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Review Article

Methamphetamine abuse, HIV infection, and neurotoxicity

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Abstract: Methamphetamine (Meth) use and human immunodeficiency virus (HIV) infection are major public health problems in the world today. Ample evidence indicates that HIV transfection risk is greatly enhanced with Meth use. Studies have shown that both HIV infection and Meth abuse can cause neuronal injury leading to neurodegeneration. While many studies have focused on the individual effects of Meth and HIV on the brain, few investigations have been carried out on their co-morbid effect in the nervous system. In this review, we try to summarize recent progress on individual effects of Meth and HIV on neurodegeneration and their potential underlying mechanisms, in addition to exploring their co-morbid effect on the brain.

Key words: HIV-1, AIDS, methamphetamine, neurotoxicity, neurodegeneration

Introduction

Methamphetamine (Meth) use represents a major public health concern with greater than 35 million users worldwide. In the United States, 10-15% of human immunodeficiency virus-1 (HIV-1) positive individuals acknowledge Meth use [1] with greater than 7% of American high school students having tried Meth [2,3]. Due to its ability to be synthesized in small clandestine laboratories [4], this highly addictive drug [5] is difficult to combat. Meth is very desirable to illicit drug users due to its inexpensive cost of manufacturing, low cost to purchase and its long duration of action [6]. With an elimination half-life between 10-12 hours [7], its pharmacokinetics allow it to produce effects lasting 10-times longer than that of cocaine [8]. Meth abuse has been associated with many health disorders, such as stroke, increased blood pressure, cardiac arrhythmia, hyperthermia, central nervous system (CNS) abnormalities and most notably HIV-1 infection [9, 10]. As the most widely used recreational drug among men who have sex with men (MSM) [11-14], Meth is associated with a doubling of the risk of HIV-1 acquisition [15], higher blood viral loads, alterations in anti-retroviral medication concentrations, and greater high-risk sexual behaviors, which may lead to HIV super infection [16-18]. Current estimates of overall HIV-1 prevalence among young injection drug users is about 2.8 percent [19], with transmission through injection drug use representing 13 percent of all new cases of HIV-1 in 2006 [20].

HIV-1 infection of the brain, or NeuroAIDS, results in a chronic neurological disorder termed HIV-1 associated dementia (HAD) in approximately 20-30% of patients infected with HIV-1 [21, 22]. HAD is characterized by deficits in attention, impairments of short-term memory, compromised fine motor skills, tremors, slowness of movements, and abnormal gait [22, 23]. While the prevalence of HAD has been greatly reduced in the modern era of highly active anti-retroviral therapy (HAART), other complexes of milder symptoms, specifically the minor cognitive motor disorder (MCMD), have been growing in prevalence [24]. This is generally believed to be due to a chronic low level persistent viral infection of mononuclear phagocytes (MP; blood-borne tissue and perivascular macro-

