

Methamphetamine and HIV Infection, Role in Neurocognitive Dysfunction

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Abstract: The use of methamphetamine is steadily increasing worldwide. Its use is associated with high-risk sexual behavior and subsequent infection with HIV. Methamphetamine has profound effects on the brain both as an acute intoxicant and following chronic exposure. The combined effects of HIV and methamphetamine appear to result in widespread neuronal and white matter injury. These changes are most prominent in the basal ganglia and frontal lobe, and are not restricted to dopaminergic neurons. Additionally, methamphetamine and HIV proteins disrupt the blood brain barrier, cause glial cell activation and impair the function of neural progenitor cells. Methamphetamine also results in increased HIV replication via activation of chemokine receptors involved in HIV entry. Common pathways in several of these effects seem to involve induction of oxidative stress. Characterization of these subcellular pathways and identification of common targets is essential for development of therapeutic strategies for HIV-infected methamphetamine abusers.

Keywords: HIV, AIDS, methamphetamine, brain, neuron, dopamine, Tat, gp120.

EPIDEMIOLOGY

Methamphetamine is used by over 35 million people worldwide, and is often referred to by several popular terms such as speed, meth, crystal, crank, tweak, go-fast, ice, glass, uppers or black beauties. In the United States methamphetamine abuse has reached epidemic proportions. According to the National Survey on Drug Use and Health, approximately 11.7 million people, representing 5% of all U.S. residents aged 12 and over, reported trying methamphetamine at least once during their lifetimes resulting in an annual prevalence of 1.4% [1]. In some areas of the United States up to 40% of arrestees tested positive for methamphetamine and the majority of substance abuse treatment admissions excluding alcohol were for methamphetamine. Methamphetamine use is associated with increased HIV risk behavior [2, 3] and increased suicide attempts [4]. Methamphetamine can affect multiple organs and deaths from methamphetamine use often occur from cardiac arrest. However, the drug has profound effects on the brain causing anxiety, euphoria, paranoia, and depression in the short term [5]. Through mechanisms that are not yet well understood, long term use results in a variety of neurocognitive deficits, including behavioral changes, executive dysfunction, deficits in perceptual speed and information manipulation, and impairment of verbal and spatial memory. Neurocognitive deficits may persist after cessation of methamphetamine abuse, are slow to improve, and may not completely reverse [6, 7]. Methamphetamine can also adversely impact development, as evidenced by smaller brain volumes in infants exposed during the prenatal period [8].

The condition of many methamphetamine abusers in the United States is complicated by the co-occurrence of human immunodeficiency virus (HIV) infection. On its own, HIV infection leads to cognitive impairment in 30% of indi-

viduals, and frank dementia in 5 to 15%. Although the use of highly active antiretroviral therapy (HAART) over the past several years has significantly reduced the incidence of severe HIV dementia, in most studies this has been counterbalanced by an increase in prevalence due to improved survival rates (reviewed in [9]). HIV-related cognitive deficits are reminiscent of those incurred by methamphetamine; HIV infected individuals demonstrate impairment in attention, executive function, psychomotor speed, and motor and learning skills (reviewed in [7, 10]). Mounting evidence suggests that HIV infected patients who abuse methamphetamine have accelerated and more severe neurocognitive dysfunction compared with non-methamphetamine-abusing patients [11-13].

CLINICO-PATHOLOGICAL EFFECTS OF METHAMPHETAMINE USE IN HIV-INFECTED PATIENTS

Methamphetamine use has been associated with abnormalities in both the gray and white matter of the brain, some of which can persist long after abstinence from methamphetamine. This is supported by studies of animal models, pathological specimens, and magnetic resonance spectroscopy brain imaging [14-16]. Autopsy studies confirm injury to dopaminergic neurons [14, 15]. Based on evidence from a rat model, interaction between the HIV Tat protein and methamphetamine, as well as other drugs of abuse, may contribute to the damage in the dopaminergic system of the basal ganglia in patients with HIV dementia [17]. Methamphetamine users with HIV encephalitis (HIVE) also demonstrated more pronounced loss of synaptophysin and calbindin immunoreactivity, suggesting greater damage to non-pyramidal neurons. However, the methamphetamine-using patients also had less gp41 staining, suggesting the presence of fewer HIV infected macrophages/microglia, and, clinically, they had less severe dementia, but a higher frequency of ischemic events [18]. In addition, HIV-infected methamphetamine users had more severe loss of interneurons that was associated with cognitive impairment. Overall, com-

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pared with other markers, loss of calbindin and parvalbumin interneurons in the frontal cortex was the most significant correlate to memory deficits, suggesting a role in neurobehavioral alterations of HIV-infected methamphetamine users [19]. One study suggested a complex interaction and even opposing effects on cerebral volume with methamphetamine and HIV infection. Neurocognitive impairment was associated with decreased cortical volumes in HIV-positive participants, but with increased cortical volumes in methamphetamine-dependent participants [20]. The authors suggested that methamphetamine-induced increases in brain volumes may result from aberrant neuritic sprouting or glial cell activation. Indeed, a severe microglial reaction has been found in methamphetamine abusing patients with HIV compared to patients with HIV who did not use methamphetamine.

SYNERGISTIC NEUROTOXICITY WITH METHAMPHETAMINE AND HIV PROTEINS

It is clear that both HIV and methamphetamine independently cause neuronal damage, thus when individuals are exposed to both several theoretical possibilities exist. They may negate the effects of one another or enhance the neurotoxicity. This enhancement may either be additive, less than additive or be synergistic where by the effects of the two together may be greater than additive. A magnetic resonance spectroscopy study evaluating subjects with and without HIV infection and with and without methamphetamine use history found additive, not synergistic, effects on brain metabolites indicative of neuronal injury and glial activation [21]. In another study of HIV-infected methamphetamine abusers concentrations of cerebral metabolites are deranged if plasma viral loads are poorly controlled. These changes, consistent with neuronal disruption, are most prominent in the frontal lobe and far greater than that seen with methamphetamine or HIV infection alone, suggesting a synergistic effect [22].

Several experimental studies support these clinical observations. Methamphetamine synergizes with Tat and gp120 to cause increased neurotoxicity [23, 24]. An *in vivo* study has also demonstrated the synergism between methamphetamine and Tat [25]. Animals treated with methamphetamine alone showed only a 7% reduction in striatal dopamine levels and Tat-treated animals showed only an 8% decline, but animals treated with both methamphetamine and Tat demonstrated a 65% reduction in striatal dopamine. This study might be particularly relevant, because the doses of methamphetamine and Tat used were equivalent to what might be seen in human disease. Subsequent microdialysis studies in this same animal model showed that the synergistic reduction in striatal dopamine is accompanied by significant decrease in dopamine release from the striatum [17] and a decrease in dopamine transporter due to loss of dopamine terminals [26, 27].

