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METHAMPHETAMINE TOXICITY AND MESSENGERS OF DEATH

Irina N. Krasnova and **Jean Lud Cadet**
Molecular Neuropsychiatry Reasearch Branch, Intramural Research Program, NIDA/NIH/DHHS, Baltimore, MD 21224, USA

Abstract

Methamphetamine (METH) is an illicit psychostimulant that is widely abused in the world. Several lines of evidence suggest that chronic METH abuse leads to neurodegenerative changes in the human brain. These include damage to dopamine and serotonin axons, loss of gray matter accompanied by hypertrophy of the white matter and microgliosis in different brain areas. In the present review, we summarize data on the animal models of METH neurotoxicity which include degeneration of monoaminergic terminals and neuronal apoptosis. In addition, we discuss molecular and cellular bases of METH-induced neuropathologies. The accumulated evidence indicates that multiple events, including oxidative stress, excitotoxicity, hyperthermia, neuroinflammatory responses, mitochondrial dysfunction, endoplasmic reticulum stress converge to mediate METH-induced terminal degeneration and neuronal apoptosis. When taken together, these findings suggest that pharmacological strategies geared towards the prevention and treatment of the deleterious effects of this drug will need to attack the various pathways that form the substrates of METH toxicity.

Keywords

methamphetamine; neurotoxicity; dopamine; oxidative stress; serotonin; cell death

Epidemiology of Methamphetamine Abuse

Abuse of the illegal psychostimulant, methamphetamine (METH), has become an international public health problem with an estimated 15–16 million users worldwide, a total which exceeds the number of people who abuse heroin and cocaine and makes METH the second most widely abused drug after cannabis (United Nations Office on Drugs and Crime, 2007). The inexpensive production of METH, its low cost, and long duration of action have made it a very desirable commodity. Indeed, METH is a popular drug of abuse in Australia (Australian Institure for Health and Welfare, 2005), Canada (Canadian Centre on Substance Abuse, 2005), Czech Republic and Slovakia (European Monitoring Center for Drugs and Drug Addiction, 2007). During the last decade, Southeast Asia and East Asia have become global hubs for METH production and trafficking, with a coincident epidemic of psychostimulant abuse in these regions (United Nations Office on Drugs and Crime, 2007). It is estimated that over half of the world's METH consumers reside in Southeast Asia and East Asia (United Nations Office on Drugs and Crime, 2007). Japan, in particular, has experienced several epidemics of crystal METH abuse, including a peak in 1999–2000. Since the late 1990s, METH use rose to epidemic

Correspondence: Jean Lud Cadet M.D., Chief, Molecular Neuropsychiatry Reasearch Branch, Intramural Research Program, NIDA/NIH/DHHS, 251 Bayview Boulevard, Baltimore, MD 21224, USA, jcadet@intra.nida.nih.gov, Tel: 443-740-2656, Fax: 443-740-2856.

proportions in Thailand, Taiwan, the Philippines and Brunei (United Nations Office on Drugs and Crime, 2007). METH abuse is also a major problem in China, Cambodia, Indonesia, Malaysia, Singapore and Vietnam where smoking of the crystal form of the drug occurs concurrently with pill use (United Nations Office on Drugs and Crime, 2007). Mexico is another country with a growing prevalence of METH use. The proportion of people admitted to treatment for primary psychostimulant problem in this country increased from 3% in 1996 to 20% in 2006 (Mexican National Comorbidity Survey, 2007). In addition, Mexico is a major manufacturer of METH in the world (Dye, 2006). More than a half of METH abused in the USA comes from Mexican cartels primarily in the crystal from known as “ice”, with a purity ranging from 75 to 90% (Dye, 2006). METH is the most commonly synthesized illegal drug in the USA with the highest prelevance of abuse in Western, Southern and Midwestern states; there is an increasing pattern of use in some states in the Eastern corridor of the country (Substance Abuse and Mental Health Services Administration, 2007). A 2006 survey showed that 5.8% of Americans aged 12 years or older used METH at least once (Substance Abuse and Mental Health Services Administration, 2007). METH-related emergency room admissions have increased from 10 to 68 per 100,000 people between 1992 and 2005 (Substance Abuse and Mental Health Services Administration, 2007). Although METH abuse has been associated, traditionally, with white males, blue-collar construction workers, truck drivers, and motorcycle gangs in the USA, the profile of the typical METH abusing individual has shifted due to the increased popularity among minorities, high school students, women, and young professionals (Gettig et al., 2006; Gonzales et al., 2008; Maxwell and Rutkowski, 2008). In addition, METH use is high in men who have sex with men, with a greater frequency of METH abuse being observed in homosexual and bisexual men in comparison to the general population (Reback et al., 2008; Shoptaw and Reback, 2007).

Clinical Toxicology of METH Abuse

Immediately after taking the drug, users experience a sense of euphoria, increased productivity, hypersexuality, decreased anxiety and increased energy (Homer et al., 2008; Meredith et al., 2005). These effects can last for several hours because the elimination half-life of METH ranges from 10 to 12 hours (Schepers et al., 2003). METH abuse is also associated with a number of negative consequences in humans. These include acute toxicity, altered behavioral and cognitive functions, and neurological damage (Albertson et al., 1999; Barr et al., 2006; Murray, 1998; Scott et al., 2007). METH users might experience agitation, aggression, tachycardia, hypertension, and hyperthermia (Albertson et al., 1999; Lynch and House, 1992; Murray, 1998). Impaired judgment, euphoric disinhibition and psychomotor agitation are also associated with METH abuse (Meredith et al., 2005). Ingestions of large doses of the drug can cause more serious consequences that include life-threatening hyperthermia above 41°C, renal and liver failure, cardiac arrhythmias, heart attacks, cerebrovascular hemorrhages, strokes and seizures (Albertson et al., 1999; Darke et al., 2008; Perez et al., 1999). Chronic abuse of METH contributes to anxiety, depression, aggressiveness, social isolation, psychosis, mood disturbances, and psychomotor dysfunction (Darke et al., 2008; Homer et al., 2008; Scott et al., 2007). Neuropsychological studies have detected deficits in attention, working memory, and decision-making in chronic METH addicts (Gonzalez et al., 2004; Paulus et al., 2002; Rippeth et al., 2004; Salo et al., 2002; Semple et al., 2005; Sim et al., 2002; Simon et al., 2002, 2004; Verdejo-Garcia et al., 2006; Woods et al., 2005). Withdrawal from METH can produce anhedonia, irritability, fatigue, impaired social functioning, and intense craving for the drug (Brecht et al., 2004; Darke et al., 2008; Homer et al., 2008; Sekine et al., 2006; Zweben et al., 2004). There is compelling evidence that the negative neuropsychiatric consequences of METH abuse are due, at least in part, to drug-induced neuropathological changes in the brains of these METH-exposed individuals (Scott et al., 2007).

Neuroimaging studies have revealed that METH can indeed cause neurodegenerative changes in the brains of human addicts (Aron and Paulus, 2007; Chang et al., 2007). These abnormalities include persistent decreases in the levels of dopamine transporters (DAT) in the orbitofrontal cortex, dorsolateral prefrontal cortex, and the caudate-putamen (McCann et al., 1998, 2008; Sekine et al., 2003; Volkow et al., 2001a, 2001c). The density of serotonin transporters (5-HTT) is also decreased in the midbrain, caudate, putamen, hypothalamus, thalamus, the orbitofrontal, temporal, and cingulate cortices of METH-dependent individuals (Sekine et al., 2006). Psychostimulant addicts also show abnormal glucose metabolism in cortical and subcortical brain areas (Volkow et al., 2001b; Wang et al., 2004). In addition, a recent positron emission tomography (PET) study has demonstrated prominent microglial activation in the midbrain, striatum, thalamus, orbitofrontal and insular cortices of METH abusers (Sekine et al., 2008). The levels of microglial activation correlated inversely with duration of METH abstinence (Sekine et al., 2008). Structural magnetic resonance imaging (MRI) studies in METH addicts have revealed substantial morphological changes in their brains. These include loss of gray matter in the cingulate, limbic and paralimbic cortices, significant shrinkage of hippocampi, and hypertrophy of white matter (Thompson et al., 2004). In addition, the brains of METH abusers show evidence of hyperintensities in white matter (Bae et al., 2006; Ernst et al., 2000), decreases in the neuronal marker, N-acetylaspartate (Ernst et al., 2000; Sung et al., 2007), reductions in a marker of metabolic integrity, creatine (Sekine et al., 2002) and increases in a marker of glial activation, myoinositol (Chang et al., 2002; Ernst et al., 2000; Sung et al., 2007; Yen et al., 1994). Elevated choline levels, which are indicative of increased cellular membrane synthesis and turnover are also evident in the frontal gray matter of METH abusers (Ernst et al., 2000; Salo et al., 2007; Taylor et al., 2007).