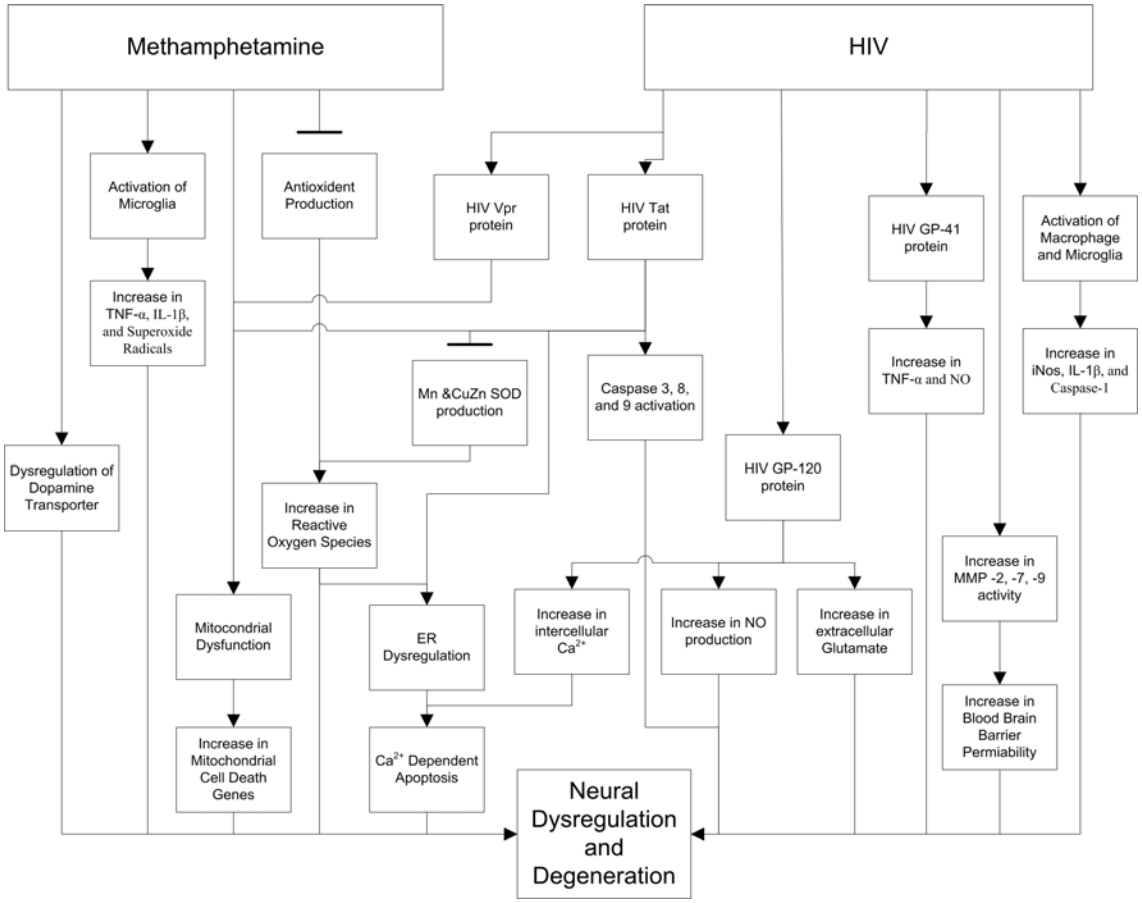

Figure 1. Effects of Meth and HIV-1 on neural dysregulation and degeneration

phages and microglia) having supplanted high-level productive HIV replication as the pivotal mechanism for the pathogenesis of HIV-associated neurocognitive disorders (HAND). Evidence suggests that HIV-infected individuals who use illicit stimulants, in particular Meth, are more likely to have HAND compared with non-drug abusing HIV-infected individuals. This may be because stimulants compound the effects of the neurotoxic substances released during HIV infection, with dopaminergic and glutamatergic systems being particularly vulnerable [25-28].

Meth use and HIV-1 infection, two major public health problems worldwide today, have been associated with detrimental changes in neuropsychology. Using a variety of psychological tests, it has been shown that chronic Meth users show significant deficits in attention, spatial learning and memory, and executive functions [29-31]. HIV-1 infected individuals usually manifest changes in personality, apathy, and depression levels, as well as social withdraw and psychotic symptoms [32, 33]. Asymptomatic HIV-1 positive individuals often display minor deficits in attention [34], cognitive speed [35], and fine motor skills [36]. Individuals with co-morbid HIV-1 infection and Meth use have been demonstrated to show greater reductions in cognitive abilities compared to either individuals with HIV-1 infection or Meth use alone [37, 38].

While many studies have focused on the individual effects of Meth and HIV-1 on the brain, limited investigations have been done on their intersecting influence. In this review, we attempt to summarize the individual

effects of both Meth use and HIV-1 infection on neurodegeneration, and to evaluate their intersecting effects on neurodegeneration as well. A summary chart diagram illustrating the effects of Meth and HIV-1 on neurodegeneration is shown **Figure 1**.

Meth-associated neurotoxic activity

Neuroimaging studies have documented extensive changes in the brains of Meth abusing individuals. Various studies using positron emission tomography (PET) on the brains of Meth abusers have found remarkably consistent decreases in dopamine (DA) transporter (DAT) levels in the caudate nucleus, putamen, nucleus accumbens, orbitofrontal cortex, and the dorsolateral prefrontal cortex [39-44], as well as reductions in postsynaptic D_2 dopamine receptors in the caudate and putamen [39, 45]. While this represents major physiological changes, it may also reflect a neuroadaptive change in response to repeated exposure to Meth [46].

