages, but may hold promise, especially if HIV-proteins may be easily induced. One future direction that is needed is the development of awake/live rodent models to study behavior and neurochemical alterations with techniques such as microdialysis or voltammetry in one of the aforementioned rodent models. Implicit in this argument and in the literature is a lack of rodent research on the systemic level, which would bridge the gap between molecular and behavioral levels. Behavioral and neurochemical analyses would allow for HAD behavioral correlates, and to test novel therapeutic approaches on behavior and on synaptic transmission. Unfortunately to date, most of the effects on neurotransmission and function of the DA system are inferred from molecular and behavioral data.

Of further interest is the development of a rodent model of HIV and drug abuse. A few investigators have made strides in developing an animal model of HIV and drug abuse using the rat (e.g., Bansal et al. 2001 for intravenous drug admin.; Cass et al., 2003; Maragos et al., 2002 for intraperitoneal drug admin.). Indeed, sound animal models for the "drug" aspect of the HIV-infected drug abuser have been developed (e.g., Mactutus et al., 1994). Implantable catheters have provided an intravenous access port that reduces stress to the animals and provides a means to administer psychostimulant drugs that mimic the peak and latency (i.e., kinetic aspects) of those drugs in humans who recreationally abuse. Bansal et al. (2001) built upon this animal model for drug abuse developed by Mactutus and colleagues (1994) by adding an intracerebral injection of HIV proteins into various regions of the brain. This model allows for *in vivo* study of synergistic effect of HIV virotoxins and drugs of abuse, while maintaining and mimicking the kinetic aspects of drugs of abuse in humans. As discussed earlier,

researchers have recently utilized the SCID mouse model in combination with intraperitoneal administration of COC (Griffin et al., 2007; Roth et al., 2005), and with oral administration of ethanol intake (Potula et al., 2005). Regardless of the advances that have been made, very little work is done on *in vivo* models of HIV+COC or METH relative to any one of these alone, and many rodent models still remain in developmental stages.

5.2. Implications for the HIV-infected Cocaine Abuser

The purpose of this section is to speculate a possible scenario/mechanism in which a chronic COC abuser, newly infected with HIV, may present a more severe manifestation of HIV-induced neuropsychological impairment relative to non-drug abusers. This scenario reiterates themes presented throughout the review on the individual and concerted effects of HIV and COC abuse, consequently bringing together loose ends into possible implications for this population. Specific references are withheld, but each step in the scenario can be confirmed in research presented in sections on the individual and concerted effects of COC and HIV. Figure 3 provides a schematic analogue to this particular section, providing a corresponding illustration of the possible scenario described herein.

Research has demonstrated that synaptic plasticity associated with chronic COC abuse may diverge from, or have an inverse relationship to, the synaptic alterations/neurotoxicity associated with HIV-infection/HIV-proteins. Further, it is unknown how HIV and related proteins affect the brain of a chronic COC abuser, which possesses a host of up-regulated pre-synaptic proteins and molecules. Nevertheless, research has noted that HIV-proteins disturb mitochondrial membrane potential, increase ROS, and reduce DAT uptake within two hours of exposure; and to date, there is no reason to suspect a different scenario for the brain of a chronic COC abuser. The brain's exposure to the virus and to Tat/gp120 may be elevated as a result of an already compromised BBB and COC-mediated upregulation of chemoattractant proteins. Thus, in a chronic COC abuser under these circumstances, DA overflow may initially potentiate with exposure to HIV-infection. The potentiation of DA to elevated HIV(-proteins) may originate from at least 2 sources; one, the early HIV-induced reduction in DAT which effectively offsets the compensatory upregulation of DAT in response to chronic COC administration, and two, the chronic COC-induced upregulation of TH that may not reduce in HIV-infection until well after the loss of DAT function. This may effectively result in increased DA production from TH, and decreased DA uptake by DAT. Upon administration of COC, the pre-HIV levels (i.e., possibly sensitized) of DA may be released and ineffectively taken back up by DAT. These levels may approximate or even exceed levels of DA associated with DA releasing agents like METH, which in turn are known to induce DAergic neurotoxicity. Since DAT is the primary mechanism by which DA actions are terminated in the synapse, increased levels of DA may innervate the extracellular milieu for extended periods of time. If imaging research on the downregulation of D2 receptors in human COC-abusers is correct, then D2 receptor mediated autoregulation of DA release may be desensitized, consequently facilitating the continued release of DA. High levels of DA may auto-oxidize into ROS and reactive quinones, effectively breaking down pre- and post-synaptic biomolecules. Further, post-synaptic receptors may be overly excited from sustained DA release, increasing the likelihood of triggering D1 receptor mediated apoptotic cascades, ROS mediated apoptotic cascades, and/or even NMDAR/D1 coupled calcium influx and excitotoxicity. If in fact initial research indicating HIV-induced reductions in cAMP and CREB is further supported, this may effectively up-regulate D1 receptors on the post-synaptic terminal, increasing the probability of D1 mediated over-excitation. Meanwhile, aberrant immune response would facilitate increases on ROS and triggering of apoptotic cascades. Unfortunately, cessation of COC abuse or even irregular intake of the drug, may induce a compensatory upregulation of D1 receptors, increasing the likelihood of post-synaptic excitation and D1 mediated apoptosis, even in the presence of basal DA levels. The damaging or death of neurons would then recruit increasing