Another possible mechanism for HIV-methamphetamine interaction is via oxidative stress. In one study [28], administration of either Tat or methamphetamine to mice increased markers of oxidative stress, including redox-regulated transcription factors, in cortical, striatal, and hippocampal brain regions. Furthermore, the DNA-binding activities of these transcription factors were greater in mice injected with both Tat and methamphetamine, than with either Tat or methamphetamine alone.

This same study also suggested Tat and methamphetamine may interact through changes in cell signaling and cytokine/chemokine expression. Mice treated with both agents had synergistic upregulation of intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor- α , and interleukin-1 β gene expression compared to mice treated with either agent alone. Interestingly, tumor necrosis factor receptor knock out animals had no effect on dopamine levels when treated with Tat, suggesting that the Tat-mediated increase in tumor necrosis factor may contribute to the loss of dopaminergic terminals [29]. Another study showed that Tat and methamphetamine interact to cause damage to calbindin-immunoreactive nonpyramidal neurons by dysregulating mitochondrial calcium metabolism, associated with increased levels of oxidative stress [30].

METHAMPHETAMINE AND OXIDATIVE/NITROSATIVE STRESS

Although methamphetamine was initially thought to only damage monoaminergic nerve terminals, subsequent studies have consistently shown that widespread neuronal cell death results (reviewed in [31]). Cell death involves not only the striatum and cortex, but the hippocampus and olfactory pathways as well [32, 33]. Methamphetamine can enter cells directly through cationic lipophilicity or through the dopamine transporter [34]. Although the molecular mechanisms underlying methamphetamine neurotoxicity are likely multifactorial, several key findings support a significant role for both oxidative and nitrosative stress. Mice overexpressing superoxide dismutase, an antioxidant, show markedly decreased methamphetamine-induced apoptosis. Suppression of nitric oxide (NO) production, through both pharmacologic and genetic means, also protects against methamphetamine-mediated neurotoxicity [35]. In addition, methamphetamine causes increased levels of 3-nitrotyrosine adduct formation, reflective of oxidative and nitrosative stress [36, 37]. These studies, among many others, demonstrate the important role of oxidative and nitrosative stress in the pathogenesis of methamphetamine-induced neurotoxicity.

HIV-TAT PROTEIN AND METHAMPHETAMINE POTENTIATE NEUROTOXICITY VIA OXIDATIVE/NITROSATIVE STRESS

Although HIV does not productively infect neurons, extensive neuronal loss in many brain areas has been widely demonstrated in HIV dementia [38-40]. Perivascular macrophages and microglia are a major target of HIV infection within the brain, leading to the hypothesis that the observed neurotoxicity is an indirect effect of HIV-infected cells [41]. Inflammatory mediators and viral proteins have been hypothesized to play a major role in HIV neurotoxicity. Of the latter, HIV proteins gp120 and Tat have emerged as likely mediators of the neurotoxic effects of the virus [42]. Tat plays a critical role in regulating transcription from the long terminal repeat (LTR) promoter region of HIV [43]. Several lines of evidence suggest that Tat is involved in HIV-mediated neurotoxicity. Tat has been demonstrated in both HIV infected cells and in extracellular matrix of brains of infected patients with HIV encephalopathy [44, 45], and Tat derived from patients with HIV dementia is more neurotoxic than Tat derived from infected patients without dementia

[46]. When applied to neurons, Tat causes neuronal death through multiple molecular mechanisms including induction of changes in neuronal calcium flux, sensitization of neurons to glutamate excitotoxicity and direct interactions with the NMDA receptor [47-50], and upregulation of neurotoxic inflammatory cytokines from monocytes/macrophages and astrocytes [51-55]. Importantly, Tat is released extracellularly from HIV infected cells [50, 56, 57].

Tat-induced neurotoxicity is relevant even in HIV-infected individuals treated with highly active antiretroviral therapy (HAART). It is clear that HAART can control viral replication in the peripheral blood and can result in some improvement in cognitive and psychomotor function [58, 59]. However, once cells in the brain are infected and viral integration has occurred, currently available antiretroviral drugs have no effect on the production of nonstructural proteins such as Tat, which may still be released unchecked from infected microglia/macrophages and astrocytes, thereby causing neurotoxicity [60].

One common pathway by which Tat induces neurotoxicity is by increasing the production of reactive oxygen species in neurons. Parallel changes are observed in cultured neurons exposed to Tat, suggesting that Tat induces oxidative stress (reviewed in [61]). In addition, protein carbonyl moieties, which can arise from direct oxidation of several amino acids, are increased in rat striatum upon injection of Tat [62]. Tat also affects the glutathione system, one of the major endogenous anti-oxidant pathways, by downregulating activity of glutathione synthetase resulting in decreased glutathione mRNA levels [63]. Mounting evidence suggests that Tat primarily exerts oxidative and nitrosative stress through interactions with astrocytes, microglia, and brain endothelial cells to increase expression of inducible nitric oxide synthase (iNOS) and oxidative-stress inducing cytokines, with concomitant neurotoxic effects (reviewed in [61]). Importantly, iNOS levels and nitrosylated proteins in the CSF correlate with severity of HIV-associated dementia [64, 65]. Thus, the emerging paradigm is that excessive nitric oxide and upregulated cytokines released from macrophages, microglia, and astrocytes contribute to oxidative and nitrosative stress-mediated neuronal toxicity in HIV dementia. Tat likely plays an important role in neurotoxicity by inducing oxidative and nitrosative stress both directly in neurons and indirectly through effects on astrocytes and other glial cells.

It has become increasingly clear that the HIV Tat protein and methamphetamine can potentiate each other's neurotoxicity. Several investigators have demonstrated that the neurotoxic effects of Tat and methamphetamine together are more severe than either one alone [23, 25]. Methamphetamine and Tat synergize to destroy dopaminergic terminals in the rat striatum [26] and cause mitochondrial dysregulation in neurons [18]. Importantly, the mechanism of synergy appears to be explained, at least in part, by potentiation of oxidative stress by methamphetamine and Tat together [28, 30].

POTENTIAL ROLES FOR HIV AND METHAMPHETAMINE IN MODULATION OF ADULT HIPPOCAMPAL NEUROGENESIS

Much of the effort to understand how HIV and methamphetamine affect the central nervous system has focused on

the deleterious effects on mature neurons. However, the extent to which neuronal precursor cells (NPC) are affected by these processes, and whether alterations of NPC function and survival may contribute to HIV- and methamphetamine-associated neurologic changes, remains largely unknown. Several lines of evidence suggest that HIV can interact with NPCs. The HIV envelope protein gp120 interacts with the chemokine receptor CXCR4 on the surface of NPCs, and can block chemokine-mediated signaling in these cells [66]. HIV can also cause a transient productive infection of NPCs, followed by the establishment of viral latency [67]. A recent study investigated adult hippocampal neurogenesis in HIV-infected humans; immunohistochemistry of autopsy tissue suggested a reduction in proliferation of hippocampal NPCs in patients with HIV-associated dementia as compared to non-demented HIV-infected patients and controls [68]. These findings, coupled with evidence that CNS inflammatory mediators such as interleukin-6 can decrease neurogenesis [69, 70], suggest that impairment of neurogenesis may occur during HIV infection, contributing to the course of HIV-dementia.