Morphological changes in the brains of Meth users have been characterized using structural magnetic resonance imaging (MRI) technique. These changes include decreased volumes of the medial cingulate gyrus, limbic and paralimbic cortices, and the bilateral hippocampus [47], and an increase in the volumes of the putamen and the globus pallidus [48].

A significant number of proton magnetic resonance spectroscopy (MRS) studies have been conducted on Meth abusers who have recently abstained from Meth use. These studies showed decreased levels of N-acetylaspartate (NAA), a marker for neuronal integrity and density, in the basal ganglia, frontal white and gray matter and anterior cingulated cortex [49-52]. Increased levels of choline-containing compounds (CHO), a measure of cell membrane degradation and lipid changes, have been found in the frontal gray and white matter and the anterior cingulated cortex, while decreased levels of CHO have been found in the basal ganglia of recently abstained Meth users [50-53]. Increased levels of myo-inositol (MI), a putative marker of glial content, were seen in frontal white and gray matter [49], and decreased levels of creatine (CR) and phosphocreatine, a marker of energy stores and energy metabolites, have been shown in the basal ganglia and the anterior cingulated cortex [50, 52].

Potential mechanisms underlying Meth-associated neurotoxic activity

Oxidative Stress

Meth is known to cause persistent damage to DA and serotonin (5HT) nerve terminals in animal models of drug abuse [54-56], as well as to human abusers of Meth [39, 47]. While not fully understood, oxidative stress, the cytotoxic consequences of reactive oxygen species (ROS) (e.g. H_2O_2, O_2, OH), is believed to play a major role in the neurodegeneration associated with the use of Meth. Yamamoto and Zhu demonstrated this by showing an increase in the extracellular concentrations of the hydroxylated products of salicylate and d-phenylalanine in the brain after administration of a four-injection regimen of Meth [57]. This increase in ROS has also been shown to be present in a time dependent manner with respect to the last dose of Meth in a neurotoxic regiment [58]. With ROS also being produced as a byproduct of normal aerobic metabolism, cells contain elaborate antioxidant systems for dealing with ROS [59]. Cumulative evidence suggests that Meth is able to cause oxidative stress by affecting the balance between ROS production and enzymatic and non-enzymatic antioxidant systems [60-62]. Increases in ROS concentration can affect DNA resulting in nucleotide oxidation [63], lipids resulting in lipid peroxidation [57, 60, 64, 65], and cellular proteins resulting in protein nitration [60].

The role of oxidative stress in Meth-associated neurotoxicity is also confirmed by the observations that antioxidants such as ascorbic acid, ethanol, mannitol, vitamin E, *N*-acetyl-L-cysteine, and selenium [66-68] are able to attenuate striatal DA and 5-HT depletions, while inhibition of superoxide dismutase (SOD), an antioxidant enzyme, by diethyldithiocarbamate exacerbates both DA and 5-HT depletions [66]. Similarly, transgenic mice with over-expression of copper/zinc SOD show resistance to Meth induced neurotoxicity [69].

Another possible mechanism associated with Meth-induced neurotoxicity may be the formation of hydroxyl radicals in the synaptic cleft. Upon administration, Meth causes the release of DA from synaptic vesicles inside of

synaptic monoaminergic terminals. Following its release, inter-terminal DA is transported into the synaptic space by reverse transport by DAT [70]. This reverse transport of DA by DAT is encouraged by Meth ability to enhance the phosphorylation of the DAT via protein kinase C [71]. The reverse transport of DA by DAT is required for neurodegeneration, because DAT knockout mice don't exhibit Meth-induced terminal degeneration [72]. Once in the synaptic cleft, DA is metabolized by monoamine oxidase (MAO) to produce hydrogen peroxide. Interaction of the hydrogen peroxide with metal ions can produce toxic hydroxyl radicals [73].