Post-mortem analyses have also provided evidence of decreases in dopamine (DA), tyrosine hydroxylase (TH), and DAT levels in the caudate-putamen and in the nucleus accumbens (Kitamura et al., 2007; Moszczynska et al., 2004; Wilson et al., 1996) and reductions in 5-HTT levels in the orbitofrontal and occipital cortices (Kish et al., 2008) of chronic METH users. In addition, increased levels of the lipid peroxidation products, 4-hydroxynonenal and malonedialdehyde, are found in the caudate and frontal cortex of chronic METH users (Fitzmaurice et al., 2006). Finally, the levels of antioxidant compounds, CuZn superoxide dismutase (CuZnSOD), glutathione, and uric acid are increased in the caudate of METH abusers (Mirecki et al., 2004).

Animal Models of METH Toxicity

In agreement with the clinical literature, a number of animal studies have shown that METH can cause long-term destruction of presynaptic dopaminergic and serotoninergic terminals. It has also been shown that the drug can elicit neuronal death in the brain by causing apoptosis. In what follows, we review some of the animal models of METH toxicity and further discuss mechanisms that might underlie these drug-induced neurodegenerative effects.

Monkeys

In order to better reproduce human drug-taking behavior and tolerance related to chronic METH abuse, Seiden et al. (1976) studied the effects of long-term intravenous escalating-dose METH administration to rhesus monkeys. Animals treated for 2 weeks or 3–6 months with increasing doses of the psychostimulant showed acute reductions in norepinephrine (NE) levels in the frontal cortex, midbrain, hypothalamus and pons-medulla and 70–80% decreases in DA levels in the caudate nucleus that lasted up to 6 months after cessation of drug injections (Seiden et al., 1976). Later studies from the same group have demonstrated that treatment with increasing doses of METH causes persistent depletion of DA levels in the caudate (Ando et al., 1985; Finnegan et al., 1982; Preston et al., 1985a, 1985b) that is accompanied by a reduction in the number of DA uptake sites (Preston et al., 1985b). In addition, there are significant drug-

related decreases in 5-HT concentrations in the striatum, cortex and hippocampus of nonhuman primates (Ando et al., 1985; Preston et al., 1985a). A study which used long-term escalating doses of METH in vervet monkeys in order to approximate human psychostimulant use has also shown that such a treatment regimen causes 20% reduction in DA levels and 35% decreases in DAT binding in the striatum (Melega et al., 2008).

In agreement with these findings, PET studies in vervet monkeys and baboons have described METH-induced reduction in DA synthesis (Melega et al., 1997), DA levels (Melega et al., 2000; Villemagne et al., 1998), and decreases in DAT binding sites (Melega et al., 2000; Villemagne et al., 1998) in the striatum. In contrast, DA neuronal cell bodies in the substantia nigra were not affected by METH treatment (Melega et al., 1997). The absence of damage to DA neuronal cell bodies in the substantia nigra is thought to account for the time-dependent partial recovery of DA synthesis and DA concentrations observed in the striatum after injections of toxic doses of METH in nonhuman primates (Melega et al., 1997). Nevertheless, METH-induced decreases in brain DA and 5-HT levels in primates can be persistent, evident even at 4 years after administration of high doses of the drug (Woolverton et al., 1989). Because monkeys, like humans, metabolize METH mainly by side-chain deamination, whereas rats metabolize the drug by ring hydroxylation (Caldwell, 1976), the findings in non-human primates are thought to be more parallel to the effects of the drug in humans. Because post-mortem data have shown that the drug can cause respective ~60% and ~40% decreases in DA levels and DAT binding in the striatum of chronic abusers (Moszczynska et al., 2004; Wilson et al., 1996), it remains to be determined what patterns of METH injections in nonhuman primates will actually better mimic human conditions since humans also differ in their patterns of use. The results of the studies showing evidence of METH toxicity in nonhuman primates are summarized in Table 1.

Rats

Rats treated acutely with various doses of injected METH show long-lasting decreases in DA levels (Bittner et al., 1981; Cappon et al., 2000; Chapman et al., 2001; Eisch et al., 1992; Fukumura et al., 1998; Green et al., 1992; Kogan et al., 1976; Morgan and Gibb, 1980; Ricaurte et al., 1980; Richards et al., 1993; Truong et al., 2005; Wagner et al., 1979, 1980; Walsh and Wagner, 1992), long-term reductions in the activity of TH (Hotchkiss and Gibb, 1980; Hotchkiss et al., 1979; Morgan and Gibb, 1980), and marked decreases in the number of DAT (Eisch et al., 1992; Guilarte et al., 2003; Wagner et al., 1980) in the striatum. In addition, METH causes depletions of 5-HT levels in the rat striatum (Bakhit et al., 1981; Cappon et al., 2000; Friedman et al., 1998; Fukumura et al., 1998; Ricaurte et al., 1980; Richards et al., 1993; Walsh and Wagner, 1992) accompanied by decreases in tryptophan hydroxylase (TPH) activity (Bakhit et al., 1981; Hotchkiss and Gibb, 1980; Hotchkiss et al., 1979; Morgan and Gibb, 1980) and loss of 5-HTT (Armstrong and Noguchi, 2004; Guilarte et al., 2003). Similar METH injections have also been reported to cause decreases in vesicular monoamine transporter 2 (VMAT-2) binding (Guilarte et al., 2003; Segal et al., 2005) and immunoreactivity (Eyerman and Yamamoto, 2007) in the rat striatum. Morphological studies suggest that the reductions in the markers of DA and 5-HT system integrity are related to degeneration of DA and 5-HT axonal terminals (Axt and Molliver, 1991; Fukui et al., 1989; Lorez, 1981; Ricaurte et al., 1982, 1984). The neurotoxic damage to striatal axonal terminals is accompanied by reactive astrocytosis (Bowyer et al., 1994; Cappon et al., 2000; Fukumura et al., 1998) and microglial activation (Pubill et al., 2002).

In addition to the striatum, METH has been shown to cause decreases in 5-HT levels in medial prefrontal and somatosensory cortices, nucleus accumbens, hippocampus, hypothalamus and amygdala (Bakhit et al., 1981; Baldwin et al., 1993; Commins and Seiden, 1986; Friedman et al., 1998; Green et al., 1992; Ohmori et al., 1993; Ricaurte et al., 1980; Richards et al., 1993).

There was also a significant decrease in 5-HTT binding in the anterior cingulate, nucleus accumbens, amygdala, hippocampus, somatosensory cortex, hypothalamus, thalamus and septum (Armstrong and Noguchi, 2004; Guilarte et al., 2003). TPH activity in the cortex, hippocampus and nucleus accumbens is also affected by METH (Bakhit et al., 1981; Hotchkiss and Gibb, 1980; Morgan and Gibb, 1980). Moreover, binge doses of METH cause significant depletion of NE in the striatum, cortex and hippocampus (Graham et al., 2008). Similar to the observations in monkeys, rats showed some recovery in the levels of monoamines measured several months after the psychostimulant injections (Friedman et al., 1998). In addition to damage to monoaminergic terminals, METH treatment can cause death of neuronal cell bodies in the striatum (Jayanthi et al., 2005), the medial prefrontal (Kadota and Kadota, 2004) and in somatosensoty cortices (Commins and Seiden, 1986; Eisch and Marshall, 1998; O'Dell and Marshall, 2000) of the rat.

Because single day binge METH injections are not thought to mimic the pattern of human METH use, which involves a gradual escalation of doses and frequency of intake, several groups of investigators focused their attention on using escalating METH dosing to evaluate its impact on monoaminergic systems (Danaceau et al., 2007; Graham et al., 2008; Johnson-Davis et al., 2003, 2004; Kuczenski et al., 2007; Schmidt et al., 1985b; Segal and Kuczenski, 1997; Segal et al., 2003, 2005; Stephans and Yamamoto, 1996). These studies have shown that the pretreatment with multiple low-dose injections of METH or with gradually escalating doses of the drug followed by a high-dose challenge METH administration may afford partial protection against its deleterious effects on DA and 5-HT systems when compared to the patterns of single-day multiple drug injections (Danaceau et al., 2007; Graham et al., 2008; Johnson-Davis et al., 2003, 2004; Schmidt et al., 1985b; Segal et al., 2003; Stephans and Yamamoto, 1996). Specifically, METH pretreatment attenuates acute decreases in TH and TPH activity in the striatum and hippocampus (Gygi et al., 1996; Schmidt et al., 1985b) as well as reductions in DA and 5-HT levels in the striatum and cortex of rats (Danaceau et al., 2007; Graham et al., 2008; Schmidt et al., 1985b) 18 and 24 hours after the last dose of the drug. In addition, pretreatment with METH prior to high-dose METH challenge attenuates long-term depletion of DA levels in the striatum (Johnson-Davis et al., 2003, 2004; Segal et al., 2003; Stephans and Yamamoto, 1996), reductions in 5-HT levels in the striatum, cortex and hippocampus (Johnson-Davis et al., 2003; Stephans and Yamamoto, 1996) and decline in DAT binding (Segal et al., 2003) in the striatum as shown 4 – 7 days after injections. Interestingly, a recent study demonstrated that the protection afforded by escalating dose regimen is diminished and eventually disappears if the duration between the initial METH insult and the challenge treatment was increased to 14 – 31 days (Danaceau et al., 2007). Together, these results suggest that DA and 5-HT axons become resistant to toxic effects of high doses of METH in animals previously exposed to the drug.