Although several drugs of abuse have been shown to influence neurogenesis, limited data are available with respect to the effects of methamphetamine. However, an intriguing link between methamphetamine and neurogenesis was demonstrated in a model of acute methamphetamine toxicity in adult gerbils, in which acute methamphetamine exposure resulted in a significant decrease in proliferating NPCs within the hippocampal dentate gyrus [71]. Similarly in a chronic self administration model impaired neurogenesis was also noted [72]. It is likely that HIV and methamphetamine will interact to affect NPC survival and function.

Several recent studies have begun to address the effects of oxidative stress and NO on function and survival of NPCs. Increasing evidence suggests that NO and NO donors also modulate NPC function. Though the effects of NO on hippocampal dentate NPCs remain controversial [73], several studies suggest that NO donors decrease NPC proliferation and drive differentiation toward the neuronal lineage, while inhibitors of NOS increase proliferation and decrease differentiation [74]. Because oxidative stress and NO can have multiple effects on NPCs, including impairment of survival, reduced proliferation, and modulation of differentiation, it is reasonable to speculate that the combined effects of HIV and methamphetamine would be detrimental to NPC function via these pathways.

EFFECT OF METHAMPHETAMINE AND HIV ON THE BLOOD BRAIN BARRIER

Methamphetamine and HIV envelope protein, gp120, individually and in combination, modulate tight junction expression in brain endothelial cells leading to decreased transendothelial resistance across the blood brain barrier and enhanced transendothelial migration of immunocompetent cells [75]. Acute intoxication with methamphetamine is associated with breakdown of the blood brain barrier with cerebral edema and massive ion shifts. While most of these acute structural and functional abnormalities appear to be reversible, they could trigger subsequent cellular alterations in the brain and accelerate neurodegeneration [76]. Metham-

phetamine also induces disturbances in cellular redox status and activation of transcription factors AP-1 and NF-kappaB which play critical roles in the signaling pathways leading to upregulation of inflammatory genes in human brain endothelial cells [77]. These alterations in the blood brain barrier could potentially enhance HIV entry into the brain as well as viral proteins and other inflammatory mediators. This could in turn lead to glial cell activation and neurodegeneration.

EFFECT OF HIV INFECTION AND METHAMPHETAMINE ABUSE ON MATRIX METALLOPROTEINASES

Matrix metalloproteinases (MMPs) are zinc dependent endopeptidases that were named for their ability to act on proteins of the extracellular matrix. MMPs have been well studied for their ability to degrade matrix proteins of the blood brain barrier and thus facilitate the CNS ingress of inflammatory molecules and/or serum derived toxins. However, while MMPs were named for their ability to process matrix, it is becoming ever more apparent that they play a critical role in the processing of non-matrix proteins including chemokines and a variety of cell surface receptors [78] widely expressed on neurons, astrocytes and blood brain barrier endothelial cells. In addition, by means of effects that include the processing of binding proteins, MMPs can also influence the bioavailability of proteins such as IGF-1 and EGF receptor ligands [78, 79].

MMPs are expressed in the CNS by a variety of cell types. It has been shown, for example, that astrocytes can release MMP-1, -2 and -3, and that microglia can release MMP-7, -9 and -12 [79-81]. Neurons may also release MMPs in an activity dependent manner, and release may be increased in the setting of an excitotoxic injury [82, 83]. Of interest, MMPs are also released from activated monocytes and T cells, with monocytes releasing MMP-1, -7, -9 and -12. [84].

Transcription factors including AP-1 and NF-kB are important to the expression of a variety of MMPs. Not surprisingly, HIV proteins and inflammatory cytokines that are known to increase the DNA binding activity of these transcription factors have been shown to increase MMP expression and/or release in leukocytes and neural cells. That a substantial increase in MMP expression may be affected in turn supported by studies which have shown increased MMP levels in cerebrospinal fluid samples from HIV infected individuals [80]. Of interest, the levels of select MMPs are further increased in that subset of HIV infected individuals who show cognitive impairment [80].

Methamphetamine has also been associated with increased MMP expression, release, and/or activation [85]. Thought to increase extracellular dopamine through mechanisms that include a redistribution of the catecholamine from synaptic vesicles to the cytoplasm and reverse flux through cell surface dopamine transporters, methamphetamine may increase MMP expression via dopamine receptor mediated signaling [86, 87]. Catecholamine receptor activation on neurons and glia has been shown to increase the DNA binding activity of AP-1. It is also possible that methamphetamine associated changes in dopamine might stimulate release of proteinases from preformed stores.

Methamphetamine can also increase glutamate levels [86]. This is thought to occur via D₁-associated striatonigral GABA release [86]. Given that glutaminergic transmission potently upregulates MMP release [82, 88], methamphetamine might also increase neuronal MMP release via this less direct dopaminergic mechanism. Finally, in a variety of studies, methamphetamine has been linked to the generation of reactive oxygen intermediates. Increased MMP expression, and activation, is known to occur in association with increased levels of such species.

In previously published work, we have shown that both the HIV protein Tat and methamphetamine increased the release of MMP-1 from cultures of neurons and glia [89]. This is consistent with results from rodent studies in which methamphetamine stimulates increased binding of AP-1, a transcription factor critical to the expression of MMPs including MMP-1 [90, 91].

It has been shown that methamphetamine increases levels of MMP-2 and -9 and that increases in the level of these proteinases may contribute to behavioral effects of the drug [92]. This is significant in that behavioral effects and toxicity are often linked. Of interest, MMPs might influence dopamine release [92]. It is tempting to speculate that dopamine stimulates MMP release and vice versa, thus establishing a cycle of potentiation.

We and others have also observed that methamphetamine can stimulate the release of the MMP activator urokinase plasminogen activator (uPA) [89]. Of additional interest, it was shown by a variety of techniques that methamphetamine could increase dendritic cell expression of pro-inflammatory cytokines known to stimulate MMP expression [93]. Increased MMP expression may contribute to synaptic damage and neuronal damage through a variety of mechanisms that includes processing of integrin binding extracellular matrix components and stimulation of cell death via interactions with select cell surface integrins [94]. In addition, soluble molecules such as SDF-1alpha may be processed by MMPs into neurotoxic fragments [95]. And while it has not been shown, MMPs might increase thrombin receptor mediated signaling on neurons so that GSK-3 beta dependent cell death ensues. MMP-1 can activate the thrombin receptor PAR-1 which can mediate neuronal death in select circumstances [96].