Neurotoxicity resulting from oxidative stress may also be related to changes in the functionality and concentration of vesicular monoamine transporter 2 (VMAT-2), an integral membrane protein that acts to transport DA from cellular cytosol in synaptic vesicles. Exposure to Meth leads to a reduction in the binding of tetrabenazine to VMAT-2 [74], resulting in a reduction of DA transport into vesicles [75]. Thus, changes in functionality of VMAT-2 can lead to increases in the amount of cytoplasmic DA available to form ROS and DA quinones [58, 76, 77]. DA quinones can form protein-bound cysteinyl catechols, which are selectively toxic to DA terminals [77], however this effect can be attenuated by exposure to antioxidants (ascorbic acid and glutathione) [78]. Further, it has been shown that repeated swim stress is able to down-regulate the concentration of VMAT-2 in the striatum and nucleus accumbens [79]. With the likelihood of stress being associated with Meth addiction, it seems reasonable to conclude that stress-related changes in VMAT-2 concentration accompanied by the effects of Meth on VMAT-2 concentration may represent an enhanced pathway to neurotoxicity due to oxidative damage.

Activation of Mitochondria cell death genes

The mitochondrial Bcl-2 family of genes plays an important role in regulating cellular apoptosis. The Bcl-2 gene family regulates mitochondrial outer membrane permeability, and can be divided into either pro-apoptotic (BAX, BAD, BAK, and BID among others) or anti-apoptotic (Bcl-2, Bcl-w, and Bcl-X_L among others) splice variants. Several studies have documented the role of the Bcl-2 gene family in Meth-induced neurodegeneration [62, 80, 81]. While over-expression of Bcl-2 in immortalized neural cells offers significant protection from Meth-induced apoptosis [82], treatment of primary cortical neurons with Meth results in changes in the regulation of Bcl-2 splice variants [81]. Specifically, Meth has been shown to cause an increase in the levels of the pro-apoptotic genes BAX, BAD, BAK and BID, and a reduction in the anti-apoptotic genes Bcl-2 and Bcl-X_L [83], with the peak of pro-death gene expression at approximately eight hours after exposure to Meth and peak cell death at three days post-exposure [84]. These changes in the intrinsic ratios of cell death promoters to cell death repressors are consistent with the finding that Meth exposure results in the release of mitochondrial cytochrome C, Smac/DIABLO, endonuclease G and AIF into the cytosol [85, 86]. Following this release, increases in caspase-3 activity and cleavage of PARP, DFF-45 and lamin A can be observed [87]. When taken together with the *in vitro* demonstration that Meth can cause release of cytochrome C from mitochondria, activation of caspases 3 and 9, as well as activation of DFF40, and its transit to the nucleus [88], the *in vivo* data strongly support the role of mitochondria in Meth-induced neuronal degeneration [89, 90].

The Endoplasmic Reticulum and Neural Apoptosis

In addition to the mitochondria, oxidative stress is also able to cause neuronal dysfunction in the Endoplasmic Reticulum (ER) [91, 92]. In its regular state, the ER is responsible for the synthesis, folding and transport of proteins, as well as functioning as the main store for intracellular Ca^{2+} [91, 93]. Under normal conditions, the ER releases Ca^{2+} for use by the mitochondria to enhance metabolite flow on the outer mitochondrial membrane and to increase ATP production; however sustained release of Ca^{2+} from the ER can initiate calcium-dependent apoptosis via the permeabilization of the mitochondrial membrane [94]. Changes in calcium homeostasis have been implicated with Meth-induced cellular demise, because Meth has been shown to activate calpain [85, 95], a Ca^{2+} responsive cytosolic cysteine protease that is an important mediator of ER-dependent cell death [96]. Further evidence for the participation of the ER in Meth-related cell death is demonstrated in the finding that

apoptotic doses of Meth influence the expression of the proteins caspase-12, GRP78/Bip, and CHOP/GADD153 [85], proteins known to participate in ER-induced apoptosis and the ER-mediated unfolded protein response [97, 98]. Despite this evidence, Meth-induced ER dysfunction may play a secondary role to Meth-related oxidative stress [62, 73, 99] and to increases in the BAX/Bcl-2 ratio [83].

Reactive Microgliosis

Microglia, the resident immune cells within the central nervous system, function in immune surveillance in the intact brain and are activated during neurodegenerative processes [100]. It is believed that activated microglia might contribute to the progressive course of neurodegenerative disorders, including Parkinson's [101], Alzheimer's disease [102] and HAD [103]. More recently, it has also been shown that abstinent Meth abusers show significant increases in the levels of activated microglia in the midbrain, striatum, thalamus, orbitofrontal cortex, and the insular cortex in comparison to control (i.e. individuals with no self-reported history of methamphetamine use) [104]. These data are also consistent with increases in activated microglia that have been observed in mice following Meth injections designed to mimic a recreational dosing regimen in humans [105].

