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REVIEW

Methamphetamine toxicity and its implications during HIV-1 infection

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Abstract Over the past two decades methamphetamine (MA) abuse has seen a dramatic increase. The abuse of MA is particularly high in groups that are at higher risk for HIV-1 infection, especially men who have sex with men (MSM). This review is focused on MA toxicity in the CNS as well as in the periphery. In the CNS, MA toxicity is comprised of numerous effects, including, but not limited to, oxidative stress produced by dysregulation of the dopaminergic system, hyperthermia, apoptosis, and neuroinflammation. Multiple lines of evidence demonstrate that these effects exacerbate the neurodegenerative damage caused by CNS infection of HIV perhaps because both MA and HIV target the frontostriatal regions of the brain. MA has also been demonstrated to increase viral load in the CNS of SIV-infected macaques. Using transgenic animal models, as well as cultured cells, the HIV proteins Tat and gp120 have been demonstrated to have neurotoxic properties that are aggravated by MA. In addition, MA has been shown to exhibit detrimental effects on the blood–brain barrier (BBB) that have the potential to increase the probability of CNS infection by HIV. Although the effects of MA in the periphery have not been as extensively studied as have the effects on the CNS, recent reports demonstrate the potential effects of MA on HIV infection in the periphery including increased expression of HIV co-receptors and increased expression of inflammatory cytokines.

Keywords Methamphetamine · HIV-1 · Dopamine · CNS · Immune system

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Through the 1990s and well into the first decade of the twenty-first century, methamphetamine (MA) abuse has been responsible for an increase in admissions to publicly funded drug treatment programs (Gonzales et al. 2010). In 2005, it was estimated that 10.4 million people of age 12 years and over had used MA at least once in their life, and over half a million people reported current use of the drug (Office of Applied Studies 2007). Furthermore, hospital emergency department visits related to MA abuse exhibited a dramatic increase between 1995 and 2002. The problem of MA abuse is not limited to the USA, since significant use is also reported in Eastern Europe and Southeast Asia (Degenhardt et al. 2010). The abuse of MA is particularly high among men who have sex with men (MSM; Gonzales et al. 2009). In this group, MA use is associated with an increase in high-risk sexual activities such as decreased condom use and increased numbers of sexual partners (Gonzales et al. 2010; Shoptaw and Reback 2007). Studies have indicated that the HIV incidence is doubled or tripled in MSM who use amphetamines compared with MSM who do not use drugs (Buchacz et al. 2005). In addition, resistance to antiretroviral drugs has been shown to be positively correlated with MA abuse in MSM (Gorbach et al. 2008). Although research studies can be confounded by factors such as the abuse of multiple drugs (i.e., polydrug abuse) and differential levels of sexual activity and exposure, the study by Gorbach et al. accounted for some of these factors and still demonstrated a significant correlation between MA abuse and the acquisition of drug-resistant virus.

This review focuses on MA toxicity in both the CNS and the periphery, especially in the context of HIV-1 infection. The mechanisms responsible for the toxicity, as well as the mechanisms involved in mediating interactions between the effects of MA and HIV infection will be discussed.

Furthermore, evidence that MA abuse affects the outcome of HIV-1 infection will be reviewed.

The dopaminergic system and methamphetamine

MA is very similar in chemical structure to the neurotransmitter dopamine, and this is thought to be the basis for many of the effects of this drug (Riddle et al. 2006; Sulzer et al. 2005). Early work that demonstrated the role of dopamine in MA-mediated effects utilized various methods of regulating dopamine synthesis, metabolism and disposition, followed by a determination of the effects of these agents on MA-mediated neurotoxicity. In the neostriatum of MA-treated rats, it was reported that the activity of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine biosynthesis, was inhibited (Gibb and Kogan 1979). It was also demonstrated that a-methyl-*r*-tyrosine, an inhibitor of TH, abrogates the MA-induced decrease in TH activity in the neostriatum. The protective effect of α-methyl-*r*-tyrosine was abrogated by administration of L-DOPA, which served to restore cytoplasmic dopamine levels. The depressive effects of MA are even more pronounced on tryptophan hydroxylase (TPH), the enzyme responsible for serotonin synthesis (Hotchkiss and Gibb 1980; Schmidt et al. 1985). Experiments utilizing the administration of a-methyl-*r*-tyrosine and L-DOPA strongly suggested that the effects of MA on TPH were mediated by the dopaminergic system (Hotchkiss and Gibb 1980; Schmidt et al. 1985). The effects of MA on the serotonergic system are blocked by compounds that inhibit the effects of MA on the dopaminergic system (e.g., α-methyl-*r*-tyrosine). However, agents that specifically target the serotonergic system (e.g., 5-HT uptake inhibitors) have no influence on MA-induced effects on the dopaminergic system. This suggests the overriding importance of dopamine in regulating both systems in response to MA.

Components of the dopaminergic system

Dopamine receptors

Dopamine receptors comprise a family of G protein-coupled receptors that are prominent in the CNS, as well as in certain cell types and tissues in the periphery. In addition to the CNS, dopamine receptors have also been reported to be expressed in the cardiovascular and renal systems, as well as in the retina and adrenal glands (Ozono et al. 1997; Pivonello et al. 2004). In the cardiovascular system, dopamine affects contractility (Ruffolo and Messick 1985) and vasodilation (Munch et al. 1991), it controls renal filtration (Olsen 1998), whereas in the retina it is responsible for circadian rhythm and retinal development (Witkovsky 2004). Dopamine receptors are also expressed on various immune cells in the body. D_1–D_5 receptor expression on human lymphocytes has been demonstrated through the use of radioligand binding (Amenta et al. 1999; Ricci and Amenta 1994; Ricci et al. 1998; Ricci et al. 1997; Ricci et al. 1999).

The availability of antagonists for the dopamine receptors D_1 and D_2 has facilitated the identification of these proteins as key players in the effects of MA. Sonsalla et al. (Sonsalla et al. 1986) demonstrated that both a D_1 antagonist, SCH23390, and a D_2 antagonist, sulpiride, decreased the MA-induced effects on the striatal dopaminergic parameters. However, only the D_1 antagonist was effective at reducing the effects of MA on the striatal serotonergic parameters. The ability of the D_1 antagonist SCH23390 to protect against MA-induced neurotoxicity has also demonstrated (Angulo et al. 2004; Xu et al. 2005). The report by Xu et al. also showed that raclopride, a D_2 antagonist, as well as SCH23390, ameliorated MA-induced astrogliosis, depletion of the dopamine transporter (DAT), and cell death. Jayanthi et al. (Jayanthi et al. 2005) demonstrated the induction of the FasL-Fas death pathway by MA treatment. Treatment with SCH23390 reduced the level of TUNEL staining and blocked the MA-induced cleavage of caspase 8. Taken together, these results strongly suggest a role for both D_1 and D_2 receptors in the modulation of MA-induced neurotoxicity.

Dopamine transporters

Dopamine transporters and their regulation will obviously have profound effects upon the disposition of dopamine. The effects of MA on dopamine transporters have been examined by numerous investigators. Early work by Wagner et al. (Wagner et al. 1980) showed that multiple doses of MA were followed by striatal dopamine depletion and loss of dopamine uptake. Other work that demonstrated the importance of the DAT in mediating MA toxicity was performed by Schmidt and Gibb (Schmidt and Gibb 1985). These investigators demonstrated that amfonelic acid, an inhibitor of DAT, prevented the MA-induced reduction of TH activity in rats. Similarly, Marek et al. demonstrated that dopamine uptake inhibitors, including amfonelic acid, were able to ameliorate the neurotoxic effects of MA (Marek et al. 1990). Additional confirmation of the role of DAT in MA-induced toxic effects was provided using knock-out mice that lacked DAT expression (Fumagalli et al. 1998). In homozygous KO mice, the lack of DAT expression abrogated the MA-induced depletion of striatal DA levels. Animals heterozygous for DAT expression displayed levels of striatal DA that were intermediate between the wild-type and DAT knock-out animals. Similar differences between wild-type and knock-out mice were observed in terms of

levels of MA-induced astrogliosis and oxygen radical production. Taken together, these results confirm a central role for DA and DAT in various MA-induced effects.

Vesicular monoamine transporter 2 (VMAT-2) is another transporter that is important in terms of DA disposition [reviewed in (Fleckenstein et al. 2009)]. In addition to expression in neurons, VMAT-2 is expressed in β-cells of the pancreas (Saisho et al. 2008) and mononuclear cells (Anlauf et al. 2006; Tang et al. 2003). The function of this transporter is to package monoamine transmitters such as DA into synaptic vesicles in neurons. Mice that are heterozygous for VMAT-2 expression were utilized to demonstrate that altered vesicular transport of DA resulted in increased neurotoxicity associated with altered distribution of DA and its metabolites (Fumagalli et al. 1999). MA-treatment of mice was demonstrated to reduce binding of a VMAT-2 ligand to its transporter (Hogan et al. 2000). The role of VMAT-2 in DA transport and MA-associated toxicity was confirmed by (Brown et al. 2002) who demonstrated that the DA transport inhibitor methylphenidate (MPD) caused a redistribution of VMAT-2 from the fraction associated with the plasmalemmal membrane to the fraction associated with the cytoplasmic vesicles. Multiple administrations of MA have been demonstrated to cause a decrease in VMAT-2 immunoreactivity in the vesicular subcellular fraction, while causing little change in the plasmalemmal membrane or whole synaptosomal fractions (Sandoval et al. 2003). Treatment with MPD after MA treatment attenuated the MA-induced decrease in vesicular DA uptake and vesicular DA content without altering the total striatal dopamine content (Sandoval et al. 2003). Further evidence for the importance of VMAT-2 in modulating MA toxicity comes from a report that utilized lobeline, an alkaloid that had been shown to inhibit MA-induced behavioral characteristics (Eyerman and Yamamoto 2005). These investigators found that although lobeline did not affect the MA-induced increase in extracellular striatal DA, MA-induced hyperthermia and the loss of VMAT-2 immunoreactivity were ameliorated by the alkaloid. As described above, MA, through its effects on DAT and VMAT, has a major impact on the expression of transporters modulating dopamine disposition. It is undoubtedly through this mechanism that MA exerts at least a portion of its effects on the CNS.