EFFECT OF METHAMPHETAMINE ON HIV REPLICATION

Methamphetamine induces increased HIV-1 infection in association with an increase in the HIV-1 coreceptors, CXCR4 and CCR5, and infection is mediated by downregulation of extracellular-regulated kinase and the upregulation of p38 mitogen-activated protein kinase demonstrating that the methamphetamine-induced effect is mediated via the dopamine receptors and the dopamine receptor antagonists can reverse methamphetamine-induced upregulation of CCR5 [97, 98]. In a feline immunodeficiency virus model, methamphetamine markedly increased viral replication in feline astrocytes for cell-associated infection [99]. Thus methamphetamine use leads to poor viral control and promotes resistance to antiretroviral drugs [100]. In the brain of HIV infected methamphetamine users, there is induction of

interferon inducible genes, suggesting a dysregulation of the innate immune responses [101].

CONCLUSION

In conjunction with HIV infection, methamphetamine has multiple effects on the brain, which includes neuronal and glial cell dysfunction as well as disruption of the blood brain barrier. Its ability to enhance HIV replication and induce chemokine production leads to the establishment of positive feedback loops. These pathways are largely driven by induction of oxidative stress, hence targeting these pathways may have therapeutic potential.

ACKNOWLEDGEMENTS

Supported in part by grants from the National Institute of Drug Abuse, National Institutes of Health, USA.

LIST OF ABBREVIATIONS

HIV	=	Human Immunodeficiency Virus
HAART	=	Highly Active anti-retroviral Treatment
AIDS	=	Acquired Immunodeficiency Syndrome
HIVE	=	HIV Encephalitis
ICAM	=	1-Intercellular Adhesion Molecule-1
NO	=	Nitric Oxide
LTR	=	Long Terminal Repeat
NMDA	=	n-Methyl-D-Aspartate
iNOS	=	Inducible Nitric Oxide Synthase
mRNA	=	Messenger Ribonucleic Acid
NPC	=	Neuronal Precursor Cell
CXCR4	=	CXC Type Chemokine Receptor 4
MMP	=	Matrix Metalloproteinase
AP-1	=	Activator Protein 1
NF- κ B	=	Nuclear Factor Kappa B (B cells)
IGF	=	Insulin Like Growth Factor
EGF	=	Epidermal Growth Factor
DNA	=	Deoxyribonucleic Acid
uPA	=	Urokinase Plasminogen Activator
GSK	=	Glycogen Synthase Kinase
PAR	=	Protease Activated Receptor
CCR5	=	CC Type Chemokine Receptor 5

REFERENCES

- Maxwell, J.C.; Rutkowski, B.A. The prevalence of methamphetamine and amphetamine abuse in North America, a review of the indicators, 1992-2007. *Drug Alcohol Rev.*, **2008**, *27*(3), 229-235.
- Rawson, R.A.; Gonzales, R.; Pearce, V.; Ang, A.; Marinelli-Casey, P.; Brummer, J. Methamphetamine dependence and human immunodeficiency virus risk behavior. *J. Subst. Abuse Treat.*, **2008**, *35*(3), 279-284.
- Semple, S.J.; Zians, J.; Strathdee, S.A.; Patterson, T.L. Sexual marathons and methamphetamine use among HIV-positive men who have sex with men. *Arch. Sex Behav.*, **2008**.
- Glasner-Edwards, S.; Mooney, L.J.; Marinelli-Casey, P.; Hillhouse, M.; Ang, A.; Rawson, R. Risk factors for suicide attempts in methamphetamine-dependent patients. *Am. J. Addict.*, **2008**, *17*(1), 24-27.
- Glasner-Edwards, S.; Mooney, L.J.; Marinelli-Casey, P.; Hillhouse, M.; Ang, A.; Rawson, R. Clinical course and outcomes of methamphetamine-dependent adults with psychosis. *J. Subst. Abuse Treat.*, **2008**, *35*(4), 445-450.
- Rendell, P.G.; Mazur, M.; Henry, J.D. Prospective memory impairment in former users of methamphetamine. *Psychopharmacology (Berl)*, **2009**, *203*(3), 609-616.
- Scott, J.C.; Woods, S.P.; Matt, G.E.; Meyer, R.A.; Heaton, R.K.; Atkinson, J.H.; Grant, I. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. *Neuropsychol. Rev.*, **2007**, *17*(3), 275-297.
- Chang, L.; Smith, L.M.; LoPresti, C.; Yonekura, M.L.; Kuo, J.; Walot, I.; Ernst, T. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatr. Res.*, **2004**, *132*(2), 95-106.
- McArthur, J.C.; Brew, B.J.; Nath, A. Neurological complications of HIV infection. *Lancet Neurol.*, **2005**, *4*(9), 543-555.
- Dawes, S.; Suarez, P.; Casey, C.Y.; Cherner, M.; Marcotte, T.D.; Letendre, S.; Grant, I.; Heaton, R.K. Variable patterns of neuropsychological performance in HIV-1 infection. *J. Clin. Exp. Neuropsychol.*, **2008**, *30*(6), 613-626.
- Letendre, S.L.; Cherner, M.; Ellis, R.J.; Marquie-Beck, J.; Gragg, B.; Marcotte, T.; Heaton, R.K.; McCutchan, J.A.; Grant, I. The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance, biological correlates of disease. *Aids*, **2005**, *19*(Suppl 3), S72-78.
- Carey, C.L.; Woods, S.P.; Rippeth, J.D.; Gonzalez, R.; Heaton, R.K.; Grant, I. Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. *AIDS Behav.*, **2006**, *10*(2), 185-190.
- Nath, A.; Maragos, W.; Avison, M.; Schmitt, F.; Berger, J. Accelerated HIV dementia with methamphetamine and cocaine use. *J. Neurovirol.*, **2001**, *7*, 66-71.
- Wilson, J.M.; Kalasinsky, K.S.; Levey, A.I.; Bergeron, C.; Reiber, G.; Anthony, R.M.; Schmunk, G.A.; Shannak, K.; Haycock, J.W.; Kish, S.J. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nat. Med.*, **1996**, *2*(6), 699-703.
- Wilson, J.M.; Levey, A.I.; Bergeron, C.; Kalasinsky, K.; Ang, L.; Peretti, F.; Adams, V.I.; Smialek, J.; Anderson, W.R.; Shannak, K.; Haycock, J.W.; Kish, S.J. Striatal dopamine, dopamine transporter, and vesicular monoamine transporter in chronic cocaine users. *Ann. Neurol.*, **1996**, *40*(3), 428-439.
- Ernst, T.; Chang, L.; Leonido-Yee, M.; Speck, O. Evidence for long-term neurotoxicity associated with methamphetamine abuse, A 1H MRS study. *Neurology*, **2000**, *54*, 1344-1349.
- Cass, W.A.; Harned, M.E.; Peters, L.E.; Nath, A.; Maragos, W.F. HIV-1 protein Tat potentiation of methamphetamine-induced decreases in evoked overflow of dopamine in the striatum of the rat. *Brain Res.*, **2003**, *984*(1-2), 133-142.
- Langford, D.; Adame, A.; Grigorian, A.; Grant, I.; McCutchan, J.A.; Ellis, R.J.; Marcotte, T.D.; Masliah, E. Patterns of selective neuronal damage in methamphetamine-user AIDS patients. *J. Acquir. Immune Defic. Syndr.*, **2003**, *34*(5), 467-474.
- Chana, G.; Everall, I.P.; Crews, L.; Langford, D.; Adame, A.; Grant, I.; Cherner, M.; Lazzaretto, D.; Heaton, R.; Ellis, R.; Masliah, E.; HNRC Group. Cognitive deficits and degeneration of interneurons in HIV+ methamphetamine users. *Neurology*, **2006**, *67*(8), 1486-1489.
- Jernigan, T.L.; Gamst, A.C.; Archibald, S.L.; Fennema-Notestine, C.; Mindt, M.R.; Marcotte, T.L.; Heaton, R.K.; Ellis, R.J.; Grant, I. Effects of methamphetamine dependence and HIV infection on cerebral morphology. *Am. J. Psychiatry*, **2005**, *162*(8), 1461-1472.
- Chang, L.; Ernst, T.; Speck, O.; Grob, C.S. Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. *Am. J. Psychiatry*, **2005**, *162*(2), 361-369.
- Taylor, M.J.; Schweinsburg, B.C.; Alhassoon, O.M.; Gongvatana, A.; Brown, G.G.; Young-Casey, C.; Letendre, S.L.; Grant, I. Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy. *J. Neurovirol.*, **2007**, *13*(2), 150-159.
- Turchan, J.; Anderson, C.; Hauser, K.F.; Sun, Q.; Zhang, J.; Liu, Y.; Wise, P.M.; Kruman, I.; Maragos, W.; Mattson, M.P.; Booze,