Pretreatment with gradually escalating doses of METH followed by high-dose METH binge also causes cell death manifested by loss of pyramidal neurons in the rat cortex and in the CA3 region of the hippocampus 30 days after last injection (Kuczenski et al., 2007). In addition, some pyramidal neurons show loss of their dendrite complexity, tortuous processes and dystrophic neurites consistent with neurodegeneration in the frontal cortex and in both CA1 and CA3 regions of the hippocampus (Kuczenski et al., 2007). Moreover, escalating dose-multiple binge METH injections induce loss of calbinding interneurons in the cortex and dentate gyrus (Kuczenski et al., 2007). This regimen also causes microglial activation at 3 days and at 30 days after METH treatment (Kuczenski et al., 2007), in a manner similar to the observations of microgliosis in the brains of METH-addicted individuals (Sekine et al., 2008). The data on METH toxicity in rats are presented in Table 2.

Mice

Mice given repeated doses of METH experience significant loss of DA in the striatum (Achat-Mendes et al., 2005; Cadet et al., 1994b; Fantegrossi et al., 2008; Green et al., 1992; Ladenheim et al., 2000; O'Callaghan and Miller, 1994) and cortex (Achat-Mendes et al., 2005; Fantegrossi et al., 2008; Ladenheim et al., 2000); decreases in DAT binding (Achat-Mendes et al., 2005; Hirata et al., 1996; Ladenheim et al., 2000; Xu et al., 2005; Zhu et al., 2005) and DAT protein levels in the striatum (Deng et al., 1999; Fumagalli et al., 1999) and in the olfactory bulb (Deng et al., 2007), as well as decreased striatal TH immunoreactivity (Bowyer et al., 2008; Deng et al., 1999) and TH protein levels (O'Callaghan and Miller, 1994; Xu et al., 2005; Zhu et al., 2005). The majority of the mice strains studied have shown resistance to METH toxicity against 5-HT systems in contrast to the effects of the drug in rats and monkeys (Achat-Mendes et al., 2005; Anderson and Itzhak, 2006; Kita et al., 1998). Nevertheless, C57BL/6J and C57BL/129sVj mice do show METH-induced depletion of 5-HT levels in the striatum and hippocampus (Fumagalli et al., 1998; Ladenheim et al., 2000).

METH can also cause neuronal death in the striatum, frontal and parietal cortices, hippocampus and olfactory bulb of mice (Deng et al., 1999, 2001, 2007; Ladenheim et al., 2000; Schmued and Bowyer, 1997; Zhu et al., 2005, 2006a, 2006b). This occurs through processes akin to neuronal apoptosis (Cadet et al., 2005, 2007; Cunha-Oliveira et al., 2008). In the striatum, METH-induced cell death involves medium spiny projection neurons that express enkephalin, cholinergic, and parvalbumin-positive interneurons, but not somatostatin/neuronal nitric oxide synthase (nNOS)-positive interneurons (Thiriet et al., 2005; Zhu et al., 2006a). METH injections also cause reactive astrocytosis (Achat-Mendes et al., 2007; Deng et al., 1999; Zhu et al., 2005) and microgliosis (Bowyer et al., 2008; Fantegrossi et al., 2008; Thomas and Kuhn, 2005a; Thomas et al., 2004c) in the mouse striatum. Table 3 summarizes data on METH toxicity in mice.

Role of Dopamine and Oxidative Stress in METH toxicity

The toxic effects of METH are thought to depend on the similarity of its chemical structure to DA, which allows the drug to enter DA axons (Iversen, 2006), followed by DA release from synaptic vesicles into cytoplasm and by reverse transport into the synaptic cleft (Sulzer et al., 2005). Indeed, numerous studies have conclusively shown that DA is an important component of the mechanisms that subserve METH neurotoxicity (Figure 1). For example, agents that decrease DA levels in the brain, such as the TH inhibitor, α-methyl-*p*-tyrosine, also protect against METH-induced damage to striatal DA axons (Axt et al., 1990; Gibb and Kogan, 1979; Hotchkiss and Gibb, 1980; Schmidt et al., 1985a; Thomas et al., 2008; Wagner et al., 1983), whereas treatment with immediate DA precursor, L-DOPA, that restores cytoplasmic DA levels, reverses this protective effect and enhances drug toxicity (Gibb and Kogan, 1979; Schmidt et al., 1985a; Thomas et al., 2008) (Figure 1). Pretreatment with L-DOPA alone which causes ~50% increase in striatal DA levels prior to METH injections also exacerbates drug-induced DA depletion at 2, 7 and 14 days after treatment (Thomas et al., 2008; Weihmuller et al., 1993). In addition, the MAO inhibitors, pargyline and clorgyline, which cause increases in cytoplasmic DA levels, exacerbate METH neurotoxicity (Kita et al., 1995; Thomas et al., 2008; Wagner and Walsh, 1991) (Figure 1). The role for DA in the mediation of METH toxicity is also supported by studies showing that it causes reactive oxygen species (ROS) production and oxidative stress in ventral midbrain cultures that contain DA neurons, but not in cultures of cells obtained in the nucleus accumbens that do not contain DA neurons (Cubells et al., 1994). The observations of METH-induced ROS in normal but not in DA-depleted striatal synaptosomes (Pubill et al., 2005) further support the involvement of DA in METH toxicity.

Studies have also emerged to show that DA plays an important role in the toxic effects of METH towards 5-HT axons. For example, α-methyl-*p*-tyrosine, which was shown to protect

against METH-induced toxicity towards DA axons, also prevents long-term decrease in TPH activity (Hotchkiss and Gibb, 1980; Schmidt et al., 1985a) and reductions in 5-HT levels (Axt et al., 1990; Schmidt et al., 1985a) in the striatum and hippocampus. However, when cytoplasmic DA levels were restored by pretreatment with L-DOPA, α-methyl-*p*-tyrosine failed to protect against decreases in TPH activity and 5-HT concentrations caused by METH treatment (Schmidt et al., 1985a). In addition, α-methyl-*p*-tyrosine also blocked METH-induced decreases in 5-HT levels in the rat somatosensory cortex (Axt et al., 1990; Commins and Seiden, 1986). Together, these findings support the idea that DA participates in METH-induced 5-HT toxicity in the rodent brain.

After its displacement to the cytoplasm by METH, DA rapidly auto-oxidizes to form potentially toxic substances including superoxide radicals, hydroxyl radicals, hydrogen peroxide and DA quinones (Acikgoz et al., 1998; Cubells et al., 1994; Kita et al., 1999; Larsen et al., 2002; LaVoie and Hastings, 1999; Lazzeri et al., 2007; Miyazaki et al., 2006; Stokes et al., 1999). Stone et al. (1989) were among the first investigators to report that METH can reduce the activity of TPH in the rat hippocampus within 1 hour after treatment by causing oxidation of thiol groups of the enzyme, therefore suggesting a role for ROS and oxidative stress in the deleterious effects of the drug. Later, LaVoie and Hastings (1999) found that administration of neurotoxic doses of METH to rats caused DA oxidation to DA quinones that bind to cysteinyl residues on proteins, leading to an increase in protein cysteinyl-DA levels in the striatum. Increases in DA oxidation occurred only under conditions resulting in toxicity, suggesting that the oxidation of DA may contribute to the mechanism of METH-induced damage to DA terminals (LaVoie and Hastings, 1999). DA metabolism by MAO is also accompanied by increased production of hydrogen peroxide which interacts with metal ions such as iron, whose level is elevated by METH treatment (Melega et al., 2007), to form toxic hydroxyl radicals (Cadet and Brannock, 1998). Indeed, METH has been shown to induce increased levels of 2,3-dihydroxybenzoic acid, a marker for hydroxyl radical production, in the rat striatum 2 hours after treatment (Giovanni et al., 1995). The accumulated evidence indicates that METH can also cause oxidative stress by switching the balance between ROS production and the capacity of antioxidant enzyme systems to scavenge ROS (Chen et al., 2007; Gluck et al., 2001; Harold et al., 2000; Iwazaki et al., 2006; Jayanthi et al., 1998; Kobeissy et al., 2008; Li et al., 2008). For example, METH administration causes decreases in the levels of CuZnSOD, catalase, glutathione, and peroxiredoxins in the brain (Chen et al., 2007; Gluck et al., 2001; Harold et al., 2000; Iwazaki et al., 2006; Jayanthi et al., 1998; Kobeissy et al., 2008; Li et al., 2008) accompanied by elevated lipid peroxidation and substantial increases in the levels of protein carbonyls (Chen et al., 2007; Gluck et al., 2001; Harold et al., 2000; Iwazaki et al., 2006; Jayanthi et al., 1998; Kobeissy et al., 2008; Li et al., 2008). Increased levels of the lipid peroxidation products, 4-hydroxynonenal and malonedialdehyde observed in the brains of chronic METH addicts provide evidence for the generation of ROS by the drug and subsequent oxidative damage in the brains of human addicts (Fitzmaurice et al., 2006). The elevated levels of antioxidants, such as CuZnSOD and glutathione, in the brains of METH abusers also suggest compensatory responses to oxidative stress (Mirecki et al., 2004). Excessive production of ROS that overwhelm this protective antioxidant system can damage cellular components such as lipids, proteins, mitochondrial and nuclear DNA (Potashkin and Meredith, 2006). These deleterious effects might be responsible, in part, for both METH-induced terminal degeneration and neuronal apoptosis (Figure 1).