As can be seen from the brief review above, the dopaminergic system plays a key role in mediating MA-induced neurotoxicity. The effects of MA can be modulated by alteration of DA levels, either through affecting DA metabolism or it can be mediated through DAT or VMAT-2. D_1 or D_2 receptors are also capable of affecting MA-induced effects. Taken together, these results strongly argue for a central role of the dopaminergic system in mediating MA toxicity.

Methamphetamine-associated toxicity

The toxicity of MA has been studied in rodents, monkeys, and humans at behavioral, cellular, and molecular levels.

Studies in rodent model systems

Rodent models have been used to study the effects of MA at the cellular and molecular levels. In addition, these models have been used to study MA-mediated hyperthermia and oxidative stress.

a. Effects of Methamphetamine at the Cellular and Molecular Levels. Siegel and colleagues have shown that long-term MA exposure increases the expression of muscarinic acetylcholine receptors in the hippocampus, resulting in impaired novel location recognition in female but not in male mice (Siegel et al. 2010). In contrast to adult mice, exposure of adolescent mice to MA results in impaired novel object recognition; the level of impairment observed is equal in both male and female mice (Siegel et al. 2011). In addition, MA exposure of adolescent mice does not affect anxiety-like behavior, sensorimotor gating, and contextual and cued fear conditioning. As seen in adolescent mice and unlike that observed in adult mice, juvenile mice do not show a gender difference in terms of MA-induced neurotoxicity or increase in body temperature (Dluzen et al. 2010).

Using in vitro cell cultures as well as a mouse model, Narita and colleagues demonstrated that MA induces long-lasting activation of astrocytes in the cingulate cortex and nucleus accumbens through the protein kinase C pathway (Narita et al. 2005). In MA-treated mice, the ratio of activated microglia to non-activated microglia increases from day 1 to day 7, as opposed to the control groups in which the ratio is below 0.15. MA-induced glial activation has been suggested to occur through inflammatory cytokines based on the fact MA induces IL6 in the hippocampus and striatum and it induces TNF-α in the hippocampus and frontal cortex (Goncalves et al. 2008).

Genc and colleagues have shown that MA causes cytotoxicity in rat oligodendrocyte cultures through the induction of apoptotic cell death, which is evident from the expression of pro-apoptotic proteins (Genc et al. 2003). Exposure of cultured adult rat ventricular cardiomyocytes (RVC) to acute MA treatment increases the size of RVC, while chronic MA treatment decreases its size (Ruffolo and Messick 1985). Furthermore, while acute MA exposure increases microtubule (MT) assembly, chronic MA exposure causes a reduction in MT assembly.

Overall, these studies have demonstrated that MA can have a range of toxic effects on cells by induction of pathways that include activation, cytokine induction, and apoptosis.

b. The Effects of Methamphetamine on Oxidative Stress. Using a rat model, Acikgoz et al. demonstrated that acute repeated administration, as well as chronic administration, of MA causes an increase in SOD activity along with an increase lipid peroxidation in the striatum (Acikgoz et al. 1998). Fluorescein derivatives, along with cell cultures derived from VMAT-2 wild-type and mutant mice, were used to demonstrate that MA exposure caused an increase in ROS (Larsen et al. 2002). It was also demonstrated that the loss of VMAT-2 expression was associated with higher levels of ROS and increased levels of cysteinyl-DA, a metabolite associated with oxidized DA. Using a rat model of MA-induced neurotoxicity, it was demonstrated that MA administration at toxic levels resulted in an increase in protein-cysteinyl DA as a result of an increase in the oxidative metabolites of DA (LaVoie and Hastings 1999). Using mice subjected to repeated doses of MA, Jayanthi et al. demonstrated that levels of glutathione peroxidase, catalase, and Cu/Zn-SOD were decreased in the striatum of these animals (Jayanthi et al. 1998). Significantly, this correlated with an increase in the products of lipid peroxidation. MA has also been shown to have a similar effect on most, but not all, peroxiredoxins in rat brain (Chen et al. 2007). In a model similar to that of Jayanthi et al., repeated injections of MA produced elevated levels of protein carbonyls and thiobarbituric acid reactive substances, both of which are markers of oxidative stress, in brain (Gluck et al. 2001). Proteomic analysis has also been utilized to confirm the upregulation of enzymatic markers of oxidative stress in MA-treated rats (Iwazaki et al. 2006). In another study, MA-induced toxicity was found to be associated with an increase in protein bound quinone and increased expression of quinone reductase (Miyazaki et al. 2006). Furthermore, pre-treatment of animals with an inducer of quinone reductase, which is known to be protective against quinine-induced toxicity, protected against MA-induced toxicity.

c. The Effects of Methamphetamine on Hyperthermia and Microglial Activation. Several studies on MA-induced hyperthermia in a rat model have been reported by Kiyatkin and colleagues. MA induces both brain and body hyperthermia but brain hyperthermia is much stronger and more rapid than body hyperthermia (Brown et al. 2003). Unlike body hyperthermia, brain hyperthermia is dramatically enhanced at warm ambient temperatures, often resulting in lethality in mice (Brown and Kiyatkin 2005). In general, MA-induced brain hyperthermia causes damage to brain cells, including neurons, glia, epithelial, and endothelial cells (Kiyatkin 2005; Kiyatkin 2010; Kiyatkin et al. 2007). MA-induced brain hyperthermia also causes acute glial activation and edema. Furthermore, chronic MA-induced brain and body hyperthermia, as well as acute MA intoxication-induced brain hyperthermia have been correlated with increased permeability of the BBB (Kiyatkin et al. 2007; Sharma and Kiyatkin 2009). An earlier study demonstrated that MA-induced hyperthermia induces heat shock protein (HSP) (Kuperman et al. 1997), which is consistent with the general phenomenon that hyperthermia can induce the expression of heat shock proteins (HSPs). A recent study confirms that acute MA intoxication in rats causes induction of wide-spread HSP expression in neural and glial cells, as well as in the cortex, hippocampus, thalamus, and hypothalamus (Kiyatkin and Sharma 2011). The induction of HSPs in these cells correlates with brain hyperthermia, permeability of BBB, acute glial activation, and brain edema. Although the induction of HSP is an adaptive mechanism to counteract hyperthermia, it does not counteract the damaging effects of oxidative stress, hyperthermia, and edema in rats.

In addition to hyperthermia, MA has been shown to induce microglial activation (Kuhn et al. 2008; Thomas et al. 2004a; Thomas et al. 2004b). Microglial activation was determined by staining brain sections with isolectin B_4, and activation was found to be independent of hyperthermia. Agents that changed dopamine disposition, such as L-DOPA and reserpine, enhanced the effects of MA on microglial activation but had no effects on microglial activation by themselves. It is of particular interest that reserpine caused hypothermia in mice, while L-DOPA caused hyperthermia. However, attenuation of MA-induced microglial activation by minocycline that resulted in reduction of IL-1a and IL-6 levels did not afford neuroprotection (Sriram et al. 2006). Thus, although microglial activation is not dependent upon hyperthermia, microglial activation alone could not account for the observed neurotoxicity.

Studies in monkey model systems

Since acute high MA dosing regimens can lead to considerable toxicity and even death in experimental animals, a non-lethal chronic MA administration procedure for the rhesus macaque that utilizes an escalating dose protocol has been developed by Madden and colleagues (Madden et al. 2005). This regimen produces several behavioral and physiological effects, including decreased food intake and increased cortisol excretion, which are similar to MA-induced effects in humans. In vervet monkeys, MA exposure has been correlated with the oxidative stress that occurs during aging (Melega et al. 2007). They showed that, after 1 month of MA treatment, there is an increase in iron levels in the substantia nigra pars reticulata and the globus pallidus, along with a concurrent increase in ferritin-immunoreactivity and a decrease in tyrosine hydroxylase-immunoreactivity in the substantia nigra. While the increase in tyrosine hydroxylase-immunoreactivity is observed after 1.5 years of simulated MA abuse, iron levels

of the adult MA-exposed animals (age 5–9 years) are comparable with those of drug-naive, aged animals (19–22 years). In a subsequent study, these investigators demonstrated that multiple doses of MA administered to socially housed vervet monkeys cause a progressive increase in abnormal behavior and a decrease in social behavior (Melega et al. 2008). In this study, the vervet monkeys exhibited an increase in anxiety on 'no injection' days and a decrease in aggression was observed throughout the study. Finally, since some behavioral and pharmacological patterns of chronic MA abuse and schizophrenia are similar, a primate animal model of schizophrenia has been established using chronic phencyclidine (PCP) monkeys. An acute MA injection to the chronically treated PCP monkeys exacerbated the behavioral effects of PCP, suggesting that these monkeys can be used as a primate model of schizophrenia (Mao et al. 2008).

Clinical studies

Clinical studies have been used to study the effects of MA at behavioral, cellular, and molecular levels. In addition, clinical investigations have also focused on MA-mediated oxidative stress.

a. The Effects of Methamphetamine at the Cellular and Molecular Levels. Chung and colleagues have shown that the chronic use of MA in humans decreases the cerebral blood flow in subcortical and dorsal cortical brain regions (Chung et al. 2010). However, its binge use is associated with severe neurotoxicity to the monoaminergic neurotransmitter system as a result of long-term changes in both global and regional blood flows. This produces a pattern of hypoperfusion, which resembles the pattern of atypical Parkinson's disease. Thus, binge use of MA has been employed as an experimental model of Parkinson's disease in animals (Garcia de Yebenes et al. 2000; Romero et al. 2006).