Current evidence indicates that over activation of microglia can result in neuronal damage through proinflammatory processes, including, but not limited to, the production of tumor necrosis factor-α, interleukin-1β, and interleukin-6 or through oxidative mechanisms via the generation of superoxide radicals [106-109]. When combined with the observation that Meth-induced neurotoxicity is attenuated in interleukin-6-null mice [110] and that activation of microglia appears to precede Meth-induced damage to striatal dopaminergic terminals in rodents [105, 111-113], it seems reasonable to suggest that reactive microgliosis is indeed associated with Meth-induced neurodegeneration.

HIV-induced neurotoxic activity

HIV brain infection produces progressive neural damage. Studied using MRI techniques, patients suffering from HAD have shown greater losses of white matter than non-demented HIV positive individuals [114]. Specifically, decreases in the volume of the cerebellum, caudate nucleus and the hippocampus have been shown [115]. Perfusion MRI (pMRI) has been shown to be sensitive to the changes in cerebral blood flow (CBF) that have been associated with reductions in motor functioning in HIV positive individuals; including decreases in CBF in the lateral frontal and medial parietal lobes and increased CBF in the posterior parietal white matter [116]. In addition, a single-photon emission computed tomography (SPECT) study also showed changes in CBF, specifically a decrease in the temporoparietal white matter [117]. It has also been shown that CD4 counts in HIV positive individuals correlate with changes in CBF detected by pMRI [116] and accelerated ventricular volume enlargement and reduction in the volume of white matter and of the caudate nucleus seen using MRI [118].

Computer tomography (CT) studies have demonstrated diffuse cerebral atrophy, and enlarged ventricles, which progress with the evolution of HIV infection [119, 120]. PET has shown the differences in glucose uptake between HIV positive individuals and HIV negative controls [121], and the time course of glucose metabolism levels in the basal ganglia (BG) [122]. Briefly, initial changes in motor performance are associated with diverse hypermetabolism in the BG. A change from hypermetabolism to hypometabolism is associated with moderate changes in motor performance. Later severe deficits in motor performance are associated with widespread hypometabolism in the BG.

MRS studies in HIV positive individuals have shown reductions in NAA in the frontal white matter and basal ganglia [123-130], and reduced NAA/CR and NAA/CR ratios in the centrum semiovale, frontal white matter and thalamus [125, 129, 130]. It should be noted that a partial reversal of the decreased NAA levels in the frontal white matter has been shown with HAART therapy [128]. Reduced CR levels have been shown in the basal ganglia [117, 124], while increased levels of CR have been shown in the frontal lobe [131]. Increased levels of MI have been shown to be present in the basal ganglia, frontal lobe, and temporoparietal white matter [117, 131], as well as an increase in the MI/CR ratio in the basal ganglia and the frontal white matter [125]. MI levels have also been shown to

correlate with lower CD4 counts and higher viral loads [131]. Despite improvements in CD4 count and viral load with HAART, increased MI and CHO remain in the basal ganglia after treatment [132]. It was also demonstrated that HIV positive individuals show age related changes in metabolic composition with respect to the normal variations seen. Individuals showed greater than expected levels of glial markers, cholines, and MI in the frontal white matter, while simultaneously showing further depressed levels of NAA and CR and phosphocreatine in the basal ganglia [124].

Understanding HIV-induced neurotoxic activity

Roles of macrophages and glial cells

HIV-infected macrophages and glial cells produce a variety of neurotoxins, including cytokines, chemokines, ROS, nitric oxide and excitatory amino acids. These toxins, alone or together, can influence the various types of cells in the brain [133-140]. Examination of brain sections from HIV demented and control brains with antibodies against iNOS, IL-1β, and caspase-1 revealed that the levels of all three markers of inflammation and oxidative stress are elevated in HIV demented brains [141]. Increases in markers of oxidative stress were also seen in microglia and astrocytes, suggesting that these cells may represent a site for the production of ROS [141]. Increased levels of macrophage inflammatory protein- 1α and 1β were found in the CSF of demented HIV-1 patients when compared with non-demented HIV patients [142]. In a study of rat cerebrocortical cultures containing neurons, astrocytes, and microglia, gp120 toxicity was blocked by tuftsin-derived tripeptide (TKP), an inhibitor of reactive microgliosis [143]. It has also been shown that gp120-related toxicity in hippocampal cultures is dependent on the presence of glial cells [144], and that activation of the p53 pathway appears to be necessary for the induction of gp120-related neurotoxicity in both neurons and microglia [145].