A potent role for oxidative mechanisms in METH toxicity is also consistent with findings that pretreatment with antioxidants such as N-acetyl-L-cysteine, ascorbic acid and vitamin E affords protection against psychostimulant-induced depletion of monoaminergic axons (De Vito and Wagner, 1989; Fukami et al., 2004; Hashimoto et al., 2004; Wagner et al., 1985). The involvement of superoxide radicals in the neurotoxic effects of METH on DA terminals was tested by injecting the drug to transgenic mice that overexpress the human CuZnSOD, a

cytosolic enzyme that catalyzes the breakdown of superoxide radicals (Cadet et al., 1994a, 1994b; Hirata et al., 1996; Jayanthi et al., 1998). These mice which have much higher CuZnSOD enzyme activity in the cytosol than control wild-type animals (Jayanthi et al., 1998) were protected against METH toxicity (Cadet et al., 1994a, 1994b; Hirata et al., 1996). METH neurotoxicity is also attenuated in striatum of mice that overexpress human manganese superoxide dismutase (MnSOD) that catalyzes detoxification of superoxide radicals within mitochondria (Maragos et al., 2000). These data are consistent with the demonstration that METH-induced depletions of DA and 5-HT levels in the rat striatum are exacerbated by the SOD inhibitor, diethyldithiocarbamate (De Vito and Wagner, 1989). In addition, the fact that the scavenger of hydroxyl radicals, bromocriptine, also protects against METH-related DA depletion in the brain supports a role for these radicals in causing the toxicity associated with the use of the drug (Kondo et al., 1994). The idea that oxygen-based free radicals are involved in METH neurotoxicity is further strengthened by reports that the drug can reduce the levels of glutathione (Harold et al., 2000; Moszczynska et al., 1998) and of antioxidant enzymes (Chen et al., 2007; D'Almeida et al., 1995; Iwazaki et al., 2006; Jayanthi et al., 1998; Kobeissy et al., 2008; Li et al., 2008), can induce lipid peroxidation (Acikgoz et al., 1998; Gluck et al., 2001; Jayanthi et al., 1998), and can cause the formation of protein carbonyls (Gluck et al., 2001). Together, these findings support the proposition that METH-induced DA release is accompanied by redox cycling of DA quinones and consequent formation of superoxide and hydroxyl radicals.

In addition to their potential participation in damaging monoaminergic axons, ROS formation and associated oxidative stress may be involved in METH-related neuronal apoptosis because psychostimulant-induced poly (ADP-ribose) polymerase (PARP) cleavage, increase in caspase-3 activity, and neuronal death are all attenuated in the striata of CuZnSOD transgenic mice (Deng and Cadet, 2000) (see Figure 1). METH-induced death in CATH.a cells is also attenuated by the antioxidant, glutathione, and by inhibitors of DA synthesis and release (Choi et al., 2002). Moreover, overexpression of glutathione peroxidase in PC12 cells protects against drug-related increases in ROS production, lipid peroxidation and cell death (Hom et al., 1997). The idea that oxidative stress may play a role in METH-induced cell death is also supported by findings showing that decline in mitochondrial membrane potential, increase in the levels of ROS and apoptosis in human dopaminergic neuroblastoma SH-SY5Y cell line are attenuated by vitamin E (Wu et al., 2007).

Attempts to further identify mechanisms that underlie METH-induced oxidative stress have revealed that the drug causes DA-dependent production of ROS in striatal synaptosomes, and that ROS production can be suppressed by antioxidants and by inhibitors of nNOS and protein kinase C (Pubill et al., 2005). EGTA and the antagonist of α7 nicotinic acetylcholine receptors, methylcaconitine, also prevented increased production of ROS, thus implicating Ca^{2+} and α7 nicotinic receptors in METH toxicity (Escubedo et al., 2005; Pubill et al., 2005). Together, these studies suggest that METH-induced ROS production might depend, in part, on the activation of α7 nicotinic receptors which stimulate increases in intrasynaptosomal Ca^{2+} (Escubedo et al., 2005; Pubill et al., 2005). This could lead to nNOS activation and stimulation of protein kinase C, with oxidation of cytosolic DA and subsequent ROS formation (Escubedo et al., 2005; Pubill et al., 2005).

Role of DAT, VMAT-2 and 5-HTT in METH-induced Toxicity

As mentioned above, METH is known to interact with both the DAT and VMAT-2 to release DA withing the cytosol of DA terminals and into the extracellular space (Sulzer et al., 2005). Thus, it was not surprising to suggest that these proteins might play an important role in METH neurotoxicity. Indeed, the involvement of DAT in METH toxicity is supported by studies showing that the DAT inhibitor, amphoneic acid, was able to protect against drug-induced

striatal DA depletion (Marek et al., 1990) and decrease in striatal TH activity (Schmidt and Gibb, 1985a) by blocking reversed transport of DA into the synaptic cleft (Figure 1). A role of DAT in METH toxicity is also supported by studies using DAT knockout mice that are protected against drug-induced DA depletion, reactive astrocytosis, and ROS production in the striatum (Fumagalli et al., 1998). Further studies have shown that administration of the DAT inhibitor, methylphenidate, 1 hour after METH treatment could reverse decreases in vesicular DA uptake, reductions in VMAT-2 ligand binding and decreases in VMAT-2 immunoreactivity in vesicular subcellular fractions 6 hours after injections of the drugs (Sandoval et al., 2003). The methylphenidate post-treatment also protected against long-term DA deficits, suggesting that alterations in VMAT-2 functions might contribute to METH toxicity (Sandoval et al., 2003). A role for VMAT-2 in METH-induced damage to striatal DA terminals is also supported by studies showing that pretreatment with the irreversible inhibitor of vesicular transport, reserpine, exacerbates toxicity of the psychostimulant (Albers and Sonsalla, 1995; Kuhn et al., 2008; Thomas et al., 2008; Wagner et al., 1983) although these observations might be more related to the DA depletion associated with such treatments (Figure 1). Further evidence of the involvement of VMAT-2 in METH-induced terminal degeneration is provided by observations that decreases in DA concentrations and reductions in DAT protein levels are potentiated in the striata of VMAT-2 heterozygote mice (Fumagalli et al., 1999). METH also causes increased degeneration of DA neurites and accumulation of ROS in ventral midbrain neuronal cultures derived from VMAT-2 deficient mice in comparison to cultures obtained from wild-type animals (Larsen et al., 2002). Other supportive studies on the role of VMAT-2 in METH toxicity have shown that the administration of the alkaloid, lobeline (Eyerman and Yamamoto, 2005), after injections of METH could reverse the decreases in synaptosomal, membrane-associated and vesicular VMAT-2 immunoreactivity 24 hours after psychostimulant treatment and was able to protect against striatal DA depletion measured 7 days later. Taken together, these results suggest that dysregulation of VMAT-2 function and/or trafficking is important for manifestation of persistent DA deficits caused by METH treatment.