- R.; Nath, A. Estrogen protects against the synergistic toxicity by HIV proteins, methamphetamine and cocaine. *BMC Neurosci.*, **2001**, 2(1),3.
- [24] Cai, N.S.; Cadet, J.L. The combination of methamphetamine and of the HIV protein, Tat, induces death of the human neuroblastoma cell line, SH-SY5Y. *Synapse*, **2008**, 62(7), 551-552.
- [25] Maragos, W.F.; Young, K.L.; Turchan, J.T.; Guseva, M.; Pauly, J.R.; Nath, A.; Cass, W.A. Human immunodeficiency virus-1 Tat protein and methamphetamine interact synergistically to impair striatal dopaminergic function. *J. Neurochem.*, **2002**, 83(4), 955-963.
- [26] Theodore, S.; Stolberg, S.; Cass, W.A.; Maragos, W.F. Human immunodeficiency virus-1 protein tat and methamphetamine interactions. *Ann. NY Acad. Sci.*, **2006**, 1074, 178-190.
- [27] Theodore, S.; Cass, W.A.; Nath, A.; Maragos, W.F. Progress in understanding basal ganglia dysfunction as a common target for methamphetamine abuse and HIV-1 neurodegeneration. *Curr. HIV Res.*, **2007**, 5(3), 301-313.
- [28] Flora, G.; Lee, Y.W.; Nath, A.; Hennig, B.; Maragos, W.; Toborek, M. Methamphetamine potentiates HIV-1 Tat protein-mediated activation of redox-sensitive pathways in discrete regions of the brain. *Exp. Neurol.*, **2003**, 179(1), 60-70.
- [29] Theodore, S.; Cass, W.A.; Nath, A.; Steiner, J.; Young, K.; Maragos, W.F. Inhibition of tumor necrosis factor- α signaling prevents human immunodeficiency virus-1 protein Tat and methamphetamine interaction. *Neurobiol. Dis.*, **2006**, 23(3), 663-668.
- [30] Langford, D.; Grigorian, A.; Hurford, R.; Adame, A.; Crews, L.; Masliah, E. The role of mitochondrial alterations in the combined toxic effects of human immunodeficiency virus Tat protein and methamphetamine on calbindin positive-neurons. *J. Neurovirol.*, **2004**, 10(6), 327-337.
- [31] Cadet, J.L.; Jayanthi, S.; Deng, X. Methamphetamine-induced neuronal apoptosis involves the activation of multiple death pathways, review. *Neurotox. Res.*, **2005**, 8(3-4), 199-206.
- [32] Deng, X.; Ladenheim, B.; Jayanthi, S.; Cadet, J.L. Methamphetamine administration causes death of dopaminergic neurons in the mouse olfactory bulb. *Biol. Psychiatry*, **2007**, 61(11), 1235-1243.
- [33] Cai, N.S.; McCoy, M.T.; Ladenheim, B.; Lyles, J.; Ali, S.F.; Cadet, J.L. Serial analysis of gene expression in the rat striatum following methamphetamine administration. *Ann. NY Acad. Sci.*, **2006**, 1074, 13-30.
- [34] Davidson, C.; Gow, A.J.; Lee, T.H.; Ellinwood, E.H. Methamphetamine neurotoxicity, necrotic and apoptotic mechanisms and relevance to human abuse and treatment. *Brain Res. Brain Res. Rev.*, **2001**, 36(1), 1-22.
- [35] Deng, X.; Cadet, J.L. Methamphetamine administration causes overexpression of nNOS in the mouse striatum. *Brain Res.*, **1999**, 851(1-2), 254-257.
- [36] Imam, S.Z.; Newport, G.D.; Islam, F.; Slikker, W. Jr.; Ali, S.F. Selenium, an antioxidant, protects against methamphetamine-induced dopaminergic neurotoxicity. *Brain Res.*, **1999**, 818(2), 575-578.
- [37] Imam, S.Z.; el-Yazal, J.; Newport, G.D.; Itzhak, Y.; Cadet, J.L.; Slikker, W. Jr.; Ali, S.F. Methamphetamine-induced dopaminergic neurotoxicity, role of peroxynitrite and neuroprotective role of antioxidants and peroxynitrite decomposition catalysts. *Ann N Y Acad Sci* **2001**, 939, 366-380.
- [38] Masliah, E.; Ge, N.; Achim, C.L.; Hansen, L.A.; Wiley, C.A. Selective neuronal vulnerability in HIV encephalitis. *J. Neuropathol. Exp. Neurol.*, **1992**, 51(6), 585-593.
- [39] Everall, I.; Barnes, H.; Spargo, E.; Lantos, P. Assessment of neuronal density in the putamen in human immunodeficiency virus (HIV) infection, application of stereology and spatial analysis of quadrats. *J. Neurovirol.*, **1995**, 1(1), 126-129.
- [40] Petito, C.K.; Kerza-Kwiatecki, A.P.; Gendelman, H.E.; McCarthy, M.; Nath, A.; Podack, E.R.; Shapshak, P.; Wiley, C.A. Review, neuronal injury in HIV infection. *J. Neurovirol.*, **1999**, 5(4), 327-341.
- [41] Gartner, S. HIV infection and dementia. *Science*, **2000**, 287(5453), 602-604.
- [42] Nath, A. Human immunodeficiency virus (HIV) proteins in neuropathogenesis of HIV dementia. *J. Infect. Dis.*, **2002**, 186(Suppl 2), 193-198.
- [43] Rosen, C.A.; Terwilliger, E.; Dayton, A.; Sodroski, J.G.; Haseltine, W.A. Intragenic cis-acting art gene-responsive sequences of the human immunodeficiency virus. *Proc. Natl. Acad. Sci. USA*, **1988**, 85(7), 2071-2075.