To understand MA-induced neuronal changes in humans, several imaging techniques have been utilized as described below. Iyo and colleagues used single photon emission computed tomography, magnetic resonance spectroscopy, and positron emission tomography to investigate MA-mediated psychosis (Iyo et al. 2004). In MA users, these studies have shown (1) a high incidence of multiple patchy deficits in cerebral blood flow, (2) a significantly reduced ratio of creatine plus phosphocreatine/choline-containing compounds in the brain, and (3) a decrease in the density of dopamine transporter in the nucleus accumbens and caudate/putamen. These effects correlate with the duration of MA use and the severity of residual psychotic symptoms. High-resolution genetic resonance imaging (Gorbach et al.) and surface-based computational image analyses in MA abusers have revealed severe gray-matter deficits in the cingulate, limbic, and paralimbic cortices, as well as a decrease in hippocampal volumes and white-matter hypertrophy (Thompson et al. 2004). In addition, MA abuse causes a selective cerebral deterioration resulting in impaired memory and damage to the medial temporal lobe and cingulate-limbic cortex. Furthermore, findings from functional magnetic resonance imaging (fMRI) suggest a relationship between decision-making dysfunction and neural activation in different prefrontal areas (Paulus et al. 2002). MA abusers show a decrease in the activation of dorsolateral prefrontal cortex and fail to activate the ventromedial cortex during the two-choice prediction task compared with the two-choice response task.

A recent finding from a study that focused on prenatal exposure to MA using neuroimaging suggests that MA exposure in utero is toxic to dopamine-rich basal ganglia regions (Roussotte et al. 2010). High levels of MA exposure during pregnancy have been associated with increased lethargy and physiological stress; first trimester produces more stress, while third trimester results in lethargy, poorer quality of movement, and hypotonicity (LaGasse et al. 2011; Smith et al. 2008).

b. The Effects of Methamphetamine on Oxidative Stress. MA-induced oxidative stress has also been studied using human cell cultures. Cubells and colleagues have demonstrated MA-induced neurite damage and ROS production in neuronal cultures using differential interference contrast and fluorescence techniques, respectively (Cubells et al. 1994). MA exposure has also been shown to increase the permeability of brain microvascular endothelial cell (BMVEC) monolayers by decreasing the expression of tight junction (TJ) proteins and increasing ROS formation (Ramirez et al. 2009). It has also been shown that MA modulates TJ expression, leading to decreased transendothelial resistance and enhanced transendothelial migration of immunocompetent cells across the BBB (Mahajan et al. 2008). Furthermore, N27 dopaminergic neuronal cells have been used to demonstrate the role of cathepsin-D in MA-induced autophagy and apoptosis as a result of increased oxidative stress (Kanthasamy et al. 2006).

c. The Effects of Methamphetamine on Behavior. Although acute use of MA is known to elevate energy and alertness, its chronic use is associated with increases in psychosis, anxiety, and depression(Glasner-Edwards et al. 2010; Gonzales et al. 2009; Gonzales et al. 2010; Rawson et al. 2002; Zweben et al. 2004). Furthermore, MA intoxication is associated with violent, agitated, and suicidal behaviors (Newton et al. 2004). The severity of MA-mediated effects is related to the quantity and frequency of MA administration. The route of administration as well as individual genetic differences has an effect upon behavioral

outcomes. The symptoms of MA-induced psychosis are similar to the symptoms of schizophrenia, such as paranoid ideation, delusions, and auditory and visual hallucinations (Zweben et al. 2004). Although in most users, psychosis occurs temporarily and is typically abolished within a week of abstinence, it may persist for several months in a small fraction of users.

Taken together (overview presented in upper half of Fig. 1 and Table 1), the studies described above demonstrate that MA exposure has a wide range of toxic effects in both the CNS and the periphery. These toxic effects include brain and body hyperthermia, induction of apoptotic pathways, increased levels of markers of oxidative stress, as well as behavioral effects (Krasnova and Cadet 2009). Even in the absence of additional agents, the toxic effects of MA are rather significant. In the context of viral infection, they will show themselves to be even more deleterious.

Methamphetamine and HIV

Effects of methamphetamine on the CNS

Globally, at least 33.3 million people are estimated to be living with HIV as of 2009. At least 20–30% of the patients infected with HIV-1 will eventually be diagnosed with HIV-associated dementia (HAD; McArthur et al. 1993; Nath et al. 2000; Navia et al. 1986a; Navia et al. 1986b). The neurotoxic effects of HIV-1 are primarily attributed to its ability to readily penetrate into the central nervous system (CNS) early during the course of infection. Deficiency in the functionality of dopaminergic neurons has been observed to be associated with early stage HIV-1 infection (Berger et al. 1994). Although the introduction of highly active antiretroviral therapy (HAART) has significantly reduced the incidence of HAD (Clifford 2008), milder neurotoxicity, including minor cognitive motor disorders and HIV-associated neurodegenerative disorders (HAND) have increased in incidence (Antinori et al. 2007). Many anti-retroviral drugs fail to penetrate the blood brain barrier (BBB), thus making it difficult to treat HAND patients (Thomas 2004). HIV-associated neurotoxicity is primarily thought to be mediated by the neurotoxins released from infected cells, mostly resident microglia, after migration of the infected cells through the BBB (Gendelman and Meltzer 1989; Meltzer and Gendelman 1992; Meltzer et al. 1990). The frontostriatal regions of the brain are highly vulnerable to this so-called "Trojan Horse" mechanism by which HIV-1 penetrates the CNS (Itoh et al. 2000; Reyes et al. 1991). MA also targets these frontostriatal regions by increasing DA and glutamate transmission, which further leads to neuronal damage and cell death (Davidson et al. 2001; Langford et al. 2003; Stephans and Yamamoto 1994; Wilson et al. 1996). Multiple models for MA-mediated neurotoxicity have been proposed (Cadet and Krasnova 2007; Reiner et al. 2009). However, MA-mediated neuronal damage is chiefly attributed to depletion of dopamine and 5-HT (Cadet et al. 1994; Wagner et al. 1980), dopamine transporters (DAT) (Xu et al. 2005), and vesicular monoamine oxidase (Mao et al.) in the corpus striatum (Frey et al. 1997).

The effects of methamphetamine and viral proteins on CNS toxicity

In an early study, it was demonstrated that treatment with MA and Tat increased neuronal cell death when human fetal neurons were exposed to these agents in culture (Magnuson et al. 1995). Based upon their earlier studies, along with other relevant data, Nath et al. proposed that dopaminergic

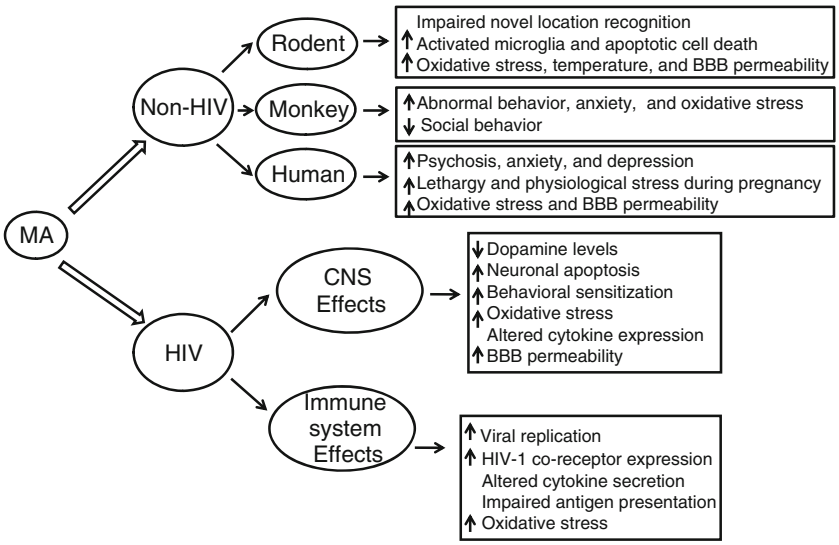

Fig. 1 Schematic of an overview of the effects of MA and MA in the context of HIV infection. The *upper* portion of the figure focuses on the effects of MA in rodent and monkey model systems, as well as those results derived from clinical studies on humans. The *bottom* portion of the figure focuses on the effects of MA in the context of HIV infection

Table 1 Overview of the effects of MA and MA +HIV/Tat or gp120 in different model systems