numbers of glial cells and immune response from peripherally HIV-infected leukocytes/macrophages. This increased immune response to the brain may facilitate HIV infiltration of other subcortical areas proximal to the compromised BBB. Ultimately, neuropsychological impairments may manifest from the repeated barrage of cellular level trauma as more neurons die and DA levels deplete.

5.3. Implications for the HIV-infected Methamphetamine Abuser

It is likely that the neurotoxic profile of the HIV-infected COC abuser is similar in many respects to the profile of the HIV-infected METH abuser; however, differences may be present due to differences in each drug's mechanism of action on the presynaptic terminal and level of sole neurotoxicity. Thus, it may not be sufficient to categorize all psychostimulants as having identical interactions with the HIV. Therefore to reiterate, the purpose of this section is to speculate a possible scenario/mechanism in which a chronic METH abuser, newly infected with HIV, may present a more severe manifestation of HIV-induced neuropsychological impairment relative to non-drug abusers. This scenario reiterates themes presented throughout the review on the individual and concerted effects of HIV and METH abuse, consequently bringing together loose ends into possible implications for this population. Again specific references are withheld, but each step in the scenario can be confirmed in research presented in Sections on the individual and concerted effects of METH and HIV.

Surprisingly, a synergistic scenario for HIV+METH may be more difficult to provide than for HIV+COC. This is due to the fact that research has demonstrated that synaptic alterations/neurotoxicity associated with chronic METH abuse may correspond to the synaptic alterations/neurotoxicity associated with HIV-infection/HIV-proteins. Thus, the potential for an additive effect of METH and HIV-induced neurotoxicity is easily conceived, whereby chronic METH induced loss of DAT/VMAT2 function, down-regulation of TH, increased ROS/oxidative stress, and mitochondrial dysfunction is further potentiated by the similar effects of HIV(-proteins) on these proteins/molecules.

Nevertheless, research has repeatedly demonstrated a synergistic effect of *in vivo* and *in vitro* METH+HIV. As in COC abuse, the exposure to the virus and to Tat/gp120 may be elevated as a result of an already compromised BBB and METH-mediated upregulation of chemoattractant proteins. Furthermore, in the course of chronic METH abuse, DAT activity is down-regulated, although not fully. An HIV+METH-induced augmentation in loss of DAT function would exacerbate long term DA overflow already induced by METH's reversal of DAT/VMAT2 and inhibition of MAO; thus, increasing the likelihood of triggering D1 receptor mediated apoptotic cascades, ROS mediated apoptotic cascades, and/or even NMDAR/D1 coupled calcium influx and excitotoxicity. METH induced reductions presynaptic DA molecules like TH may not mitigate effect of auto-oxidizing DA released by DAT/VMAT2 reversals. Furthermore, DA may auto-oxidize intracellularly via a METH-induced release of DA from VMAT2. HIV's effect on VMAT2 has not been studied to date, but it is plausible that HIV may down-regulate VMAT2 function as well, exacerbating increases in intracellular DA, coupled with "leaking" ROS from vulnerable mitochondria. It may *not* be the case that there is a one-to-one, or linear, correspondence between augmented DA overflow, and consequent triggering of apoptotic cascades and generation of reactive quinones. The ensuing damage to neurons may result in a net effect of synergistic neurotoxicity when accounting for increased likelihood of apoptotic cascades, excitotoxicity, and oxidative stress. This is further compounded by release of inflammatory cytokines from aberrant immune response.