- [44] Hudson, L.; Liu, J.; Nath, A.; Narayan, O.; Male, D.; Jones, M.; Everall, I. Detection of human immunodeficiency virus regulatory protein tat in CNS tissues. *J. Neurovirol.*, **2000**, 6, 145-155.
- [45] Valle, L.D.; Croul, S.; Morgello, S.; Amini, S.; Rappaport, J.; Khalili, K. Detection of HIV-1 Tat and JCV capsid protein, VP1, in AIDS brain with progressive multifocal leukoencephalopathy. *J. Neurovirol.*, **2000**, 6(3), 221-228.
- [46] Johnston, J.B.; Zhang, K.; Silva, C.; Shalinsky, D.R.; Conant, K.; Ni, W.; Corbett, D.; Yong, V.W.; Power, C. HIV-1 Tat neurotoxicity is prevented by matrix metalloproteinase inhibitors. *Ann. Neurol.*, **2001**, 49(2), 230-241.
- [47] Magnuson, D.S.; Knudsen, B.E.; Geiger, J.D.; Brownstone, R.M.; Nath, A. Human immunodeficiency virus type 1 tat activates non-N-methyl-D-aspartate excitatory amino acid receptors and causes neurotoxicity. *Ann. Neurol.*, **1995**, 37, 373-380.
- [48] Cheng, J.; Nath, A.; Knudsen, B.; Hochman, S.; Geiger, J.D.; Magnuson, D.S.K. Neuronal excitatory properties of human immunodeficiency virus type 1 tat protein. *Neuroscience*, **1998**, 82, 97-106.
- [49] Song, L.; Nath, A.; Geiger, J.D.; Moore, A.; Hochman, S. Human immunodeficiency virus type 1 Tat protein directly activates neuronal N-methyl-D-aspartate receptors at an allosteric zinc-sensitive site. *J. Neurovirol.*, **2003**, 9(3), 399-403.
- [50] Li, W.; Huang, Y.; Reid, R.; Steiner, J.; Malpica-Llanos, T.; Darden, T.A.; Shankar, S.K.; Mahadevan, A.; Satishchandra, P.; Nath, A. NMDA receptor activation by HIV-Tat protein is clade dependent. *J. Neurosci.*, **2008**, 28(47), 12190-12198.
- [51] Chiao, C.; Bader, T.; Stenger, J.E.; Baldwin, W.; Brady, J.; Barrett, J.C. HIV type 1 Tat inhibits tumor necrosis factor α -induced repression of tumor necrosis factor receptor p55 and amplifies tumor necrosis factor α activity in stably tat-transfected HeLa Cells. *AIDS Res. Hum. Retroviruses*, **2001**, 17(12), 1125-1132.
- [52] Chen, P.; Mayne, M.; Power, C.; Nath, A. The Tat protein of HIV-1 induces tumor necrosis factor- α production, Implications for HIV associated neurological diseases. *J. Biol. Chem.*, **1997**, 272(36), 22385-22388.
- [53] Nath, A.; Conant, K.; Chen, P.; Scott, C.; Major, E.O. Transient exposure to HIV-1 Tat protein results in cytokine production in macrophages and astrocytes, a hit and run phenomenon. *J. Biol. Chem.*, **1999**, 274(24), 17098-17102.
- [54] Kutsch, O.; Oh, J.; Nath, A.; Benveniste, E.N. Induction of the chemokines interleukin-8 and IP-10 by human immunodeficiency virus type 1 tat in astrocytes. *J. Virol.*, **2000**, 74(19), 9214-9221.
- [55] Weiss, J.M.; Nath, A.; Major, E.O.; Berman, J.W. HIV-Tat induces MCP-1 mediated monocyte transmigration and upregulates CCR5 expression on human monocytes. *J. Immunol.*, **1999**, 163, 2953-2959.
- [56] Chauhan, A.; Turchan, J.; Pocernich, C.; Bruce-Keller, A.; Roth, S.; Butterfield, D.A.; Major, E.O.; Nath, A. Intracellular human immunodeficiency virus Tat expression in astrocytes promotes astrocyte survival but induces potent neurotoxicity at distant sites via axonal transport. *J. Biol. Chem.*, **2003**, 278(15), 13512-13519.
- [57] Chang, H.C.; Samaniego, F.; Nair, B.C.; Buonaguro, L.; Ensoli, B. HIV-1 tat protein exits from cells via a leaderless secretory pathway and binds to extracellular matrix-associated heparan sulfate proteoglycan through its basic region. *AIDS*, **1997**, 11, 1421-1431.
- [58] Letendre, S.; Marquie-Beck, J.; Capparelli, E.; Best, B.; Clifford, D.; Collier, A.C.; Gelman, B.B.; McArthur, J.C.; McCutchan, J.A.; Morgello, S.; Simpson, D.; Grant, I.; Ellis, R.J.; CHARTER Group. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch. Neurol.*, **2008**, 65(1), 65-70.
- [59] Sacktor, N.; McDermott, M.P.; Marder, K.; Schifitto, G.; Selnes, O.A.; McArthur, J.C.; Stern, Y.; Albert, S.; Palumbo, D.; Kieburtz, K.; De Marcaida, J.A.; Cohen, B. Epstein LHIV-associated cognitive impairment before and after the advent of combination therapy. *J. Neurovirol.*, **2002**, 8(2), 136-142.
- [60] Nath, A.; Hersh, L.B. Tat and amyloid, multiple interactions. *Aids* **2005**, 19(2), 203-204.
- [61] Steiner, J.; Haughey, N.; Li, W.; Venkatesan, A.; Anderson, C.; Reid, R.; Malpica, T.; Pocernich, C.; Butterfield, D.A.; Nath, A. Oxidative stress and therapeutic approaches in HIV dementia. *Antioxid. Redox. Signal*, **2006**, 8(11-12), 2089-2100.
- [62] Aksenov, M.Y.; Hasselrot, U.; Bansal, A.K.; Wu, G.; Nath, A.; Anderson, C.; Mactutus, C.F.; Booze, R.M. Oxidative damage in-