Treatment	Tissue/cell type	Effect	Reference
MA	Rat neostiatum	Tyrosine hydroxylase ↓	Gibb and Kogan 1979
	Rat neostiatum	Tryptophan hydroxylase ↓	Hotchkiss and Gibb 1980
	Rat caudate	DAT ↓ ; DA ↓	Wagner et al. 1980
	Rat body, rat brain	Hyperthermia↑	Brown et al. 2003
			Brown and Kiyatkin 2005
			Sharma and Kiyatkin 2009
	Rat striatum	Altered VMAT-2 localization	Brown et al. 2002
			Sandoval et al. 2003
		VMAT-2↓	Eyerman and Yamamoto 2005
		Oxidative stress markers ↑ Oxidative metabolites ↑	LaVoie and Hastings 1999
		Quinone levels ↑	
		Oxidative stress markers ↑	Iwazaki et al. 2006
	Rat neurons	Neurite degeneration↑	Cubells et al. 1994
	Rat neural and glial cells	HSP expression ↑	Kiyatkin and Sharma 2011
	Mouse neurons	Apoptosis ↑	Jayanthi et al. 2005
	Mouse hippocampus	Muscarinic acetylcholine receptor ↑	Siegel et al. 2010
	Mouse hippocampus	Impaired novel location recognition	Siegel et al. 2011
	Mouse hippocampus	IL-6 ↑ ; TNF-α ↑	Goncalves et al. 2008
	Mouse striatum/hippocampus	DA levels ↓ ; 5-HT levels ↓	Fumagalli et al. 1998
	Mouse striatum	Altered VMAT-2 ligand binding	Hogan et al. 2000
	Mouse striatum	Microglial activation ↑	Thomas et al. 2004a
			Kuhn et al. 2008
	Mouse neuron	Lipid peroxidation ↑	Jayanthi et al. 1998
	Mouse	HSP expression ↑	Kuperman et al. 1997
	Vervet monkey	Oxidative stress ↑	Melega et al. 2007
		Food intake ↓ Social behavior ↓	Melega et al. 2008
		Anxiety ↑	
	Rhesus macaques	Food intake ↓ Cortisol excretion ↑	Madden et al. 2005
	Human brain	Cerebral blood flow ↓	Chung et al. 2010
		DAT ↓	Iyo et al. 2004
		Neural activation ↓	Paulus et al. 2002
		Hippocampal volume↓	Thompson et al. 2004
	Human dendritic cells	TNF-α ↑, IL-1β ↑, CCR5 ↑, IL-8 ↑ p38 MAPK phosphorylation ↑	Mahajan et al. 2006
		PI3K phosphorylation ↓	
		CXCR4 ↑, CCR5 ↑ p38 MAPK phosphorylation ↑	Nair et al. 2006
		MIP-1α ↓, MIP-1β ↓, RANTES ↓	Nair and Saiyed 2010
	Human MDM	CCR5 ↑, IFN-α ↓	Liang et al. 2008
	Mixed neuron/astrocyte cultures	MMPs ↑	Conant et al. 2004
	Human brain Endothelial cells	Tight junction proteins ↓	Ramirez et al. 2009
	Human	Psychosis ↑, anxiety ↑, depression ↑	Rawson et al. 2002
			Zweben et al. 2004
		Depression ↑	Glasner-Edwards et al. 2010
		Psychosis ↑	Gonzales et al. 2009
		Anxiety ↑, depression ↑	Gonzales et al. 2010
MA+HIV	HIV-1 transgenic rats	Behavioral sensitization ↑	Liu et al. 2009

Table 1 (continued)

Treatment	Tissue/cell type	Effect	Reference
	Human immature dendritic cells	Adhesion protein (galectin-1, filamin 1)↑	Reynolds et al. 2007
	Human PBMC	Peroxiredoxin6 ↑, HSP70p5 ↑,vimentin↑	Reynolds et al. 2009
	Human MDM	Viral replication ↑	Liang et al. 2008
	T cells	Viral replication ↑	Toussi et al. 2009
	Dendritic cells	Viral replication ↑	Reynolds et al. 2007
MA+SIV	Macaque	Viral load in brain ↑	Marcondes et al. 2010
		SOD ↑, GST ↑	Pendyala et al. 2011
MA+gp120	Mouse brain	Oxidative stress markers ↑ Protein carbonylation ↑	Banerjee et al. 2010
	Transgenic mice	Behavioral changes ↑	Roberts et al. 2010
	Human BMEC	Z0-1 ↓, claudin 3/5 ↓, JAM-2 ↓	Mahajan et al. 2008
	Human fetal brain cells	Cell death ↑ Alteration of mitochondrial membrane	Turchan et al. 2001
MA+Tat	Rat striatum	MCP-1 ↑,IL-1α ↑, IL-1β ↑, TNF-α ↑	Theodore et al. 2006a, b
	Rat brain	Altered dopamine levels	Maragos et al. 2002
	Mouse striatum	TNF-α↑, lipid peroxidation ↑, AP-1 ↑	Flora et al. 2002
		Oxidative stress ↑	Flora et al. 2003
	Mixed neuron/astrocyte cultures	MMP ↑	Conant et al. 2004

activation-mediated depletion in dopamine levels impaired the function of the DA transporter and that the resultant alterations in DA reuptake (Nath et al. 2000) were responsible for the toxic effects of MA and HIV-1 on dopaminergic neurons. Later, various MRS studies (Chang et al. 2005; Schweinsburg et al. 2005) showed that MA abuse by HIV-positive individuals aggravated damage in the brain in terms of *N*-acetyl aspartate reduction.

Multiple studies have been undertaken that focus on the molecular mechanisms involved in the cross-talk between the viral proteins and MA. Studies by Maragos et al. revealed altered dopamine levels due to the combined effects of MA and HIV-1 Tat (Maragos et al. 2002). Using Sprague–Dawley rats treated with threshold doses of Tat and MA, they demonstrated greater depletion in the striatal DA levels of rats treated with both Tat and MA when compared with the depletion of DA levels upon treatment with either MA or HIV Tat. Using neuronal cultures, they also showed that MA and Tat treatment resulted in higher levels of cell death and mitochondrial dysfunction as compared with either agent alone. They also showed that Tat and MA together can cause further decreases in the overflow of dopamine as compared with either treatment alone in the striatal regions of the rats. This suggests that both the DA levels and the dynamics of DA release in the striatum are affected by the interaction of MA with HIV-1 proteins. These alterations of the DA levels and activation could be responsible for basal ganglia dysfunction in MA-abusing HIV-infected patients (Cass et al. 2003). Turchan et al. demonstrated synergistic toxicity of gp120/Tat with MA that resulted in neuronal cell death and alteration of mitochondrial membrane potential (Turchan et al. 2001). These findings suggested the possibility that oxidative stress may play a role in the synergy between MA and HIV.

Increased oxidative stress is found to be associated with HIV-associated neuroinflammation. Banerjee et al. showed that intrastriatal MA injection in mice resulted in synergistic interactions between MA and HIV that were mediated through oxidative stress (Banerjee et al. 2010). Mice treated with MA following gp120 or Tat injections showed high levels of oxidative stress markers such as malonyl dialdehyde (MDA) and protein carbonylation along with higher lipid peroxidation in the brain. In addition, the presence of both agents resulted in levels of antioxidant enzymes like GSH and GPx that were significantly decreased when compared with either treatment alone. The involvement of oxidative stress was demonstrated through the use of the antioxidant *N*-acetyl cysteine amide, which prevented the disruption of mitochondrial potential that was caused by MA+Tat or MA+gp120. Flora et al. highlighted the role of redox-sensitive pathways in the combined effects of MA and HIV-1 Tat (Flora et al. 2003; Flora et al. 2002). Interestingly, the intrahippocampal injection of Tat and MA in mice showed increased activity of transcription factors associated with oxidative stress particularly in the cortical, striatal, and hippocampal regions of the brain. The transcription factors NF–κB, AP-I, and CREB showed increased DNA binding activity in the hippocampal and cortical regions of mice treated with Tat and MA as compared with either substance alone. The increase in the

DNA binding activity of the transcription factors further led to increased expression of IL-1β, TNF-α, and ICAM-1, particularly in mouse striatum. In a later report, Langford et al. extended these findings and showed that the combination of HIV-1 Tat and MA can induce oxidative stress and alter mitochondrial membrane calcium potentials, which can further result in neuronal cell death (Langford et al. 2004).

High levels of various inflammatory cytokines are associated with the toxicities observed in neuroinflammation. In particular, increased expression of TNF-α is positively correlated with HAD (Glass et al. 1993). Flora et al. showed increased expression of TNF-α in the brains of mice treated with intrahippocampal Tat injections following IP MA administration. In addition to TNF-α induction in various regions of brain like frontal cortex, corpus striatum, hippocampus, and cerebellum, elevated levels of IL-1β and ICAM-1 were observed in the same regions. The increase in these genes was found to be associated with increased oxidative stress signaling. Because TNF-α and IL-1β also act as pro-inflammatory cytokines, the toxicities produced by MA and Tat together could prove to be a "double-edged sword" of inflammation and oxidative stress (Flora et al. 2003). Theodore et al. (Theodore et al. 2006a) confirmed the previous findings by using TNF-αR1 and TNF-αR2 double knockout mice. In the DKO mice, Tat+MA failed to deplete the DA levels as compared with the depletion observed in Tat+MA-treated WT animals. The induction of TNF-α was also found to result in increased hippocampal neuron loss. Increased levels of the pro-inflammatory cytokines MCP-1, TIMP-1, and IL-1α were found in a cytokine array prepared from rat striatum treated with MA and Tat as compared with either treatment alone. Furthermore, MCP-1 KO mice did not show the depletion of DA observed in the combined treatments as compared with the treatments by a single agent (Theodore et al. 2006a, 2006b). Together all these findings provide strong evidence for the role of cytokines in mediating the interactions observed between MA and HIV infection in terms of increasing neurodegeneration.

Blood–brain barrier integrity is essential for maintenance of brain homeostasis. Tight junction proteins are a critical component responsible for maintaining the high level of impermeability of the BBB. Mahajan et al. showed that HIV-1 gp120 and MA synergistically disrupt the BBB and deplete various tight junction proteins such as ZO-1, JAM-2, and Claudin-3/5 (Mahajan et al. 2008). Furthermore, studies by Banerjee et al. showed that mice treated with MA and viral proteins like gp120 or Tat had decreased levels of TJ proteins like ZO-1 and occludin. Treatment with antioxidants also demonstrated restoration of levels of TJ proteins. This observation confirmed the role of oxidative stress in the loss of BBB integrity Banerjee (Banerjee et al. 2010). Studies by Conant et al. also demonstrated synergy between MA and Tat in the induction of MMP levels in the striatum (Conant et al. 2004).

Behavioral effects of methamphetamine in transgenic rodents

Various transgenic rodent models have been developed that simulate conditions of HIV/AIDS. Using HIV transgenic rats, it was shown that MA increases behavioral sensitization in these animals (Liu et al. 2009). HIV-1 transgenic rats treated with MA showed increased behavioral sensitization in terms of rearing and head movements when compared with control transgenics that were not treated with MA. It was also shown that D1R expression was higher in the transgenic rats treated with MA. This cohort also showed lower brain to body weight ratios, suggestive of brain atrophy. Another study utilized a transgenic mouse model expressing gp120 to demonstrate that MA-induced stereotypic behavior and locomotion are significantly increased in HIV transgenic mice (Roberts et al. 2010). This report, in conjunction with the prior study, indicated possible behavioral alterations that underscore the complexity associated with the aggravating effects of MA abuse on HIV-associated CNS toxicity. Taken together, these findings provide strong evidence of increased CNS impairment in HIV-infected individuals consuming illicit drugs.