Secreted by neurons and glial cells [146], matrix metalloproteinases (MMPs), the Zn-containing endopeptidases that enzymatically degrade the extracellular matrix proteins of the blood-brain barrier (BBB) and neuronal synapses [147, 148], have moreover been associated with the pathogenesis of HIV infection [149-151]. A study has shown that levels of MMP-2, -7, and -9 activity, are markedly increased in individuals with HAD when compared to both HIV-1 seronegative controls and HIV-positive, non-demented individuals [152]. This study has also shown that human fetal brain-derived cells can release MMP-2, -7, and -9, and that stimulation with TNF-α can augment the release of both MMP-7 and -9. Other studies have revealed that HIV-1 gp41 and gp120 are able to induce MMP-2 [153, 154]. Taken together, these studies, with the fact that these particular MMPs are known to target critical components of the BBB, may suggest a possible mechanism for disruption of the BBB in HAD. In addition, MMPs can also cleave chemokines whose cleavage products can cause neurotoxicity [151].

HIV Tat-associated neurotoxicity

HIV Tat, the HIV trans-activator of transcription, vastly increases the amount of transcription of the HIV genome by phosphorylating other cellular factors, leading to explosive replication during infection [155]. High concentrations of Tat can be secreted by infected monocytes, resulting in altering function or killing of uninfected cells [156]. Moreover, the Tat protein causes neuronal loss, despite the inability of HIV in the infection of neurons [155, 157].

In vivo studies using direct stereotaxic injection of Tat have described the likelihood of a role for Tat in HIV-1-associated neurodegeneration. Following a single microinjection of Tat 1-72 into the striatum of rats, an increased level of protein oxidation and neuronal degeneration was produced, as well as an observation of the presence of reactive macrophages/microglia and reactive astrocytes near the lesion from injection [158]. In addition to this, stereotactic injections of Tat into the striatum of rats has been shown to produce significant cell loss and an increase in the number of reactive astrocytes [159, 160]. It has also been demonstrated that injection of Tat into the cerebral ventricles of rats can induce infiltration of neutrophils, macrophages, and lymphocytes, reactive astrocytosis, neuronal apoptosis and ventricular enlargement [161]. The consequences of long term exposure to Tat have also been examined. Rat C6 glioma cells that were genetically engineered to stably produce Tat

were stereotaxically injected into the striatum or hippocampus of rats. It was demonstrated that Tat was able to be transported via normal anatomical pathways from the dentate gyrus to the CA 3/4 region and from the striatum to the substantia nigra, leading to reactive microgliosis, neurotoxicity and behavioral abnormalities [162].

In vitro studies have helped to show possible pathways for Tat-associated neurodegeneration by demonstrating that Tat is able to cause neuronal apoptosis in embryonic rat hippocampal neurons by a mechanism involving the disruption of calcium homeostasis, mitochondrial calcium uptake, caspase activation and the generation of ROS [163, 164]. It has been shown that Tat-associated neurotoxicity is mediated by activation of caspase-3 and caspase-8, as well as activation of the mitochondrial-related cell death genes [165, 166]. The increase in ROS levels, at least in part, can be attributed with the ability of Tat to suppress Mn-superoxide dismutase (SOD) expression and CuZn-SOD activity, and is dependent on superoxide radicals and hydrogen peroxide [167, 168].

Similarly, it has also been shown that Tat is able to cause neuronal apoptosis in cultured human fetal neurons [169, 170]. The Tat-induced neuronal apoptosis was prevented by NMDA receptor antagonists in both cultured human fetal neurons [169] and rat mixed cortical cells [171]. More recently, Tat-induced neuronal apoptosis has been associated with ER-dependent cell death pathways [172], an observation that is consistent with the idea that changes in ROS levels can induce ER stress [91].