Several studies have also focused on the role of 5-HTT in METH-induced damage to 5-HT axons. A number of 5-HTT inhibitors that include fluoxetine, citalopram, and chlorimipramine, have been shown to block METH-induced reductions in TPH activity and to prevent 5-HT depletion in the striatum, hippocampus and cortex (Hotchkiss and Gibb, 1980; Ricaurte et al., 1983; Schmidt and Gibb, 1985b), suggesting a role for 5-HTT in mechanisms of drug toxicity towards 5-HT terminals. However, 5-HTT inhibitors failed to prevent decreases in striatal TH activity and DA levels caused by METH treatment (Ricaurte et al., 1983; Schmidt and Gibb, 1985b). Thus, this area deserves further investigations in view of the fact that human subsects exhibit substantial decreases in 5-HTT markers in several brain regions (Kish et al., 2008; Sekine et al., 2006).

Role of Dopamine Receptors in METH Toxicity

The review has so far demonstrated a significant involvement of presynaptic elements in METH-induced toxicity. Interestingly, several investigators have also demonstrated that DA receptors located on striatal cells post-synaptic to DA terminals are also involved in METH toxicity against striatal DA and 5-HT terminals (Angulo et al., 2004; Jayanthi et al., 2005; O'Dell et al., 1993; Sonsalla et al., 1986, Xu et al., 2005) (Figure 1). Specifically, pretreatment with DA D1 receptor antagonist, SCH23390, given before each of 5 METH injections was able to attenuate drug-induced decreases in TH activity and DA levels in the rat striatum and reductions in TPH activity and 5-HT levels in the striatum and cortex measured 18–20 hours after METH treatment (Sonsalla et al., 1986). Interestingly, the DA D2 receptor antagonist, sulpiride, also blocked METH-induced toxic effects on DA systems without affording any protection to striatal and cortical 5-HT terminals (Sonsalla et al., 1986). Similarly, treatment

with either the D1 antagonist, SCH23390, or the D2 antagonist, eticlopride, before each of binge METH injections completely prevented reductions in striatal DA levels measured 7 days later (O'Dell et al., 1993). In addition, a single injection of the DA D1 receptor antagonist, SCH23390, or DA D2 receptor antagonist, raclopride, prior to a single high-dose METH injection also attenuated long-term decreases in DA levels (Jayanthi et al., 2005), reductions in DAT binding, depletion in TH protein levels and reactive astrocytosis (Xu et al., 2005). SCH23390 also protected against METH-induced cell death in the striatum (Jayanthi et al., 2005; Xu et al., 2005). These neuroprotective effects might depend, in part, on changes in DA release because DA receptor antagonists were reported by one group of investigators to partially block METH-related increases in DA release in the striatum (O'Dell et al., 1993). Specifically, microdialysis experiments have revealed that multiple METH doses injected 2 hours apart caused marked increases in extracellular DA levels in the rat stiatum which reached ~950% of control levels 1.5 hours after cessation of drug treatment (O'Dell et al., 1993). This dramatic increase in DA release was attenuated by pretreatment with the DA receptor antagonists, SCH23390 and eticlopride, prior to each of METH injections (O'Dell et al., 1993). The protection afforded by SCH23390 against METH-mediated cell death may also depend on the Fas/FasL death pathway because pretreatment with the antagonist caused significant inhibition of increases in the expression of FasL and caspase-3 caused by METH treatment in rat striatal cells (Jayanthi et al., 2005). Because the dose of SCH23390 used in that study completely blocks METH-induced decreases in DA levels while providing only partial protection against death of striatal neurons (Jayanthi et al., 2005), the possibility exists that drug-related cell death might involve additional mechanisms independent of stimulation of DA D1 receptors. Some of these factors might include METH-induced excitotoxicity via gluatamate release in the striatum. These are discussed below.

METH Toxicity and Excitotoxicity

METH neurotoxicity has also been shown to involve excitotoxic damage following glutamate release and activation of glutamate receptors (Yamamoto and Bankson, 2005). The role for glutamate in METH toxicity is supported by findings that the psychostimulant causes glutamate release in the brain (Abekawa et al., 1994; Baldwin et al., 1993; Mark et al., 2004; Marshall et al., 1993; Nash and Yamamoto, 1992; Nash et al., 1988; Stephan sand Yamamoto, 1994). It has been reported that some glutamate receptor antagonists, including MK-801 and dizocilpine, can reduce METH-induced degeneration of DA and 5-HT terminals in different brain regions (Battaglia et al., 2002; Bowyer et al., 2001; Chipana et al., 2008; Farfel et al., 1992; Fuller et al., 1992; Golembiowska et al., 2003; Green et al., 1992; Ohmori et al., 1993; Sonsalla et al., 1989, 1991; Weihmuller et al., 1992). These drugs can protect against METH-induced death in PC12 cells (Uemura et al., 2003) and can also attenuate inhibition of mitochondrial complex II caused by METH treatment in the striatum (Brown et al., 2005). However, because MK-801 and dizocilpine also block hyperthermia which plays an important role in METH toxicity (Albers and Sonsalla, 1995; Bowyer et al., 1994; Farfel and Seiden, 1995), these results suggest that neuroprotection afforded by glutamate receptor antagonists might depend, in part, on inhibition of METH-mediated hyperthermic responses. It is to be noted that administration of low, non-neurotoxic concentrations of NMDA together with non-neurotoxic doses of METH exacerbates drug toxicity causing reduction in DA levels in mouse striatum (Sonsalla et al., 1998), further supporting the idea that DA and gluatame might interact to cause toxic effects towards striatal DA terminals. Reports that chronic stress can increase METH-induced glutamate concentrations and thereby, exacerbate damage to striatal DA and 5-HT terminals (Quinton and Yamamoto, 2007; Tata and Yamamoto, 2008) also support the involvement of glutamate in METH toxicity. The observation that treatment with the corticosterone synthesis inhibitor, metyrapon, which attenuates stress-induced enhanced glutamate release, can also reduce METH neurotoxicity (Tata and Yamamoto, 2008) provides further support for the excitotoxicity hypothesis.

It is important to note that unlike METH-induced striatal DA release, which occurs via reversed transport (Sulzer et al., 2005), glutamate release in the striatum is thought to be initiated by DA D1 receptor-dependent stimulation of striatonigral GABAergic pathway that causes increases in GABA release in the substantia nigra pars reticulata, inhibition of nigrothalamic GABAergic outflow via activation of GABAA receptors, followed by disinhibition of thalamocortical afferents with consequent increases in striatal glutamate release (Mark et al., 2004). METH has also been shown to increase the synthesis and expression of vesicular glutamate transporters that enhance vesicular glutamate uptake and can sustain increases in striatal glutamate release (Mark et al., 2007). Glutamate toxicity may depend, in part, on the production of superoxide radicals and nitric oxide (NO) because METH-induced increase in glutamate release might lead to excessive activation of NMDA receptors and subsequent formation of superoxide radicals and NO (Gunasekar et al., 1995; Lafon-Cazal et al., 1993). This suggestion is supported by observations that knockout mice deficient in nNOS or mice that overexpress CuZnSOD are protected against METH toxicity (Cadet et al., 1994b; Hirata et al., 1996; Imam et al., 2001c; Itzhak et al., 1998). The first evidence that NO might be involved in METH toxicity was reported by the Cadet's laboratory which showed that NOS inhibitors, *Nw*-nitro-L-arginine and monomethyl-L-arginine, attenuated drug-induced cell death in primary mecencephalic cultures (Sheng et al., 1996). The selective nNOS inhibitor, 7-nitroindazole, also protects against METH-induced DA and 5-HT depletion in the striatum (Ali and Itzhak, 1998; Di Monte et al., 1996; Itzhak and Ali, 1996). The participation of NO in METH neurotoxicity is also supported by findings that another nNOS inhibitor, S-methyl-L-thiocitrulline, blocks METH-related VMAT-2 protein oxidation and decreases in VMAT-2 immunoreactivity in striatal synaptosomes (Eyerman and Yamamoto, 2007). NO can react with superoxide radicals to form the strong oxidant and major neurotoxin, peroxynitrite (Pacher et al., 2007). NO-mediated toxicity is accompanied by an increased production of 3-nitrotyrosine, which is used as a marker for peroxynitrite production (Pacher et al., 2007). Imam et al. (2001a) have reported METH-induced increases in 3-nitrotyrosine in vitro and in vivo models of toxicity. The antioxidants, selenium and melatonin, have been reported to completely block the formation of 3-nitrotyrosine and striatal DA depletion (Imam et al., 2001a). The free radical scavenger, edaravone, also blocked METH-related increases in 3-nitrotyrosine immunoreactivity and attenuated striatal DA depletion and reduction in TH immunoreactivity caused by the drug (Kawasaki et al., 2006). The involvement of NO and peroxynitrite in METH effects is further supported by a study showing that the peroxynitrite scavenger, 5,10,15,20-tetrakis (2,4,6-trimethyl-3,5-sulphonatophenyl) porphinato iron III, prevents drug-induced inhibition of complex II–III of the mitochondrial electron transport chain in the rat striatum (Brown et al., 2005). Of interest to this topic are the findings that Nurr 1 heterozygote mice which show increased METH toxicity in comparison to wild-type animals also demonstrate greater drug-induced increases in nNOS activity and 3-nitrotyrosine levels (Imam et al., 2005).