The effects of methamphetamine on viral replication

One of the major contributing factors to HIV disease progression due to MA is the increase in viral load due to MA exposure. MA causes a dysregulation of dopamine disposition, which has been shown to enhance viral replication and also activate latent virus in T lymphocytes (Rohr et al. 1999). This suggests the possibility that MA may be able to increase HIV replication in the CNS. Recently, the effect of MA administration on brain viral load using macaques was determined. Rhesus macaques, when infected with simian immunodeficiency virus (SIV), can serve as a model of HIV infection in humans. Although MA administration in monkeys produced no change in the plasma viral load, the brain viral load was significantly higher (Marcondes et al. 2010). The increased activation of microglia and astrocytes in the brain demonstrates the toxic potential of MA in HIV-1 infected individuals. Activation of NK cells in the periphery and the expression of co-receptor CCR5 on brain macrophages were also observed to increase. MA was also shown to increase CD14+/CD16+ macrophages in brains of HIV-1-infected animals, and these macrophages are known targets for SIV/HIV infection in the brain. The MA-mediated increase in macrophage activation and brain viral load suggests that MA may exacerbate the CNS effects of HIV infection.

There is evidence to suggest that MA use may result in increased viral load in the periphery. Treatment of human monocyte-derived macrophages with MA was able to potentiate HIV reverse transcriptase activity in a dose dependent manner, and the effects of MA could be abrogated by blocking D1 receptors expressed on macrophages (Liang et al. 2008). Increased HIV replication was also observed in immature dendritic cells treated with MA prior to HIV-1 infection (Reynolds et al. 2007). Another study examined both the in vitro and in vivo effects of MA on HIV replication. In vitro, HIV replication was significantly increased in monocytes and $CD4^+$ T cells treated with MA. Viremia was also increased in vivo in mice transgenic for the HIV provirus and human cyclin T1 as determined by p24 antigen production in splenocytes as well as viral RNA copy numbers in serum. These effects were mediated by translocation of NFKB p65 subunit into the nucleus and subsequent transcription from the HIV-1 LTR (Toussi et al. 2009). Because of the potential for infected monocytes to cross the BBB, an increased viral load in the periphery may result in higher viral loads in the CNS.

The effects of methamphetamine and HIV on the immune system

HIV initially infects cells of the immune system and subsequently invades and compromises various other systems of the body. It is known to modulate various immune functions such as activation of T cells and NK cells as well as to disrupt cytokine balance. Because of its action as a psychostimulant, the effects of MA in the context of HIV infection have been primarily studied in the CNS. However, dopamine receptors and transporters, which are reported to mediate the effects of MA, are also expressed in the periphery on various immune cells. It is therefore relevant, and important, to study the effects of MA in the immune system of HIV-infected individuals.

As mentioned previously, MA has been shown to increase HIV replication in various immune cells such as dendritic cells, monocytes, and $CD4^+$ T-cells (Reynolds et al. 2007; Toussi et al. 2009). Several studies have also documented the ability of MA to modulate other immune functions. MA has been demonstrated to upregulate the expression of the HIV co-receptor CCR5 on macrophages while simultaneously suppressing the expression of the anti-viral cytokine IFN-α (Liang et al. 2008). Microarray studies on dendritic cells differentiated from normal human PBMC and treated with MA showed altered gene expression patterns. The expression levels of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-8 were upregulated, as was the expression of CCR5. Phosphorylation of the signal transduction molecule p38-MAPK was increased while PI3K phosphorylation was decreased (Mahajan et al. 2006). This study was followed up by performing proteomic analysis using PBMC isolated from HIV-1 patients and exposed to MA for 24 h. MA decreased expression of HSP70p5 and peroxiredoxin 6 while increasing the expression of vimentin in these cells. HSP70 prevents vpr-induced cell cycle arrest, whereas peroxiredoxins are antioxidants that inhibit HIV-1 infection. Vimentin, on the other hand, facilitates spread of HIV to adjacent cells (Reynolds et al. 2009). Proteomic analysis of MA-treated immature dendritic cells infected with HIV-1 showed increased expression of proteins that promote HIV adhesion, entry, and replication such as galectin-1, PDI, filamin 1, and talin 1 (Reynolds et al. 2007). MA may therefore act as a co-factor that promotes HIV pathogenesis by increasing the susceptibility of cells to viral invasion, activation of HIV transcriptional mechanisms, and T cell depletion through apoptosis.

Dendritic cells (DC) are among the first lines of defense against invading pathogens and consequently are among the initial targets of HIV infection. MA treatment reduces the expression of the mature DC marker CD83 that plays a role in antigen presentation and T cell activation. It also decreased secretion of the chemokines MIP-1α, MIP-1β, and RANTES which can bind to the CCR5 co-receptor and prevent entry of virus into cells (Nair and Saiyed 2010). MA and gp120 synergistically upregulate DC ICAM-3 by binding the non-integrin DC-SIGN. DC-SIGN is known to promote HIV infection in the absence of CD4 or the HIV co-receptors. In addition, MA also caused a dose-dependent increase in the HIV-1 co-receptors CXCR4 and CCR5. These effects were mediated by interaction of MA with D1 dopamine receptor and the phosphorylation of p38 MAPK (Nair et al. 2006). Talloczy et. al investigated the effects of pharmacologically relevant concentrations of MA on antigen processing, presentation, and phagocytosis in murine dendritic cells and macrophages (Talloczy et al. 2008). It was observed that MA induced alkalization in acidic organelles and thereby impaired dendritic cell function involving lysosomal degradation of foreign proteins. MA also inhibited macrophage phagocytic function while promoting fungal replication in macrophages. Therefore, the ability of MA to disrupt the pH gradient in these cells was responsible for loss of their respective functions.

A number of studies have also been carried out on non-human primates, which serve as excellent model systems to study HIV. Chronically SIV-infected rhesus macaques showed changes in virus–host interaction due to MA exposure. Though plasma viral loads were not elevated, significant changes were observed in immune cells. NK cell activation was prominent in brain, blood, and lymphoid organs as determined by degranulation and cytokine expression on the cell surface (Marcondes et al. 2010). Oxidative stress is also believed to play a pivotal role in chronic SIV and MA co-morbidity. Proteomic plasma analyses of chronically infected

macaques that were administered MA revealed significantly elevated levels of the enzymes superoxide dismutase as well as glutathione-*S*-transferase (Pendyala et al. 2011). This suggests the utilization of these compensatory mechanisms to combat oxidative stress.

Thus, MA has been implicated in exacerbating HIV-induced effects in the CNS and periphery through number of mechanisms promoting HIV replication and infectivity, altering expression of important immune components, impairing antigen presentation and elevating oxidative stress (summarized in Table 1, Fig. 1).

Summary and future directions

A review of the literature shows that the chemical similarity between MA and dopamine is thought to be the basis for the toxic effects of this drug. Early work demonstrated that treatment of rodents with MA results in altered expression of many of the enzymes involved in dopamine biosynthesis. Further work demonstrated that dopamine receptors and dopamine transporters are key players in mediating the effects of MA. The ability of MA to affect the function of DAT and VMAT-2 causes an aberrant distribution of dopamine and its metabolites. The altered distribution of dopamine not only affects signaling, but it can also produce oxidative stress. MA-abuse in humans has been demonstrated to cause altered cerebral blood flow and severe gray matter deficits in several regions of the brain. The use of rodent models has also facilitated identification of brain hyperthermia as one of the deleterious effects on the CNS associated with MA abuse.

The frontostriatal regions of the brain that are most susceptible to the deleterious effects of MA are also one of the initial targets of HIV-1 infection. The HIV-1 viral proteins Tat and gp120 interact with MA synergistically to increase neuronal cell death, oxidative stress, and inflammatory cytokine production by cells of the CNS. MA has been shown to decrease tight junction proteins in the BBB such as ZO-1 and claudin-3/5. This may facilitate HIV-1 penetration into the CNS. Using a macaque model of HIV-1 infection, one group demonstrated that MA treatment of infected animals resulted in an increase in the viral load in CNS.

More recently, MA has been shown to have the potential to affect HIV infection in the periphery. Treatment of human MDMs infected with HIV showed increased levels of viral replication. HIV infection may be exacerbated by the increased levels of inflammatory cytokines and chemokines or increased levels of the CCR5 co-receptor seen in MA-treated macrophages and dendritic cells. Such increases may potentiate viral replication in the periphery and thus increase the potential for CNS infection.

Although the biological effects of MA abuse have been extensively studied during the past two decades, much remains to be explored regarding the effects of MA abuse on HIV-1 infection. Although there have been some reports regarding the effect of HIV and its associated proteins on DAT, the effect of viral infection on the expression and function of VMAT-2 is unknown. Because recent work has demonstrated that both of these transporters affect dopamine disposition, and both are also affected by MA, this represents a major gap in our understanding of HIV-MA interactions in the CNS. Another unanswered question regards the potential role of dopamine receptors in affecting HIV replication in microglial cells. These receptors have already been demonstrated to increase HIV replication in human MDMs treated with MA. Although the data is limited, it has already been demonstrated that MA treatment of macaques increases the CNS viral load. This raises the question as to whether the primary mechanism is an increase in the permeability of the BBB or an increase in HIV replication in microglial cells. The effects of MA are obviously not limited to the CNS, and the findings that have shown an MA-induced increase in HIV-1 replication in human MDMs, and increased co-receptor expression on dendritic cells certainly suggest that further investigation of the effects of MA on HIV pathogenesis in the periphery are warranted. The next several years should yield some interesting results regarding MA–HIV interactions.