HIV gp120 and neural injury

During HIV reproduction gp160, the HIV envelope protein, is cleaved to form both the gp120 and gp41 viral proteins [173]. Exposure to HIV-gp120 protein has been shown to be able to induce cell death in human neurons [174], as well as primary rodent cultures, including cortical, hippocampal, cerebral, and retinal cells [175-177]. It has also been demonstrated that overexpression of gp120 in astrocytes of transgenic mice produces severe neuronal loss, astrogliosis, and an increase in the number of microglial cells present [178]. Behavioral studies in transgenic mice that overexpress gp120 in glial cells exhibit an age-dependent impairment in open-field and reduced spatial memory, similar to the cognitive and motor deficits seen in patients with HAD [179]. Injections of gp120 into the striatum of adult male rats resulted in significant areas of tissue loss and an increase in reactive astrocytosis [159], while injection of gp120 protein into neonatal rats caused dystrophic changes in pyramidal neurons of the cerebral cortex and the pups showed significant signs of retardation in developmental milestones that are associated with complex motor behaviors [180]. Exposure of cultures of hippocampal neurons to gp120 produced increases in the level of intracellular free calcium [177], an observation that is in agreement with the fact that NMDA antagonists are able to inhibit gp120-induced changes in intracellular calcium levels and subsequent neuronal injury [138]. Studies have shown that gp120-induced neuronal injury requires the presence of extracellular glutamate and calcium and the production of nitric oxide (NO). These results are supported by the ability of glutamate receptor antagonists and inhibitors of NO synthetase in the prevention of neurotoxicity [181]. Similarly, gp120-induced neuronal toxicity in human neurons was able to be attenuated by glutamate antagonists and the blockade of calcium channels [174]. In addition, gp120 exposure has also been associated with the activation of caspases 3 and 9 and the release of mitochondrial cytochrome c [175, 182]. Also of interest is the fact that inhibitors of both the Fas/TNF-α/death receptor and the mitochondrial death pathways can block gp120 neuronal apoptosis [182].

gp41 has been shown to be able to induce the expression of interleukin 1, tumor necrosis factor alpha, and NO via iNOS-mediated synthesis in both human and rodent glial cultures [183-185]. The detectable levels of gp41 in HIV-1 infected individuals [186-188] directly correlate with the severity and progression of HAD in humans [189].

HIV Vpr and Nef-induced Neurotoxicity

The viral protein R (Vpr) of HIV-1 regulates the import of the HIV-1 pre-integration complex, induces cell cycle arrest in replicating cells, stimulates viral transcription, and regulates activation of apoptotic pathways in infected cells [190]. *In vitro* studies using cultured neurons derived from rat hippocampal, cortical

and striatal neurons [191, 192] and an *in vivo* study using Vpr transgenic mice [193] have shown that Vpr has the ability to induce neuronal apoptosis and the Vpr-induced neuronal apoptosis requires the binding of Vpr to the adenine nucleotide translocator (ANT) in the inner membrane of the mitochondria [194-196]. These results are consistent with the findings that Vpr-related neuronal apoptosis involves increased production of ROS and the activation of caspases-3 [192] and caspases 8 [197]. Further, it has been shown that Vpr-induced apoptosis can be prevented by ectopic expression of caspases-inhibiting anti-apoptotic viral proteins [198] and the broad spectrum, irreversible caspases inhibitor Boc-D-FMK [199]. Taken together, the observation that higher levels of Vpr are found in the cerebrospinal fluid of AIDS patients with neurological disorders [200] suggest an important role for Vpr in the progressive neurodegeneration seen in HIV-1 positive individuals.

Nef (Negative Regulatory Factor) is a HIV-1 viral protein that plays both offense and defense in the battle between the AIDS viruses and the body's immune system. On one hand, Nef is associated with promoting the survival of HIV-1 infected cells and downregulating the surface level expression of major histocompatibility complex- I (MHC I) and II (MHC II) on antigen-presenting cells and the expression of CD4 and CD28 on T helper cells [201]. On the other hand, Nef is able to recruit leukocytes into the brains of rodents [202] and enhances the viral infection of primary human astrocytes [203]. It has been shown that Nef is necessary and sufficient for the progression of HIV-1 [204] and to promote AIDS development [205]. *In vitro* studies have shown that Nef is able to cause apoptosis in primary cultures of brain microvascular endothelial cells [206], and the death of primary human neurons and glia [207, 208]. However, grafting Nef-transduced macrophages in the hippocampus of a rat lead to no detectable apoptotic events [209], although Nef transgenic mice have been shown to develop a severe AIDS-like disease that effects all organ systems, including the brain [209]. It has also been shown that Nef is necessary and sufficient for the progression of HIV-1 [204] and to promote AIDS development [205].