In addition to the role in the damage of monoaminergic axons, NO and peroxynitrite may be involved in METH-related apoptotic mechanisms because nNOS knockout mice are protected against increases in the levels of pro-apoptotic protein, p53, and decreases in anti-apoptotic protein, Bcl-2 caused by the psychostimulant treatment in the striatum (Imam et al., 2001b). When taken together, these observations implicate interactions between glutamate/superoxide and glutamate/NO pathways in METH-induced neuronal damage (Imam et al., 2001c; Itzhak and Ali, 2006; Itzhak et al., 1998; Yamamoto and Bankson, 2005).

METH Toxicity and Temperature Regulation

Temperature dysregulation appears to be also an important factor in the mediation of some toxic responses to METH. Several groups of investigators carried in-depth studies of the potential connections between the hyperthermic and neurotoxic actions of the drug (Albers and

Sonsalla, 1995; Bowyer et al., 1994; Farfel and Seiden, 1995; Miller and O'Callaghan, 1994; Yuan et al., 2006). Conditions that cause hypothermia or prevent increases in core body temperature are, at least, partially protective against METH toxicity (Albers and Sonsalla, 1995; Ali et al., 1996; Bowyer et al., 1994; Tata et al., 2007). This protection is probably related to hypothermia-induced inhibitory effects on oxidative insults (Hsu et al., 2006; Zhao et al., 2007). Indeed, prevention of METH-induced hyperthermia by keeping animals at low ambient temperature blocked increases in DA oxidation products without affecting DA release while preventing long-term drug toxicity towards striatal DA and 5-HT terminals (LaVoie and Hastings, 1999). Similarly, prevention of hyperthermia blocked METH-induced increase in a marker of hydroxyl radicals, dihydroxybenzoic acid, and attenuated decrease in TPH activity 1 hour after drug treatment (Fleckenstein et al., 1997). In contrast, hyperthermia has been shown to exacerbate METH toxicity (Albers and Sonsalla, 1995; Bowyer et al., 1992), in part, because it causes increased intracellular accumulation of METH by potentiating DAT function (Xie et al., 2000). Hyperthrmia-induced increased production of free radicals in the brain (Kil et al., 1996) and its potentiation of their toxic effects (Lin et al., 1991) are also possible factors. These ideas are supported by the fact that hyperthermia significantly increases the formation of DA quinones (LaVoie and Hastings, 1999) which can cause inactivate TH (Kuhn et al., 1999), cause dysregulation of DAT function (Whitehead et al., 2001), inhibit proteasomal proteins participating in detoxification mechanisms (Zafar et al., 2006), and damage DA neurons (Montine et al., 1997; Spencer et al., 2002). Together, these data strongly suggest that hyperthermia facilitates METH-induced ROS production and that increased oxidation of DA is associated with neurotoxic effects of this drug.

Nevertheless, some pharmacological and genetic manipulations can block METH toxicity without influencing the drug-induced thermal responses (Callahan et al., 2001; Deng et al., 2002b; Itzhak et al., 2000; Ladenheim et al., 2000; Sanchez et al., 2003). For example, nNOS inhibition using S-methylthiocitrulline, 7-nitroindazole, or AR-R17477AR blocks METH toxicity without preventing hyperthermia (Itzhak et al., 2000; Sanchez et al., 2003). DA uptake inhibitors also show protection that seems to be independent of any effects on temperature (Callahan et al., 2001). Interleukin-6 knockout mice that are protected against drug-induced DA and 5-HT axonal degeneration, cell death, and microgliosis still show hyperthermia in response to METH injections (Ladenheim et al., 2000). Knockout mice that are partially deficient of c-Jun are also protected against METH-induced neuronal apoptosis, in a manner independent of temperature regulation (Deng et al., 2002b). Thus, it appears that METH-related changes in body temperature are not sine qua non to the manifestations of its toxicity.

Although METH-dependent increases in temperature are thought to contribute to neurotoxic effects of the drug, the mechanisms involved remain to be determined. DA release and activation of DA receptors seem to be critical for METH-induced hyperthermia because this thermic response can be attenuated by DA D1 and D2 receptor antagonists (Albers and Sonsalla, 1995; Broening et al., 2005; He et al., 2004). This idea is also supported by reports that administration of the D1 agonist, SKF38393, can induce hyperthermia in mice (Sanchez, 1989; Verma and Kulkarni, 1993; Zarrindast and Tabatabai, 1992), an effect which is blocked by the D1 antagonist, SCH23390 (Sanchez, 1989; Zarrindast and Tabatabai, 1992). The involvement of DA receptors is further supported by the demonstration that METH-induced hyperthermia is less prominent in D1 and D2 receptor knockout mice (Ito et al., 2008).

The role of DAT and 5-HTT in METH-associated hyperthermia has been studied using DAT and/or 5-HTT knockout mice (Numachi et al., 2007). METH administration caused hyperthermia even in animals with a single gene copy of DAT and no 5-HTT (DAT+/−5-HTT −/− mice), whereas mice with no DAT copies and a single gene copy of 5-HTT (DAT−/−5-HTT+/− mice) showed reduced hyperthermia after drug treatment, suggesting that METH can exert a hyperthermic effect through its action on the DAT or via its interactions with the 5-

HTT in the absence of the DAT protein (Numachi et al., 2007). The observations that DAT/5-HTT double knockout mice actually exhibited hypothermia in response to METH suggests the possibility that the thermic response to the drug is mediated by multiple systems that can either promote hyperthermia or hypothermia depending on the presence or absence of DA and/or 5-HT terminals (Numachi et al., 2007). Another proposed mechanism of METH-induced hyperthermia involves increases in hypothalamic concentrations of interleukin-1β (Bowyer et al., 1994) which is thought to be the major endogenous pyrogen (Leon, 2002). METH does indeed cause induction of hypothalamic interleukin-1β mRNA in mice (Halladay et al., 2003; Numachi et al., 2007) and rats (Yamaguchi et al., 1991) whereas interleukin-1 receptor antagonist reduces the hyperthermic effects of the psychostimulant (Bowyer et al., 1994). A possible role for interleukin-1β in drug-induced hypertherma is supported by the fact that it can cause a hyperthermic response when administered into the brain (Dascombe et al., 1989). Finally, the skeletal muscle uncoupling mitochondrial protein 3 (UCP-3) may also be involved in mediating METH-induced hyperthermia because UCP-3-deficient mice treated with the drug showed blunted thermic responses (Sprague et al., 2004). It is also possible that hyperthermia might potentiate some of the deleterious effects of METH by causing adverse effects on the blood-brain barrier.

Role of Blood-Brain Barrier Dysfunction in METH Toxicity

Several recent papers have examined the effects of METH on the blood-brain barrier (BBB) and their potential relationships to METH toxicity (Bowyer and Ali, 2006; Bowyer et al., 2008; Kiyatkin et al., 2007; Sharma and Ali, 2006; Sharma and Kiyatkin, 2009; Sharma et al., 2007). Using protein tracers and albumin immunohistochemistry, METH was shown to cause marked disruption of BBB at the levels of the cortex, hippocampus, thalamus, hypothalamus, cerebellum and amygdala (Bowyer and Ali, 2006; Kiyatkin et al., 2007; Sharma et al., 2007). METH-induced BBB breakdown was evidenced by diffusion of Evans blue dye and by leakage of serum albumin into the brain tissue (Kiyatkin et al., 2007; Sharma et al., 2007). Doses of METH that cause BBB disturbances also induce neuronal damage, myelin degeneration, and reactive astrocytosis in the parietal and occipital cortices (Sharma et al., 2007). These doses also cause extensive degeneration of pyramidal cells and activation of microglia in amygdala and hippocampus of rats (Bowyer and Ali, 2006). These effects appear to be temperature-dependent because magnitude of METH-induced diffusion of Evans blue dye into brain tissue and albumin immunoreactivity tightly correlated with intensity of hyperthermia (Kiyatkin et al., 2007; Sharma and Kiyatkin, 2009) and because the psychostimulant failed to induce BBB damage and neurodegeneration in the brains of animals that did not show increased temperature (Bowyer and Ali, 2006). Interestingly, mild BBB dysfunction found in the caudate-putamen after METH treatment was exacerbated by hyperthermia (Bowyer et al., 2008). In addition, a recent study has also shown distortion of neurons, damage to gilial cells, vesiculation of myelin and alterations in vascular endothelium and epithelium that occur in the cortex, hippocampus, thalamus and hypothalamus within 30–80 min following METH treatment (Sharma and Kiyatkin, 2009). Electron microscopy studies revealed acute degeneration of cellular elements, condensed cytoplasm and irregular folding of nuclear membrane, which were evident in all cell types, with the most affected cells being the epithelial cells of the choroid plexus, a critical element of blood-CSF barrier (Sharma and Kiyatkin, 2009). These acute morphological abnormalities also tightly correlated with METH-induced hyperthermia and increased BBB permeability (Sharma and Kiyatkin, 2009). It is interesting to point out that leakage of serum albumin into brain tissue caused by METH administration is attenuated by pretreatment with antioxidant, H-290/51, suggesting the involvement of free radicals in BBB damage (Sharma et al., 2007). Also of interest is the fact the antioxidant was able to attenuate METH-induced hyperthermia, neuronal damage, myelin degradation and glial response (Sharma et al., 2007).