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References

Acikgoz O, Gonenc S, Kayatekin BM, Uysal N, Pekcetin C, Semin I, Gure A (1998) Methamphetamine causes lipid peroxidation and an increase in superoxide dismutase activity in the rat striatum. Brain Res 813:200–202

Amenta F, Bronzetti E, Felici L, Ricci A, Tayebati SK (1999) Dopamine D2-like receptors on human peripheral blood lymphocytes: a radioligand binding assay and immunocytochemical study. J Auton Pharmacol 19:151–159

Angulo JA, Angulo N, Yu J (2004) Antagonists of the neurokinin-1 or dopamine D1 receptors confer protection from methamphetamine on dopamine terminals of the mouse striatum. Ann N Y Acad Sci 1025:171–180

Anlauf M, Schafer MK, Schwark T, von Wurmb-Schwark N, Brand V, Sipos B, Horny HP, Parwaresch R, Hartschuh W, Eiden LE, Kloppel G, Weihe E (2006) Vesicular monoamine transporter 2 (VMAT2) expression in hematopoietic cells and in patients with systemic mastocytosis. J Histochem Cytochem 54:201–213

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour

V, Wojna VE (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1789–1799

Banerjee A, Zhang X, Manda KR, Banks WA, Ercal N (2010) HIV proteins (gp120 and Tat) and methamphetamine in oxidative stress-induced damage in the brain: potential role of the thiol antioxidant *N*-acetylcysteine amide. Free Radic Biol Med 48:1388–1398

Berger JR, Kumar M, Kumar A, Fernandez JB, Levin B (1994) Cerebrospinal fluid dopamine in HIV-1 infection. AIDS 8:67–71

Brown PL, Kiyatkin EA (2005) Fatal intra-brain heat accumulation induced by meth-amphetamine at normothermic conditions in rats. Int J Neuroprotect Neuroregeneration 1:86–90

Brown JM, Riddle EL, Sandoval V, Weston RK, Hanson JE, Crosby MJ, Ugarte YV, Gibb JW, Hanson GR, Fleckenstein AE (2002) A single methamphetamine administration rapidly decreases vesicular dopamine uptake. J Pharmacol Exp Ther 302:497–501

Brown PL, Wise RA, Kiyatkin EA (2003) Brain hyperthermia is induced by methamphetamine and exacerbated by social interaction. J Neurosci 23:3924–3929

Buchacz K, McFarland W, Kellogg TA, Loeb L, Holmberg SD, Dilley J, Klausner JD (2005) Amphetamine use is associated with increased HIV incidence among men who have sex with men in San Francisco. AIDS 19:1423–1424

Cadet JL, Krasnova IN (2007) Interactions of HIV and methamphetamine: cellular and molecular mechanisms of toxicity potentiation. Neurotox Res 12:181–204

Cadet JL, Sheng P, Ali S, Rothman R, Carlson E, Epstein C (1994) Attenuation of methamphetamine-induced neurotoxicity in copper/zinc superoxide dismutase transgenic mice. J Neurochem 62:380–383

Cass WA, Harned ME, Peters LE, Nath A, Maragos WF (2003) HIV-1 protein Tat potentiation of methamphetamine-induced decreases in evoked overflow of dopamine in the striatum of the rat. Brain Res 984:133–142

Chang L, Ernst T, Speck O, Grob CS (2005) Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. Am J Psychiatry 162:361–369

Chen HM, Lee YC, Huang CL, Liu HK, Liao WC, Lai WL, Lin YR, Huang NK (2007) Methamphetamine downregulates peroxiredoxins in rat pheochromocytoma cells. Biochem Biophys Res Commun 354:96–101

Chung YA, Peterson BS, Yoon SJ, Cho SN, Chai S, Jeong J, Kim DJ (2010) In vivo evidence for long-term CNS toxicity, associated with chronic binge use of methamphetamine. Drug Alcohol Depend 111:155–160

Clifford DB (2008) HIV-associated neurocognitive disease continues in the antiretroviral era. Top HIV Med 16:94–98

Conant K, St Hillaire C, Anderson C, Galey D, Wang J, Nath A (2004) Human immunodeficiency virus type 1 Tat and methamphetamine affect the release and activation of matrix-degrading proteinases. J Neurovirol 10:21–28

Cubells JF, Rayport S, Rajendran G, Sulzer D (1994) Methamphetamine neurotoxicity involves vacuolation of endocytic organelles and dopamine-dependent intracellular oxidative stress. J Neurosci 14:2260–2271

Davidson C, Gow AJ, Lee TH, Ellinwood EH (2001) Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. Brain Res Brain Res Rev 36:1–22

Degenhardt L, Mathers B, Guarinieri M, Panda S, Phillips B, Strathdee SA, Tyndall M, Wiessing L, Wodak A, Howard J (2010) Meth/amphetamine use and associated HIV: Implications for global policy and public health. Int J Drug Policy 21:347–358

Dluzen DE, McDermott JL, Darvesh AS (2010) Relationships among gender, age, time, and temperature in methamphetamine-induced striatal dopaminergic neurotoxicity. Neuroscience 167:985–993

Eyerman DJ, Yamamoto BK (2005) Lobeline attenuates methamphetamine-induced changes in vesicular monoamine transporter 2 immunoreactivity and monoamine depletions in the striatum. J Pharmacol Exp Ther 312:160–169

Fleckenstein AE, Volz TJ, Hanson GR (2009) Psychostimulant-induced alterations in vesicular monoamine transporter-2 function: neurotoxic and therapeutic implications. Neuropharmacology 56 (Suppl 1):133–138

Flora G, Lee YW, Nath A, Maragos W, Hennig B, Toborek M (2002) 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. Neuromolecular Med 2:71–85

Flora G, Lee YW, Nath A, Hennig B, Maragos W, Toborek M (2003) Methamphetamine potentiates HIV-1 Tat protein-mediated activation of redox-sensitive pathways in discrete regions of the brain. Exp Neurol 179:60–70

Frey K, Kilbourn M, Robinson T (1997) Reduced striatal vesicular monoamine transporters after neurotoxic but not after behaviorally-sensitizing doses of methamphetamine. Eur J Pharmacol 334:273–279

Fumagalli F, Gainetdinov RR, Valenzano KJ, Caron MG (1998) Role of dopamine transporter in methamphetamine-induced neurotoxicity: evidence from mice lacking the transporter. J Neurosci 18:4861–4869

Fumagalli F, Gainetdinov RR, Wang YM, Valenzano KJ, Miller GW, Caron MG (1999) Increased methamphetamine neurotoxicity in heterozygous vesicular monoamine transporter 2 knock-out mice. J Neurosci 19:2424–2431

Garcia de Yebenes J, Yebenes J, Mena MA (2000) Neurotrophic factors in neurodegenerative disorders: model of Parkinson's disease. Neurotox Res 2:115–137

Genc K, Genc S, Kizildag S, Sonmez U, Yilmaz O, Tugyan K, Ergur B, Sonmez A, Buldan Z (2003) Methamphetamine induces oligodendroglial cell death in vitro. Brain Res 982:125–130

Gendelman HE, Meltzer MS (1989) Mononuclear phagocytes and the human immunodeficiency virus. Curr Opin Immunol 2:414–419

Gibb JW, Kogan FJ (1979) Influence of dopamine synthesis on methamphetamine-induced changes in striatal and adrenal tyrosine hydroxylase activity. Naunyn Schmiedebergs Arch Pharmacol 310:185–187

Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, Hillhouse M, Ang A, Rawson RA (2010) Psychopathology in methamphetamine-dependent adults 3 years after treatment. Drug Alcohol Rev 29:12–20

Glass JD, Wesselingh SL, Selnes OA, McArthur JC (1993) Clinical-neuropathologic correlation in HIV-associated dementia. Neurology 43:2230–2237

Gluck MR, Moy LY, Jayatilleke E, Hogan KA, Manzino L, Sonsalla PK (2001) Parallel increases in lipid and protein oxidative markers in several mouse brain regions after methamphetamine treatment. J Neurochem 79:152–160

Goncalves J, Martins T, Ferreira R, Milhazes N, Borges F, Ribeiro CF, Malva JO, Macedo TR, Silva AP (2008) Methamphetamine-induced early increase of IL-6 and TNF-alpha mRNA expression in the mouse brain. Ann N Y Acad Sci 1139:103–111

Gonzales R, Ang A, Marinelli-Casey P, Glik DC, Iguchi MY, Rawson RA (2009) Health-related quality of life trajectories of methamphetamine-dependent individuals as a function of treatment completion and continued care over a 1-year period. J Subst Abuse Treat 37:353–361

Gonzales R, Mooney L, Rawson RA (2010) The methamphetamine problem in the United States. Annu Rev Public Health 31:385–398