Interaction of HIV-1 and Meth on brain

The amount of literature evaluating neuro-imaging changes on co-morbid HIV-1-positive Meth abusers is much more limited than that of either of the individual groups. Using MRS, significantly lower levels of NAA where demonstrated in co-morbid individuals, than the reductions seen in either of the individual conditions when compared to HIV-1 negative controls [210]. Chang *et al.* (2005) were able to show greater cumulative reductions of NAA in co-morbid individuals, although their results were not statistically significant. They were also able to show an increase in the levels of MI in the frontal cortices and basal ganglia.

Research has shown that the consequences of co-morbid Meth use and HIV-1 infection can be especially deleterious. It has been speculated that the use of Meth has contributed to the emergence of distinct neurological variants of HIV. Administration of Meth to rats after intrastriatal HIV-1 Tat injection leads to a synergistic reduction in levels of dopamine and its metabolites [211]. These changes are also associated with neurodegeneration that specifically involves the loss of dopamine terminals and/or macrophage recruitment and microglial activation in both rodent and non-human primate models [212-214]. The synergistic toxic effects of Tat and Meth were able to be attenuated in human fetal neurons with the use of antioxidants [211]. Similar results were also seen in the survival of the HT22 hippocampal cell line and of human primary neurons. Langfor et al. showed that co-administration of Tat and Meth leads to the appearance of earlier cellular demise and extensive cell death, and was associated with mitochondrial damage, disruption of mitochondrial calcium potential, and increased oxidative stress [215]. The synergistic effects of Tat and Meth-induced neuron degeneration have been further solidified by experimental results showing that animals treated with both Tat and Meth, both in subtoxic doses, showed significant reduction in striatal DA levels and DAT binding [211, 216]. It has also been demonstrated that intra-hippocampal Tat and Meth injection caused oxidative stress and activation of redox-regulated transcription factors in the cortical, striatal and hippocampal regions of the mouse brain [213].

Nevertheless, the mechanisms underlying Tat and Meth co-morbid effects have attracted a great deal of research interest. Flora *et al.* showed that hippocampal-stereotactic inject-

tion of Tat and intraperitoneal (ip) injection of Meth produced a marked increase in the levels of TNF-α mRNA in the mouse striatum [213]. The involvement of TNF-α in the potentiation of co-morbid effects of Tat and Meth in neurodegeneration is supported by the observations that the detrimental effects associated with Tat and Meth were attenuated in mice lacking TNF-α receptors, and that TNF-α synthesis inhibitors can reduce Tat and Meth-mediated neurodegeneration in hippocampal neuronal cultures [217].

In addition to TNF-α, monocyte chemotactic protein (MCP-1) has also been shown to be involved in Tat and Meth-induced neurotoxicity. Rats treated with Tat and Meth exhibit an increase in the levels of MCP-1 in the striatum in comparison to those treated with either Tat or Meth alone[214]. Theodore *et al.* also demonstrated that MCP-1 knockout mice were protected against Tat and Meth-induced neurotoxicity.

Moreover, a recent study reported that Tat and Meth together induce an increase in the activity of MMPs [218], suggesting that astroglia may play a role in Meth and HIV-1 interactions [219]. More specifically, treatment with Tat and Meth increased the release of MMP-1 and MMP activator in human neuron/astrocytes cultures [218].

In closing, although a great deal of research has been invested in elucidating the effects behind HIV-1- and Meth-induced neurodegeneration, a great deal still stands to be understood about the co-morbid neurodegeneration seen in HIV-1 infected Meth abusers. With the popularity of Meth abuse and the substantial HIV-1 infection risk among Meth abusers, these co-morbid individuals represent a subset population requiring special considerations for future research, prognosis and clinical treatment.

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