- duced by the injection of HIV-1 Tat protein in the rat striatum. *Neurosci. Lett.*, **2001**, *305*(1), 5-8.
- [63] Flores, S.C.; Marecki, J.C.; Harper, K.P.; Bose, S.K.; Nelson, S.K.; McCord, J.M. Tat protein of human immunodeficiency virus type 1 represses expression of manganese superoxide dismutase in HeLa cells. *Proc. Natl. Acad. Sci. USA*, **1993**, *90*(16), 7632-7636.
- [64] Adamson, D.C.; Wildermann, B.; Sasaki, M.; D, G.J.; McArthur, J.C.; Christov, V.I.; Dawson, T.M.; Dawson, V.L. Immunologic NO synthase, Elevation in severe AIDS dementia and induction by HIV-1 gp41. *Science*, **1996**, *274*, 1917-1920.
- [65] Li, W.; Malpica-Llanos, T.M.; Gundry, R.; Cotter, R.J.; Sacktor, N.; McArthur, J.; Nath, A. Nitrosative stress with HIV dementia causes decreased L-prostaglandin D synthase activity. *Neurology*, **2008**, *70*(19 Pt 2), 1753-1762.
- [66] Tran, P.B.; Miller, R.J. HIV-1, chemokines and neurogenesis. *Neurotox. Res.*, **2005**, *8*(1-2), 149-158.
- [67] Lawrence, D.M.; Durham, L.C.; Schwartz, L.; Seth, P.; Maric, D.; Major, E.O. Human immunodeficiency virus type 1 infection of human brain-derived progenitor cells. *J. Virol.*, **2004**, *78*(14), 7319-7328.
- [68] Krathwohl, M.D.; Kaiser, J.L. HIV-1 promotes quiescence in human neural progenitor cells. *J. Infect. Dis.*, **2004**, *190*(2), 216-226.
- [69] Poluektova, L.; Moran, T.; Zeligvanskaya, M.; Swindells, S.; Gendelman, H.E.; Persidsky, Y. The regulation of alpha chemokines during HIV-1 infection and leukocyte activation, relevance for HIV-1-associated dementia. *J. Neuroimmunol.*, **2001**, *120*(1-2), 112-128.
- [70] Persidsky, Y.; Poluektova, L. Immune privilege and HIV-1 persistence in the CNS. *Immunol. Rev.*, **2006**, *213*, 180-194.
- [71] Teuchert-Noodt, G.; Dawirs, R.R.; Hildebrandt, K. Adult treatment with methamphetamine transiently decreases dentate granule cell proliferation in the gerbil hippocampus. *J. Neural. Transm.*, **2000**, *107*(2), 133-143.
- [72] Mandyam, C.D.; Wee, S.; Crawford, E.F.; Eisch, A.J.; Richardson, H.N.; Koob, G.F. Varied access to intravenous methamphetamine self-administration differentially alters adult hippocampal neurogenesis. *Biol. Psychiatry*, **2008**, *64*(11), 958-965.
- [73] Estrada, C.; Murillo-Carretero, M. Nitric oxide and adult neurogenesis in health and disease. *Neuroscientist*, **2005**, *11*(4), 294-307.
- [74] Packer, M.A.; Stasiv, Y.; Benraiss, A.; Chmielnicki, E.; Grinberg, A.; Westphal, H.; Goldman, S.A.; Enikolopov, G. Nitric oxide negatively regulates mammalian adult neurogenesis. *Proc. Natl. Acad. Sci. USA*, **2003**, *100*(16), 9566-9571.
- [75] Mahajan, S.D.; Aalinkeel, R.; Sykes, D.E.; Reynolds, J.L.; Bindukumar, B.; Adal, A.; Qi, M.; Toh, J.; Xu, G.; Prasad, P.N.; Schwartz, S.A. Methamphetamine alters blood brain barrier permeability via the modulation of tight junction expression, implication for HIV-1 neuropathogenesis in the context of drug abuse. *Brain Res.*, **2008**, *1203*, 133-148.
- [76] Sharma, H.S.; Kiyatkin, E.A. Rapid morphological brain abnormalities during acute methamphetamine intoxication in the rat, An experimental study using light and electron microscopy. *J. Chem. Neuroanat.*, **2009**, *37*(1), 18-32.
- [77] Lee, Y.W.; Hennig, B.; Yao, J.; Toborek, M. Methamphetamine induces AP-1 and NF-kappaB binding and transactivation in human brain endothelial cells. *J. Neurosci. Res.*, **2001**, *66*(4), 583-591.
- [78] McCawley, L.J.; Matrisian, L.M. Matrix metalloproteinases, they're not just for matrix anymore! *Curr. Opin. Cell Biol.*, **2001**, *13*(5), 534-540.
- [79] Yong, V.W.; Krekoski, C.A.; Forsyth, P.A.; Bell, R.; Edwards, D.R. Matrix metalloproteinases and diseases of the CNS. *Trends Neurosci.*, **1998**, *21*(2), 75-80.
- [80] Conant, K.; McArthur, J.C.; Griffin, D.E.; Sjulson, L.; Wahl, L.M.; Irani, D.N. Cerebrospinal fluid levels of MMP-2, 7, and 9 are elevated in association with human immunodeficiency virus dementia. *Ann. Neurol.*, **1999**, *46*(3), 391-398.
- [81] Vos, C.M.; Sjulson, L.; Nath, A.; McArthur, J.C.; Pardo, C.A.; Rothstein, J.; Conant, K. Cytotoxicity by matrix metalloprotease-1 in organotypic spinal cord and dissociated neuronal cultures. *Exp. Neurol.*, **2000**, *163*(2), 324-330.
- [82] Meighan, S.E.; Meighan, P.C.; Choudhury, P.; Davis, C.J.; Olson, M.L.; Zornes, P.A.; Wright, J.W.; Harding, J.W. Effects of extracellular matrix-degrading proteases matrix metalloproteinases 3 and 9 on spatial learning and synaptic plasticity. *J. Neurochem.*, **2006**, *96*(5), 1227-1241.
- [83] Szklarczyk, A.; Lapinska, J.; Rylski, M.; McKay, R.D.; Kaczmarek, L. Matrix metalloproteinase-9 undergoes expression and activation during dendritic remodeling in adult hippocampus. *J. Neurosci.*, **2002**, *22*(3), 920-930.