Gorbach PM, Drumright LN, Javanbakht M, Pond SL, Woelk CH, Daar ES, Little SJ (2008) Antiretroviral drug resistance and risk

behavior among recently HIV-infected men who have sex with men. J Acquir Immune Defic Syndr 47:639–643
Hogan KA, Staal RG, Sonsalla PK (2000) Analysis of VMAT2 binding after methamphetamine or MPTP treatment: disparity between homogenates and vesicle preparations. J Neurochem 74:2217–2220
Hotchkiss AJ, Gibb JW (1980) Long-term effects of multiple doses of methamphetamine on tryptophan hydroxylase and tyrosine hydroxylase activity in rat brain. J Pharmacol Exp Ther 214:257–262
Itoh K, Mehraein P, Weis S (2000) Neuronal damage of the substantia nigra in HIV-1 infected brains. Acta Neuropathol 99:376–384
Iwazaki T, McGregor IS, Matsumoto I (2006) Protein expression profile in the striatum of acute methamphetamine-treated rats. Brain Res 1097:19–25
Iyo M, Sekine Y, Mori N (2004) Neuromechanism of developing methamphetamine psychosis: a neuroimaging study. Ann N Y Acad Sci 1025:288–295
Jayanthi S, Ladenheim B, Cadet JL (1998) Methamphetamine-induced changes in antioxidant enzymes and lipid peroxidation in copper/zinc-superoxide dismutase transgenic mice. Ann N Y Acad Sci 844:92–102
Jayanthi S, Deng X, Ladenheim B, McCoy MT, Cluster A, Cai NS, Cadet JL (2005) Calcineurin/NFAT-induced up-regulation of the Fas ligand/Fas death pathway is involved in methamphetamine-induced neuronal apoptosis. Proc Natl Acad Sci U S A 102:868–873
Kanthasamy A, Anantharam V, Ali SF, Kanthasamy AG (2006) Methamphetamine induces autophagy and apoptosis in a mesencephalic dopaminergic neuronal culture model: role of cathepsin-D in methamphetamine-induced apoptotic cell death. Ann N Y Acad Sci 1074:234–244
Kiyatkin EA (2005) Brain hyperthermia as physiological and pathological phenomena. Brain Res Brain Res Rev 50:27–56
Kiyatkin EA (2010) Brain temperature homeostasis: physiological fluctuations and pathological shifts. Front Biosci 15:73–92
Kiyatkin EA, Sharma HS (2011) Expression of heat shock protein (HSP 72 kDa) during acute methamphetamine intoxication depends on brain hyperthermia: neurotoxicity or neuroprotection? J Neural Transm 118:47–60
Kiyatkin EA, Brown PL, Sharma HS (2007) Brain edema and breakdown of the blood-brain barrier during methamphetamine intoxication: critical role of brain hyperthermia. Eur J Neurosci 26:1242–1253
Krasnova IN, Cadet JL (2009) Methamphetamine toxicity and messengers of death. Brain Res Rev 60:379–407
Kuhn DM, Francescutti-Verbeem DM, Thomas DM (2008) Dopamine disposition in the presynaptic process regulates the severity of methamphetamine-induced neurotoxicity. Ann N Y Acad Sci 1139:118–126
Kuperman DI, Freyaldenhoven TE, Schmued LC, Ali SF (1997) Methamphetamine-induced hyperthermia in mice: examination of dopamine depletion and heat-shock protein induction. Brain Res 771:221–227
LaGasse LL, Wouldes T, Newman E, Smith LM, Shah RZ, Derauf C, Huestis MA, Arria AM, Della Grotta S, Wilcox T, Lester BM (2011) Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. Neurotoxicol Teratol 33:166–175
Langford D, Adame A, Grigorian A, Grant I, McCutchan JA, Ellis RJ, Marcotte TD, Masliah E (2003) Patterns of selective neuronal damage in methamphetamine-user AIDS patients. J Acquir Immune Defic Syndr 34:467–474
Langford D, Grigorian A, Hurford R, Adame A, Crews L, Masliah E (2004) The role of mitochondrial alterations in the combined toxic effects of human immunodeficiency virus Tat protein and methamphetamine on calbindin positive-neurons. J Neurovirol 10:327–337
Larsen KE, Fon EA, Hastings TG, Edwards RH, Sulzer D (2002) Methamphetamine-induced degeneration of dopaminergic neurons involves autophagy and upregulation of dopamine synthesis. J Neurosci 22:8951–8960
LaVoie MJ, Hastings TG (1999) Dopamine quinone formation and protein modification associated with the striatal neurotoxicity of methamphetamine: evidence against a role for extracellular dopamine. J Neurosci 19:1484–1491
Liang H, Wang X, Chen H, Song L, Ye L, Wang SH, Wang YJ, Zhou L, Ho WZ (2008) Methamphetamine enhances HIV infection of macrophages. Am J Pathol 172:1617–1624
Liu X, Chang L, Vigorito M, Kass M, Li H, Chang SL (2009) Methamphetamine-induced behavioral sensitization is enhanced in the HIV-1 transgenic rat. J Neuroimmune Pharmacol 4:309–316
Madden LJ, Flynn CT, Zandonatti MA, May M, Parsons LH, Katner SN, Henriksen SJ, Fox HS (2005) Modeling human methamphetamine exposure in nonhuman primates: chronic dosing in the rhesus macaque leads to behavioral and physiological abnormalities. Neuropsychopharmacology 30:350–359
Magnuson DS, Knudsen BE, Geiger JD, Brownstone RM, Nath A (1995) Human immunodeficiency virus type 1 tat activates non-*N*-methyl-D-aspartate excitatory amino acid receptors and causes neurotoxicity. Ann Neurol 37:373–380
Mahajan SD, Hu Z, Reynolds JL, Aalinkeel R, Schwartz SA, Nair MP (2006) Methamphetamine modulates gene expression patterns in monocyte derived mature dendritic cells: implications for HIV-1 pathogenesis. Mol Diagn Ther 10:257–269
Mahajan SD, Aalinkeel R, Sykes DE, Reynolds JL, Bindukumar B, Adal A, Qi M, Toh J, Xu G, Prasad PN, Schwartz SA (2008) 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 1203:133–148
Mao CV, Hori E, Maior RS, Ono T, Nishijo H (2008) A primate model of schizophrenia using chronic PCP treatment. Rev Neurosci 19:83–89
Maragos WF, Young KL, Turchan JT, Guseva M, Pauly JR, Nath A, Cass WA (2002) Human immunodeficiency virus-1 Tat protein and methamphetamine interact synergistically to impair striatal dopaminergic function. J Neurochem 83:955–963
Marcondes MC, Flynn C, Watry DD, Zandonatti M, Fox HS (2010) Methamphetamine increases brain viral load and activates natural killer cells in simian immunodeficiency virus-infected monkeys. Am J Pathol 177:355–361
Marek GJ, Vosmer G, Seiden LS (1990) Dopamine uptake inhibitors block long-term neurotoxic effects of methamphetamine upon dopaminergic neurons. Brain Res 513:274–279
McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, Becker JT, Graham NM, McArthur JH, Selnes OA, Jacobson LP et al (1993) Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. Neurology 43:2245–2252
Melega WP, Lacan G, Harvey DC, Way BM (2007) Methamphetamine increases basal ganglia iron to levels observed in aging. Neuroreport 18:1741–1745
Melega WP, Jorgensen MJ, Lacan G, Way BM, Pham J, Morton G, Cho AK, Fairbanks LA (2008) Long-term methamphetamine administration in the vervet monkey models aspects of a human exposure: brain neurotoxicity and behavioral profiles. Neuropsychopharmacology 33:1441–1452
Meltzer MS, Gendelman HE (1992) Mononuclear phagocytes as targets, tissue reservoirs, and immunoregulatory cells in human immunodeficiency virus disease. Curr Top Microbiol Immunol 181:239–263

Meltzer MS, Skillman DR, Gomatos PJ, Kalter DC, Gendelman HE (1990) Role of mononuclear phagocytes in the pathogenesis of human immunodeficiency virus infection. Annu Rev Immunol 8:169–194

Miyazaki I, Asanuma M, Diaz-Corrales FJ, Fukuda M, Kitaichi K, Miyoshi K, Ogawa N (2006) Methamphetamine-induced dopaminergic neurotoxicity is regulated by quinone-formation-related molecules. FASEB J 20:571–573

Munch G, Raether A, Schoffel E, Illes P (1991) Postsynaptic dopamine DA1- and DA2-receptors in jejunal arteries of rabbits. J Cardiovasc Pharmacol 18:468–471

Nair MP, Saiyed ZM (2010) Effect of methamphetamine on expression of HIV coreceptors and CC-chemokines by dendritic cells. Life Sci 88:987–994

Nair MP, Mahajan S, Sykes D, Bapardekar MV, Reynolds JL (2006) Methamphetamine modulates DC-SIGN expression by mature dendritic cells. J Neuroimmune Pharmacol 1:296–304

Narita M, Miyatake M, Shibasaki M, Tsuda M, Koizumi S, Yajima Y, Inoue K, Suzuki T (2005) Long-lasting change in brain dynamics induced by methamphetamine: enhancement of protein kinase C-dependent astrocytic response and behavioral sensitization. J Neurochem 93:1383–1392

Nath A, Anderson C, Jones M, Maragos W, Booze R, Mactutus C, Bell J, Hauser KF, Mattson M (2000) Neurotoxicity and dysfunction of dopaminergic systems associated with AIDS dementia. J Psychopharmacol 14:222–227

Navia BA, Cho ES, Petito CK, Price RW (1986a) The AIDS dementia complex: II. Neuropathology. Ann Neurol 19:525–535

Navia BA, Jordan BD, Price RW (1986b) The AIDS dementia complex: I. Clinical features. Ann Neurol 19:517–524

Newton TF, Kalechstein AD, Hardy DJ, Cook IA, Nestor L, Ling W, Leuchter AF (2004) Association between quantitative EEG and neurocognition in methamphetamine-dependent volunteers. Clin Neurophysiol 115:194–198

Office of Applied Studies S (2007) Methamphetamine Abuse. The NSDUH Report

Olsen NV (1998) Effects of dopamine on renal haemodynamics tubular function and sodium excretion in normal humans. Dan Med Bull 45:282–297

Ozono R, O'Connell DP, Wang ZQ, Moore AF, Sanada H, Felder RA, Carey RM (1997) Localization of the dopamine D1 receptor protein in the human heart and kidney. Hypertension 30:725–729

Paulus MP, Hozack NE, Zauscher BE, Frank L, Brown GG, Braff DL, Schuckit MA (2002) Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. Neuropsychopharmacology 26:53–63

Pendyala G, Trauger SA, Siuzdak G, Fox HS (2011) Short communication: quantitative proteomic plasma profiling reveals activation of host defense to oxidative stress in chronic SIV and methamphetamine comorbidity. AIDS Res Hum Retroviruses 27:179–182

Pivonello R, Ferone D, de Herder WW, de Krijger RR, Waaijers M, Mooij DM, van Koetsveld PM, Barreca A, De Caro ML, Lombardi G, Colao A, Lamberts SW, Hofland LJ (2004) Dopamine receptor expression and function in human normal adrenal gland and adrenal tumors. J Clin Endocrinol Metab 89:4493–4502