5.4. Concluding Remarks

It is apparent that auto-oxidizing DA and post-synaptic DA interactions are key components in the mechanisms of neurotoxicity in the two scenarios describe herein. Indeed, therapeutically

increasing synaptic DA may facilitate the auto-oxidative process, which may be why neuroleptic therapy has proven damaging. Also, researchers have noted that other compounds that increase DA overflow potentiate HIV-induced neurotoxicity (e.g., MAO inhibitors; Koutsilieri et al., 1994). The scenario described herein may not sufficiently address all that is involved in HIV+COC or METH neurotoxicity, and it may very well prove to miss the mark in some respects. Nevertheless, the mechanisms outlined in the scenario are testable, and describe a few of the future research directions for the field that are already underway in some instances. Finally with respect to the scenarios, individual differences in progression and severity of neuropsychological impairments in HIV-infected COC or METH abusers may originate from differences in COC or METH abuse history, among other variables. Differences in this history stems from differences in route of administration, frequency of use, duration of use, dose levels; all of which translate into variable amounts of DA release and ensuing compensatory neuroplasticity, as well as variable degrees of BBB vulnerability. If all factors including genetic variation, immune strength, nutrition, environmental stressors, etc. could be held constant, variation in COC abuse history alone would likely be sufficient to significantly vary HIV-induced neuropsychological outcome. Thus, the scenario described herein will not sufficiently address all variants of HIV+COC or METH induced neurological impairment, but provided a possible mechanism for the vast majority.

Given the current trends - especially the ever growing prevalence of HAD inflicted patients and HIV-infected individuals, as well as the notion that novel variants of HIV-induced neuropsychological impairment are manifesting in the context of drugs of abuse (Everall et al., 2005) – new models are needed that would allow for online investigations of neurochemical and cellular activity. This is especially true when considering the rapid molecular alterations demonstrated in the research provided in Table 2. Establishing a more concrete temporal dimension to HIV-induced neuropsychological impairment, in combination with testing novel therapeutics will likely provide for more rapid assimilation of CNS directed therapy into current ART regimens. Otherwise, HIV-infected individuals will live longer, but quality of life will still likely deteriorate over time, especially in the HIV-infected, aging, drug abusing population.

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Figure 1.

Diagram providing established examples of where and how HIV induces alterations in the human brain (sections from DeArmond et al., 1989). Blue lines indicate HIV-induced alterations, and red lines indicate both HIV-induced alterations, and synergistic alterations of HIV + COC or METH.

Figure 2.

Diagram providing established examples of Tat and/or gp120 induced alterations using rodent models, from both *in vivo* and *in vitro* (when source specified) investigations (sections from Paxinos and Watson, 1997). Blue arrows indicate protein-induced alterations, and red arrows indicate both protein-induced alterations, and synergistic alterations of Tat/gp120+COC or METH.

Figure 3.

Schematic representation of one possible scenario in which HIV (tat and/or gp120) may interact with the neuroplasticity associated with chronic cocaine abuse to trigger neurodegeneration of nerve-terminals. Each aspect of the schematic can be supported by research in the extant literature on cocaine dependence and neuroAIDS, however the extent to which individual aspects act in concert is theoretical, and need further substantiation in research. Further, the schematic does not include all neurotoxic mechanisms described in the literature (e.g., mitochondrial dysfunction, excitotoxicity, etc.) that will likely contribute to HIV-induced neurodegeneration.

Table 1

Recommended reviews for topics relevant to the current review paper.