- [84] Toth, M.; Osenkowski, P.; Heseck, D.; Brown, S.; Meroueh, S.; Sakr, W.; Mobashery, S.; Fridman, R. Cleavage at the stem region releases an active ectodomain of the membrane type 1 matrix metalloproteinase. *Biochem. J.*, **2005**, *387*(Pt 2), 497-506.
- [85] Mizoguchi, H.; Yamada, K.; Nabeshima, T. Neuropsychotoxicity of abused drugs, involvement of matrix metalloproteinase-2 and -9 and tissue inhibitor of matrix metalloproteinase-2 in methamphetamine-induced behavioral sensitization and reward in rodents. *J. Pharmacol. Sci.*, **2008**, *106*(1), 9-14.
- [86] Mark, K.A.; Quinton, M.S.; Russek, S.J.; Yamamoto, B.K. Dynamic changes in vesicular glutamate transporter 1 function and expression related to methamphetamine-induced glutamate release. *J. Neurosci.*, **2007**, *27*(25), 6823-6831.
- [87] Mizoguchi, H.; Yamada, K.; Mouri, A.; Niwa, M.; Mizuno, T.; Noda, Y.; Nitta, A.; Itoharu, S.; Banno, Y.; Nabeshima, T. Role of matrix metalloproteinase and tissue inhibitor of MMP in methamphetamine-induced behavioral sensitization and reward, implications for dopamine receptor down-regulation and dopamine release. *J. Neurochem.*, **2007**, *102*(5), 1548-1560.
- [88] Pauly, T.; Ratliff, M.; Pietrowski, E.; Neugebauer, R.; Schlicksupp, A.; Kirsch, J.; Kuhse, J. Activity-dependent shedding of the NMDA receptor glycine binding site by matrix metalloproteinase 3, a PUTATIVE mechanism of postsynaptic plasticity. *PLoS ONE*, **2008**, *3*(7), e2681.
- [89] Conant, K.; St Hillaire, C.; Anderson, C.; Galey, D.; Wang, J.; Nath, A. Human immunodeficiency virus type 1 Tat and methamphetamine affect the release and activation of matrix-degrading proteinases. *J. Neurovirol.*, **2004**, *10*(1), 21-28.
- [90] Flora, G.; Lee, Y.W.; Nath, A.; Maragos, W.; Hennig, B.; Toborek, M. Methamphetamine-induced TNF-alpha gene expression and activation of AP-1 in discrete regions of mouse brain, potential role of reactive oxygen intermediates and lipid peroxidation. *Neuromol. Med.*, **2002**, *2*(1), 71-85.
- [91] Bond, M.; Baker, A.H.; Newby, A.C. Nuclear factor kappaB activity is essential for matrix metalloproteinase-1 and -3 upregulation in rabbit dermal fibroblasts. *Biochem. Biophys. Res. Commun.*, **1999**, *264*(2), 561-567.
- [92] Mizoguchi, H.; Yamada, K.; Niwa, M.; Mouri, A.; Mizuno, T.; Noda, Y.; Nitta, A.; Itoharu, S.; Banno, Y.; Nabeshima, T. Reduction of methamphetamine-induced sensitization and reward in matrix metalloproteinase-2 and -9-deficient mice. *J. Neurochem.*, **2007**, *100*(6), 1579-1588.
- [93] Mahajan, S.D.; Hu, Z.; Reynolds, J.L.; Aalinkeel, R.; Schwartz, S.A.; Nair, M.P. Methamphetamine modulates gene expression patterns in monocyte derived mature dendritic cells, implications for HIV-1 pathogenesis. *Mol. Diagn. Ther.*, **2006**, *10*(4), 257-269.
- [94] Conant, K.; St Hillaire, C.; Nagase, H.; Visse, R.; Gary, D.; Haughey, N.; Anderson, C.; Turchan, J.; Nath, A. Matrix metalloproteinase 1 interacts with neuronal integrins and stimulates dephosphorylation of Akt. *J. Biol. Chem.*, **2004**, *279*(9), 8056-8062.
- [95] Zhang, K.M.G.; Silva, C.; Butler, G.S.; Johnston, J.B.; Holden, J.; Clark-Lewis, I.; Overall, C.M.; Power, C. HIV-induced metalloproteinase cleavage of the chemokine SDF-1alpha causes neurodegeneration. *Nat. Neurosci.*, **2003**, *6*, 1064-1011.
- [96] Turgeon, V.L.; Lloyd, E.D.; Wang, S.; Festoff, B.W.; Houenou, L.J. Thrombin perturbs neurite outgrowth and induces apoptotic cell death in enriched chick spinal motoneuron cultures through caspase activation. *J. Neurosci.*, **1998**, *18*(17), 6882-6891.
- [97] Nair, M.P.; Saiyed, Z.M.; Nair, N.; Gandhi, N.H.; Rodriguez, J.W.; Boukli, N.; Provencio-Vasquez, E.; Malow, R.M.; Miguez-Burbano, M.J. Methamphetamine enhances HIV-1 infectivity in monocyte derived dendritic cells. *J. Neuroimmune Pharmacol.*, **2009**, *4*(1), 129-139.
- [98] Liang, H.; Wang, X.; Chen, H.; Song, L.; Ye, L.; Wang, S.H.; Wang, Y.J.; Zhou, L.; Ho, W.Z. Methamphetamine enhances HIV infection of macrophages. *Am. J. Pathol.*, **2008**, *172*(6), 1617-1624.
- [99] Gavrilin, M.A.; Mathes, L.E.; Podell, M. Methamphetamine enhances cell-associated feline immunodeficiency virus replication in astrocytes. *J. Neurovirol.*, **2002**, *8*(3), 240-249.
- [100] Cachay, E.R.; Moini, N.; Kosakovsky, P.S.L.; Pesano, R.; Lie, Y.S.; Aiem, H.; Butler, D.M.; Letendre, S.; Mathews, W.C.; Smith, D.M.

Active methamphetamine use is associated with transmitted drug resistance to non-nucleoside reverse transcriptase inhibitors in individuals with HIV infection of unknown duration. *Open AIDS J.*, **2007**, *1*, 5-10.

[101] Everall, I.; Salaria, S.; Roberts, E.; Corbeil, J.; Sasik, R.; Fox, H.; Grant, I.; Masliah, E. Methamphetamine stimulates interferon inducible genes in HIV infected brain. *J. Neuroimmunol.*, **2005**, *170*(1-2), 158-71

Received: January 14, 2009 Revised: January 14, 2009 Accepted: January 19, 2009