Inflammation, Microglial Reactions and METH Toxicity

Microglia are the resident immune cells within CNS that protect the brain against injury and damage (Raivich, 2005). In the healthy brain, microglial cells exist in a resting ramified state and monitor the neuronal environment (Block et al., 2007; Raivich, 2005). However, in response to inflammation or brain damage, microglial cells increase in size, migrate to the site of the injury, and cause phagocytosis of dying and dead cells (Block et al., 2007; Raivich, 2005). While microglial activation is essential for immune responses and neuronal survival, the overactivation of microglial cells can result in neurotoxic consequences. Indeed, multiple lines of evidence have suggested that activated microglia might release a variety of cytokines, reactive oxygen and nitrogen species and prostaglandins that are known to cause neuronal damage (Block et al., 2007; Perry et al., 2007), and, therefore, might be involved in neurodegeneration through inflammatory processes. Specifically, microglial cells appear to play role in the progress of many neurodegenerative disorders, including Parkinson's (Kim and Joh, 2006), Alzheimer's (Xiang et al., 2006), and Huntington's (Sapp et al., 2001) diseases as well as AIDS-related neurological deficits (Gonzalez-Scarano and Martin-Garcia, 2005).

Microglial activation appears to be an early event in the neurotoxic cascades initiated by METH treatment. Specifically, METH induces a substantial microglial response in the areas of the brain that show neuronal degeneration (Escubedo et al., 1998; Guilarte et al., 2003; LaVoie et al., 2004; Pubill et al., 2002, 2003; Thomas and Kuhn, 2005a; Thomas et al., 2004a, 2004c). In addition, reserpine and clorgyline that exacerbate METH toxicity also cause further increases in METH-induced microglial activation in the mouse striatum (Thomas et al., 2008). In contrast, attenuation of METH neurotoxicity by MK-801, dextromethorphan and α-methyl-*p*-tyrosine is accompanied by inhibition of microglial activation (Thomas et al., 2008; Thomas and Kuhn, 2005b). The anti-inflammatory drugs, ketoprofen and indometacin, and the second-generation tetracycline, minocycline, afford protection against METH-induced microgliosis and neurotoxicity (Asanuma et al., 2003, 2004; Zhang et al., 2006). Nevertheless, because attenuation of microglial activation by itself is not sufficient to protect against METH neurotoxicity (Sriram et al., 2006), much more remains to be done in order to further clarify the role of microglia in psychostimulant-induced terminal degeneration and cell death.

Microglial cells might potentiate METH-related damage by releasing toxic substances such as superoxide radicals and NO which have already been implicated in drug neurotoxicity (see discussion above). In addition, METH causes increases in the levels of interleukin-1β (Numachi et al., 2007; Yamaguchi et al., 1991), pro-inflammatory cytokine that can also contribute to toxicity of the drug. Consistent with these findings, METH neurotoxicity and an increase in a marker for microglial activation PK11195 binding were attenuated in interleukin-6 null mice (Ladenheim et al., 2000). In fact, oxidative mechanisms and cytokines might exert their physiological and pathological effects by influencing the expression of several transcriptional factors with long-term consequences on the brain's molecular programming (Malemud and Miller, 2008; Planas et al., 2006; Poli et al., 2004; Potashkin and Meredith, 2006).

Involvement of Activator Protein 1 (AP-1) in METH-induced Neurotoxicity

In order to establish to what extent METH administration might influence the transcriptional profiles, several investigators have studied the effects of the drug on gene expression in the brain (Asanuma et al., 2004; Barrett et al., 2001; Cadet et al., 2001, 2002; Thomas et al., 2004b). For example, it has been reported that METH injections can cause increases in the expression of several members of the AP-1 family of transcription factors which include c-jun, c-fos, junB, and junD (Cadet et al., 2001). These changes, in turn, might be related to METH-induced generation of ROS because ROS participate in cellular signaling processes, which

include the regulation of transcription factors (Poli et al., 2004; Potashkin and Meredith, 2006). In particular, ROS are critical in the regulation of transcription factors in the AP-1, NF-κB, and AP-2 families that play crucial role in responses to neuronal injury, in the control of death and survival signals; they also participate in mounting cellular defense mechanisms, immunological responses, and in the regulatated expression of cytokines and cell adhesion molecules (Dalton et al., 1999; Poli et al., 2004). Induction or suppression of transcription factors with subsequent activation or repression of genes that encode proteins involved in various neuronal functions might be critical steps in METH-related cascades of toxic events. The potential role for c-fos in METH-induced neuropathological changes has been confirmed by using c-fos heterozygote mice that demonstrate increased degeneration of DA axons in the striatum as shown by reduction of DAT binding, decrease in DAT protein levels and in TH immunoreactivity in comparison to wild-type mice 1 week after drug administration (Deng et al., 1999). In addition, c-fos mutant mice showed increased cell death in the striatum and cortex 3 days after drug treatment (Deng et al., 1999). Exacerbation of METH neurotoxicity in c-fos heterozygote mice was independent of temperature regulation (Deng et al., 1999). Microarray analyses have also revealed marked differences between wild-type and c-fos heterozygote mice after drug administration (Cadet et al., 2002). Specifically, METH caused downregulation of fos-related antigen-1 (Fra-1) and FosB, which are members of AP-1 family of transcription factors, in wild-type, but not in c-fos mutant mice (Cadet et al., 2002). In addition, METH induced increases in the expression of several DNA repair genes such as APEX, PolB, LIG1, nibrin, DDB1 and DNA mismatch repair proteins MSH3 and PMS1 only in wild-type, but not in the mutant mice, implicating deficient DNA repair process in the exacerbated drug toxicity in c-fos knockout animals (Cadet et al., 2002). These findings support a protective role for c-fos against METH damage and suggest that c-fos might be involved in mechanisms of DNA repair (Cadet et al., 2002). The other factors that could be involved in this protection include cell adhesion receptors such as integrins, intrercellular adhesion molecules 1 and 2 as well as the ephrin receptor A1 because c-fos heterozygote mice show decreased basal levels of these transcripts and because METH treatment caused further reduction of their expression (Betts et al., 2002; Cadet et al., 2002). This idea is also supported by the observations that integrins promote cell survival after injury and apoptotic insults through stimulation of the PI3K-Akt pathway which leads to phosphorylation of the pro-apoptotic protein, BAD, thereby enhancing the anti-apoptotic effects of Bcl-2 (Gilcrease, 2006). The involvement of the integrins in METH-induced cell death is also supported by the report that inhibition of integrins increases apoptotic cell death (Gilcrease, 2006).

Fra-2 is another protein that might play a role in protective mechanisms against METH toxicity. Unlike other AP-1 transcription factors such as c-fos and c-jun, which are transiently expressed, Fra-2 expression is increased for a longer period of time after METH administration, starting at 3 days post-treatment and returning to basal levels by day 5 (Pennypacker et al., 2000). This effect seems to depend on METH-induced hyperthermia, because decreasing body temperature prevented drug toxicity and also blocked Fra-2 induction in the mouse striatum (Pennypacker et al., 2000). Because the non-neurotoxic amphetamine, dexfenfluramine, does not cause Fra-2 induction, it has been suggested that this transcription factor may play role in the initial regulation of regeneration and repair mechanisms activated during the early days of METH toxicity (Pennypacker et al., 2000).