	Topic	Authors	Publication Date	Other Topic(s)
Section 2	<u>Where</u>			
	Behavioral Pathology	Tse et al.	2004	
		Grant	2002	
	Molecular/Structural Pathology	Everall et al.	2005	HAART
		Bell	2004	HAART era
	Subcortical	Berger and Nath	1997	
		Paul et al.	2002	MRI and HIV-cognition
	Cortical	Masliah et al.	1993	
		Paul et al.	2002	MRI and HIV-cognition
	White Matter	Gray and Lescs	1993b	Demyelination
		Paul et al.	2002	MRI and HIV-cognition
	Dopamine System	Berger and Arendt	2000a	Basal Ganglia
Section 3	<u>What</u>			
	Proteins (general)	Di Stefano et al.	2005	
		Nath and Geiger	1998	gp120 and Tat
	gp120	D'Aversa et al.	2005	Microglial Activation
		Corasaniti et al.	2003	
	Tat	D'Aversa et al.	2005	Microglial Activation
		King et al.	2006	Glutamatergic effects
Section 4	<u>How</u>			
	Mechanisms (general)	Wallace	2006b	Therapy, Tat, gp120
		Mattson et al.	2005	Viral proteins
	Oxidative Stress	Aksenova et al.	2005	Cell culture models
		Pocernich et al.	2005	Antioxidants, Tat
		Valcour and Shiramizu	2004	Mitochondrial toxicity
	Cocaine & Methamphetamine	Anderson and Pierce	2005	neuroplasticity
		Quinton and Yamamoto	2006	MDMA
		Fleckenstein et al.	2000	Transporters/VMAT
		Riddle et al.	2006	
	Abberant Immune Response	Kaul and Lipton	2006	Therapy
		Lee et al.	2005	Immune pathways
	Antiretroviral Therapy	Nath and Sacktor	2006	
		Ellis et al.	2005	Neuropathology
		Everall et al.	2005	Encephalitis
		Bell	2004	Neuropathology
	Antioxidant Therapy	Pocernich et al.	2005	Oxidative stress, Tat
		Shor-Posner et al.	2002	Drug abuse
	Hormone Therapy	Wilson et al.	2006	Estrogen immune modulation
		Czlonkowska et al.	2003	Neurodegenerative disorders
Other	<u>Entry into the CNS</u>			
	BBB	Banks et al.	2006	
		Nottet	2005	
	Choroid Plexus	Burkala et al.	2005	

Table 2
Time-course of early molecular alterations following a single, acute administration of Tat and/or gp120.

Time Post-Administration	Tat/gp120-induced Effect	Reference(s)	Protein/Concentration	Protein Administration/Technique	Synergistic Effect with COC or METH?	Protective/Notes
30 minutes	↓ DAT reuptake ↑ Free Radicals/Oxidative Stress	Wallace et al., 2006 *	Tat:60 nM; gp120: 30 pM Tat:50-250 nM; gp120: 20-50pM	Synaptosomal Preparations Rat Cell Culture	ψ ψ	Attenuation with 17β-estradiol *
2 – 10 hours	↑ Protein Carbonyls/Oxidative Stress (2) ↑ neuronal degeneration (2) ↓ mitochondrial membrane potential (2) ↑ ROS (2) ↑ cytokines (MCP-1, IL-1α, TIMP-1) (4 h after METH, approx. 36 h after Tat) ↑ oxidative stress (5) ↑ transcription factors (AP-1, CREB, NF-κB) (5) ↑ ICAM-1 (5) ↑ TNF-α and IL-1β gene expression (5) ↓ mitochondrial membrane potential (6)	Aksenov et al., 2003 * Aksenov et al., 2006 * Theodore et al., 2006b Flora et al., 2003 * * * Maragos et al., 2002	Tat: 50 µg * Tat: 50 nM * Tat: 20 µg Tat: 25 µg * * * Tat: 80 nM	Intrastriatal Rat injection * Rat Cell Culture * Intrastriatal Rat injection Intrahippocampal Mouse Injection * * * Human Cell Culture	ψ ψ COC (1.5 µg) * METH (4 mg/kg i.p., 4 injections over 8 hrs) METH (10 mg/kg i.p.) (3hr) * * * METH (500 µM)	ψ ψ ψ ψ ψ Brain region specific effects * * * Only synergistic effect present/Abrogated with antioxidants
11 – 24 hours	↑ neuronal death (15) ↑ cytokines (MCP-1, TIMP-1) (16 h after METH, approx. 48 h after Tat) ↑ CINC-1, GNTF, MIP-3α (16 h after METH, approx. 48 h after Tat) ↑ OX-42/Microglial Response (24) ↑ neuronal degeneration (24) ↑ ROS (24)	Maragos et al., 2002 Theodore et al., 2006b * Aksenov et al., 2003 * Aksenov et al., 2006 Aksenov et al., 2005 Aksenov et al., 2006	Tat: 80 nM Tat: 20 µg * Tat: 50 µg * * Tat: 50 nM Tat: 50-250 nM	Human Cell Culture Intrastriatal Rat injection * Intrastriatal Rat injection * Rat Cell Culture Rat Cell Culture * * Intrastriatal Rat injection	METH (500 µM) # METH (4 mg/kg i.p., 4 injections over 8 hrs) ψ ψ ψ ψ COC (1.5 µg) COC (1.5 µg) # ψ	ψ ψ ψ ψ ψ ψ Attenuation of COC synergism with D1 antagonist (SCH23390; 10µM) ψ Attenuation with Trolox (10 µM) ψ
25 – 48 hours	↓ DAT binding, no change in DAT immunoreactivity (48) ↑ neuronal death (48)	Aksenov et al., 2006	Tat: 50 nM	Rat Cell Culture	ψ	ψ
5–10 days	↑ Protein Carbonyls (48) ↑ ROS (48) ↑ GFAP/Astrocytosis (Day 7)	* * Aksenov et al., 2003	Tat: 50 nM * Tat: 50 µg	* * Intrastriatal Rat injection	COC (1.5 µg) # ψ	Attenuation of COC synergism with Trolox (10 µM) ψ