Ramirez SH, Potula R, Fan S, Eidem T, Papugani A, Reichenbach N, Dykstra H, Weksler BB, Romero IA, Couraud PO, Persidsky Y (2009) Methamphetamine disrupts blood-brain barrier function by induction of oxidative stress in brain endothelial cells. J Cereb Blood Flow Metab 29:1933–1945

Rawson RA, Gonzales R, Brethen P (2002) Treatment of methamphetamine use disorders: an update. J Subst Abuse Treat 23:145–150

Reiner BC, Keblesh JP, Xiong H (2009) Methamphetamine abuse, HIV infection, and neurotoxicity. Int J Physiol Pathophysiol Pharmacol 1:162–179

Reyes MG, Faraldi F, Senseng CS, Flowers C, Fariello R (1991) Nigral degeneration in acquired immune deficiency syndrome (AIDS). Acta Neuropathol 82:39–44

Reynolds JL, Mahajan SD, Sykes DE, Schwartz SA, Nair MP (2007) Proteomic analyses of methamphetamine (METH)-induced differential protein expression by immature dendritic cells (IDC). Biochim Biophys Acta 1774:433–442

Reynolds JL, Mahajan SD, Aalinkeel R, Nair B, Sykes DE, Agosto-Mujica A, Hsiao CB, Schwartz SA (2009) Modulation of the proteome of peripheral blood mononuclear cells from HIV-1-infected patients by drugs of abuse. J Clin Immunol 29:646–656

Ricci A, Amenta F (1994) Dopamine D5 receptors in human peripheral blood lymphocytes: a radioligand binding study. J Neuroimmunol 53:1–7

Ricci A, Bronzetti E, Felici L, Tayebati SK, Amenta F (1997) Dopamine D4 receptor in human peripheral blood lymphocytes: a radioligand binding assay study. Neurosci Lett 229:130–134

Ricci A, Bronzetti E, Felici L, Greco S, Amenta F (1998) Labeling of dopamine D3 and D4 receptor subtypes in human peripheral blood lymphocytes with [3H]7-OH-DPAT: a combined radioligand binding assay and immunochemical study. J Neuroimmunol 92:191–195

Ricci A, Bronzetti E, Mignini F, Tayebati SK, Zaccheo D, Amenta F (1999) Dopamine D1-like receptor subtypes in human peripheral blood lymphocytes. J Neuroimmunol 96:234–240

Riddle EL, Fleckenstein AE, Hanson GR (2006) Mechanisms of methamphetamine-induced dopaminergic neurotoxicity. AAPS J 8:E413–E418

Roberts AJ, Maung R, Sejbuk NE, Ake C, Kaul M (2010) Alteration of methamphetamine-induced stereotypic behaviour in transgenic mice expressing HIV-1 envelope protein gp120. J Neurosci Methods 186:222–225

Rohr O, Sawaya BE, Lecestre D, Aunis D, Schaeffer E (1999) Dopamine stimulates expression of the human immunodeficiency virus type 1 via NF-kappaB in cells of the immune system. Nucleic Acids Res 27:3291–3299

Romero CA, Bustamante DA, Zapata-Torres G, Goiny M, Cassels B, Herrera-Marschitz M (2006) Neurochemical and behavioural characterisation of alkoxyamphetamine derivatives in rats. Neurotox Res 10:11–22

Roussotte F, Soderberg L, Sowell E (2010) Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: evidence from neuroimaging. Neuropsychol Rev 20:376–397

Ruffolo RR Jr, Messick K (1985) Effects of dopamine, (+/−)-dobutamine and the (+)- and (−)-enantiomers of dobutamine on cardiac function in pithed rats. J Pharmacol Exp Ther 235:558–565

Saisho Y, Harris PE, Butler AE, Galasso R, Gurlo T, Rizza RA, Butler PC (2008) Relationship between pancreatic vesicular monoamine transporter 2 (VMAT2) and insulin expression in human pancreas. J Mol Histol 39:543–551

Sandoval V, Riddle EL, Hanson GR, Fleckenstein AE (2003) Methylphenidate alters vesicular monoamine transport and prevents methamphetamine-induced dopaminergic deficits. J Pharmacol Exp Ther 304:1181–1187

Schmidt CJ, Gibb JW (1985) Role of the dopamine uptake carrier in the neurochemical response to methamphetamine: effects of amfonelic acid. Eur J Pharmacol 109:73–80

Schmidt CJ, Ritter JK, Sonsalla PK, Hanson GR, Gibb JW (1985) Role of dopamine in the neurotoxic effects of methamphetamine. J Pharmacol Exp Ther 233:539–544

Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, Ellis RJ, Letendre S, Videen JS, McCutchan JA, Patterson TL, Grant I (2005) Brain mitochondrial injury in human immunodeficiency

virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol 11:356–364

Sharma HS, Kiyatkin EA (2009) Rapid morphological brain abnormalities during acute methamphetamine intoxication in the rat: an experimental study using light and electron microscopy. J Chem Neuroanat 37:18–32

Shoptaw S, Reback CJ (2007) Methamphetamine use and infectious disease-related behaviors in men who have sex with men: implications for interventions. Addiction 102(Suppl 1):130–135

Siegel JA, Craytor MJ, Raber J (2010) Long-term effects of methamphetamine exposure on cognitive function and muscarinic acetylcholine receptor levels in mice. Behav Pharmacol 21:602–614

Siegel JA, Park BS, Raber J (2011) Long-term effects of neonatal methamphetamine exposure on cognitive function in adolescent mice. Behav Brain Res 219:159–164

Smith LM, Lagasse LL, Derauf C, Grant P, Shah R, Arria A, Huestis M, Haning W, Strauss A, Della Grotta S, Fallone M, Liu J, Lester BM (2008) Prenatal methamphetamine use and neonatal neurobehavioral outcome. Neurotoxicol Teratol 30:20–28

Sonsalla PK, Gibb JW, Hanson GR (1986) Roles of D1 and D2 dopamine receptor subtypes in mediating the methamphetamine-induced changes in monoamine systems. J Pharmacol Exp Ther 238:932–937

Sriram K, Miller DB, O'Callaghan JP (2006) Minocycline attenuates microglial activation but fails to mitigate striatal dopaminergic neurotoxicity: role of tumor necrosis factor-alpha. J Neurochem 96:706–718

Stephans SE, Yamamoto BK (1994) Methamphetamine-induced neurotoxicity: roles for glutamate and dopamine efflux. Synapse 17:203–209

Sulzer D, Sonders MS, Poulsen NW, Galli A (2005) Mechanisms of neurotransmitter release by amphetamines: a review. Prog Neurobiol 75:406–433

Talloczy Z, Martinez J, Joset D, Ray Y, Gacser A, Toussi S, Mizushima N, Nosanchuk JD, Goldstein H, Loike J, Sulzer D, Santambrogio L (2008) Methamphetamine inhibits antigen processing, presentation, and phagocytosis. PLoS Pathog 4:e28

Tang Y, Nee AC, Lu A, Ran R, Sharp FR (2003) Blood genomic expression profile for neuronal injury. J Cereb Blood Flow Metab 23:310–319

Theodore S, Cass WA, Maragos WF (2006a) Involvement of cytokines in human immunodeficiency virus-1 protein Tat and methamphetamine interactions in the striatum. Exp Neurol 199:490–498

Theodore S, Cass WA, Nath A, Steiner J, Young K, Maragos WF (2006b) Inhibition of tumor necrosis factor-alpha signaling prevents human immunodeficiency virus-1 protein Tat and methamphetamine interaction. Neurobiol Dis 23:663–668

Thomas SA (2004) Anti-HIV drug distribution to the central nervous system. Curr Pharm Des 10:1313–1324

Thomas DM, Dowgiert J, Geddes TJ, Francescutti-Verbeem D, Liu X, Kuhn DM (2004a) Microglial activation is a pharmacologically specific marker for the neurotoxic amphetamines. Neurosci Lett 367:349–354

Thomas DM, Walker PD, Benjamins JA, Geddes TJ, Kuhn DM (2004b) Methamphetamine neurotoxicity in dopamine nerve endings of the striatum is associated with microglial activation. J Pharmacol Exp Ther 311:1–7

Thompson PM, Hayashi KM, Simon SL, Geaga JA, Hong MS, Sui Y, Lee JY, Toga AW, Ling W, London ED (2004) Structural abnormalities in the brains of human subjects who use methamphetamine. J Neurosci 24:6028–6036

Toussi SS, Joseph A, Zheng JH, Dutta M, Santambrogio L, Goldstein H (2009) Short communication: methamphetamine treatment increases in vitro and in vivo HIV replication. AIDS Res Hum Retroviruses 25:1117–1121

Turchan J, Anderson C, Hauser KF, Sun Q, Zhang J, Liu Y, Wise PM, Kruman I, Maragos W, Mattson MP, Booze R, Nath A (2001) Estrogen protects against the synergistic toxicity by HIV proteins, methamphetamine and cocaine. BMC Neurosci 2:3

Wagner GC, Ricaurte GA, Seiden LS, Schuster CR, Miller RJ, Westley J (1980) Long-lasting depletions of striatal dopamine and loss of dopamine uptake sites following repeated administration of methamphetamine. Brain Res 181:151–160

Wilson JM, Kalasinsky KS, Levey AI, Bergeron C, Reiber G, Anthony RM, Schmunk GA, Shannak K, Haycock JW, Kish SJ (1996) Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat Med 2:699–703

Witkovsky P (2004) Dopamine and retinal function. Doc Ophthalmol 108:17–40

Xu W, Zhu JP, Angulo JA (2005) Induction of striatal pre- and postsynaptic damage by methamphetamine requires the dopamine receptors. Synapse 58:110–121

Zweben JE, Cohen JB, Christian D, Galloway GP, Salinardi M, Parent D, Iguchi M (2004) Psychiatric symptoms in methamphetamine users. Am J Addict 13:181–190