Time Post-Administration	Tat/gp120-induced Effect	Reference(s)	Protein/Concentration	Protein Administration/Technique	Synergistic Effect with COC or METH?	Protective/Notes
	↑ neuronal degeneration (Day 7)	*	*	*	*	Ψ
	↑ Protein Carbonyls/Oxidative Stress (Day 7)	*	*	*	*	Ψ
	↓ DA, DOPAC, HVA (Day 7 after METH, Day 8 after Tat)	Maragos et al., 2002; Theodore et al., 2006a	Tat: 20 μg	*	METH (4 and 5 mg/kg i.p., 4 injections over 8 hrs)	Ψ
	↑ nerve fiber degeneration (Day 7 after METH, Day 8 after Tat)	Theodore et al., 2006a	*	*	METH (4 mg/kg i.p., 4 injections over 8 hrs)	Only synergistic effect present
	↓ TH immunoreactivity (Day 7 after METH, Day 8 after Tat)	*	*	*	*	Only synergistic effect present in striatum, not in SN
	↓ DAT binding (Day 7 after METH, Day 8 after Tat)	Maragos et al., 2002	Tat: 80 nM	Human Cell Culture	METH (500 μM)	Ψ
	↓ DA and DOPAC (Day 7 after METH, Day 8 after Tat)	Theodore et al., 2006b	*	Intrastriatal Mouse injection	METH (3 mg/kg i.p., 4 injections over 8 hrs)	Only synergistic effect present/not present in MXP-1 KO
	↓ DA overflow in striatum (Day 7 after METH, Day 8 after Tat)	Cass et al., 2003	Tat: 25 μg	Microdialysis	METH (5 mg/kg i.p.)	Only synergistic effect present

* Note: indicates same as above; # indicates no effects despite testing; Ψ indicates effects not tested. Numbers in parenthesis in column 2 indicate exact time since protein and/or drug administration.

COC = Cocaine; CINC-3 = Cytokine-induced Neutrophil Chemoattractant-3; CNTF = Ciliary Neurotrophic Factor; CREB = Cyclic AMP Response Element Binding Protein; DA = Dopamine; DAT = Dopamine Transporter; DOPAC = 3,4-dihydroxyphenylacetic acid; GFAP = Glial Fibrillary Acid Protein; HVA = Homovanillic Acid; ICAM-1 = Intercellular Adhesion Molecule-1; IL-1 = Interleukin-1; MCP-1 = Monocyte Chemoattractant Protein-1; METH = Methamphetamine; MIP-3α = Macrophage Inflammatory Protein-3 Alpha; NF-κB = Nuclear Factor Kappa B; ROS = Reactive Oxygen Species; TH = Tyrosine Hydroxylase; TIMP-1 = Metalloproteinase-1; TNFα = Tumor Necrosis Factor Alpha.