C-jun is an AP-1 transcription factor that might contribute to the induction of METH toxicity because c-jun knockout mice show partial protection against damaging effects of the drug (Deng et al., 2002b). Specifically, c-jun mutant mice showed lower induction of apoptotic markers poly(ADP-ribose) polymerase (PARP) and cleaved caspase-3 as well as reduced DNA fragmentation in their brains after METH treatment (Deng et al., 2002b). Because c-jun knockout mice and their wild-type littermates demonstrate similar degree of dopaminergic toxicity after METH treatment, c-jun appears to only play role in the mediation of neuronal

apoptosis in cells postsynaptic to DA axons (Deng et al., 2002b). Moreover, temperature regulation does not seem to play role in the partial protection against METH neurotoxicity afforded by c-jun +/− genotype because wild-type and c-jun knockout mice showed no differences in drug-induced hyperthermia (Deng et al., 2002b). The role for c-jun in the mechanisms underlying METH neurotoxicity is also supported by the findings that METH-induced expression of c-Jun, phosphorylated c-Jun at Ser63 and Ser73 and phosphorylated Jun-N-terminal kinases (JNK) at Thr183 and Tyr185 is associated with cell death in vivo (Deng et al., 2002b; Jayanthi et al., 2002; O'Dell and Marshall, 2005) and in vitro (Wang et al., 2008); by data showing that phosphorylated c-Jun colocalized with markers of DNA fragmentation and cell death in the striatum (Deng et al., 2002b); and by observations that the JNK-specific inhibitor, SP600125, can attenuate JNK phosphorylation, activation of caspase-3 and cell death caused by psychostimulant treatment in human neuroblastoma cells (Wang et al., 2008). METH-mediated activation of the JNK-Jun pathway appears to involve several signaling events. Specifically, increased expression of Src, Cas and Crk after METH treatment in the striatum suggests a role for the Src-dependent upstream pathway (Jayanthi et al., 2002), because Src can stimulate JNK activity (Feng et al., 2001) and because Src-dependent events are mediated by the assembly of the signal transduction complex that involves Cas and Crk (Yoshizumi et al., 2000). In addition, inhibition of METH-induced JNK phosphorylation and apoptosis in differentiated human mesencephalic neuron-derived cells with the mixed-lineage kinases inhibitor, CEP1347, implies that the upstream mixed-lineage kinase signaling might also contribute to JNK-Jun pathway activation (Lotharius et al., 2005). This proposition is supported by findings showing that expression of MKK7 which mediates JNK activation by mixed-lineage kinases is increased after METH treatment (Jayanthi et al., 2002). Additionally, the finding that pretreatment with antioxidant vitamin E prevents METH-associated JNK phosphorylation suggests that the drug can cause JNK activation via ROS-depenent mechanisms (Wang et al., 2008), which can induce DNA damage such as DNA strand breaks and base excision (Barzilai, 2007; Fishel et al., 2007).

Role of DNA Damage in METH Toxicity

As mentioned earlier, METH can cause neuronal apoptosis in several brain regions, including the striatum, cortex, hippocampus and olfactory bulb (Deng and Cadet, 2000; Deng et al., 2001, 2007; Ladenheim et al., 2000; Zhu et al., 2005; 2006a, 2006b). Because METH administration is associated with ROS production and because ROS can cause apoptosis and DNA damage (Li and Trush, 1993), it is thus possible that METH might induce neuronal apoptosis through ROS-mediated DNA damage. This suggestion is supported by data obtained using microarray analyses which have shown changes in the expression of a number of genes that participate in DNA repair, including APEX, PolB, LIG1 and DNA mismatch repair proteins MSH3 and PMS1 after toxic doses of the drug (Cadet et al., 2002).

The role of DNA damage in METH toxicity is supported by the report that METH treatment causes increased DNA oxidation in the striatum, substantia nigra, hippocampus and cortex (Jeng et al., 2006). This effect appears to depend on prostaglandin H synthase-dependent increases in ROS formation and ROS-mediated DNA damage (Jeng et al., 2006). In addition, exposure to the drug during embryonic and fetal development is associated with increased DNA oxidation in the mouse brain (Jeng et al., 2005).

Involvement of Mitochondrial Pathways in METH-induced Neurodegeneration

METH is a cationic lipophilic molecule that can diffuse into mitochondria and be retained by these organelles (Asanuma et al., 2000; Davidson et al., 2001). Accumulation of positively charged molecules in the mitochondria results in dissipation of the electrochemical gradient

established by oxidative phosphorylation and inhibit ATP synthesis, causing energy deficiency and subsequent mitochondrial dysfunction (Wallace, 2005). METH is capable of inducing decreases in mitochondrial membrane potential and disturbances in mitochondrial biogenesis in neuroblastoma cell lines (Wu et al., 2007). METH has been also shown to cause rapid decreases in the activity of complex II (Brown et al., 2005) and complex IV of the mitochondrial electron transport chain, which is associated with a reduction in ATP stores in the brain (Burrows et al., 2000). In addition to reduced ATP generation, mitochondrial defects can cause increased ROS production (Wu et al., 2007), suggesting that mitochondria affected by the drug may constitute an important sources of ROS that cause damage to lipids (Jayanthi et al., 1998), and DNA (Jeng et al., 2006; Jeng et al., 2005).

In addition to the participation of mitochondrial mechanisms in METH-induced terminal degeneration, drug-related neuronal apoptosis also involves the mitochondria-dependent death pathway (Deng et al., 2002a; Jayanthi et al., 2001, 2004). Specifically, METH has been shown to cause increases in proapoptotic proteins, Bax, Bad and Bid, but decreases in antiapoptotic proteins Bcl-2 and Bcl-X_L (Deng et al., 2002a; Jayanthi et al., 2001). METH-induced alterations in their levels cause the formation of channels that result in mitochondrial membrane potential loss and lead to the release of mitochondrial proteins such as cytochrome *c* and apoptosis inducing factor (AIF) into the cytosol (Breckenridge and Xue, 2004). Indeed, AIF and Smac/DIABLO released from mitochondria have also been shown to participate in apoptosis caused by METH treatment in the striatum (Jayanthi et al., 2004). Release of cytochrome *c* is followed by activation of caspases 9 and 3, and the proteolysis of several target proteins, including PARP, lamins and DNA fragmentation factor 45 kDA subunit (DFF-45) (Deng et al., 2002a; Jayanthi et al., 2004). Cleaved capase-3, in turn, can contribute to METH-induced cytoskeletal damage because it was shown to mediate proteolysis of cytoskeletal proteins spectrin and tau in vitro (Warren et al., 2005; Warren et al., 2007a) and in vitro (Warren et al., 2007b). This discussion is consistent with the observations that overexpression of Bcl-2 (Cadet et al., 1997), as well as inhibition of caspases (Jimenez et al., 2004; Uemura et al., 2003) and PARP (Iwashita et al., 2004) can protect against METH-induced cell death. It is also consistent with our demonstration that METH causes cell death through interaction of the mitochondria- and ER-dependent death pathways (Jayanthi et al., 2004).

Endoplasmic Reticulum, Calcium-Dependent Mechanisms, and METH-induced Cell Death

The accumulated evidence had suggested that METH-induced oxidative stress can trigger neuronal damage by causing dysfunctions of cellular organelles such as the endoplasmic reticulum (ER) (Jayanthi et al., 2004) (Figure 1). In addition to regulating synthesis, folding, and transport of proteins, ER also constitutes the main intracellular store for Ca^{2+}, whose excess can contribute to cell death (Gorlach et al., 2006). At physiological levels, Ca^{2+} released from the ER is taken up by mitochondria to enhance metabolite flow on the outer mitochondrial membrane and to increase ATP production (Kroemer et al., 2007). However, sustained release of Ca^{2+} from the ER stores may initiate calcium-dependent apoptosis via the permeabilization of the outer mitochondrial membrane (Kroemer et al., 2007). ER stress and dysregulation of calcium homeostasis appear to participate in METH-induced cell death because the drug can cause activation of calpain (Jayanthi et al., 2004), a calcium-responsive cytosolic protease involved in ER-dependent apoptosis (Nakagawa and Yuan, 2000). Indeed, METH has been shown to cause cell death consequent to increases in calpain activity in spinal cord motoneurons and cortical neurons (Samantaray et al., 2006). Pretreatment with the calpain inhibitor, calpeptin, attenuated METH-induced cell death in these models (Samantaray et al., 2006). Exposure to METH is accompanied by calpain-mediated proteolysis of cytoskeletal scaffolding protein, spectrin, in primary cerebrocortical neuronal cultures (Warren et al., 2007b), in the rat cortex (Warren et al., 2005, 2007a), hippocampus (Warren et al., 2005) and

striatum (Staszewski and Yamamoto, 2006). In addition to spectrin proteolysis, METH-induced increases in the cleaved form of cytoskeletal protein tau, which functions to stabilize microtubules (Hernandez and Avila, 2007), in primary cerebrocortical neuronal cultures (Warren et al., 2007b) as well as in the cortex, striatum and hippocampus (Straiko et al., 2007; Wallace et al., 2003; Warren et al., 2005), also appear to depend on calpain activation (Warren et al., 2007b). These findings strongly implicate ER stress and calpain activation in the mechanisms of METH neuronal degeneration.

A role for the ER in METH toxicity is further supported by the findings that neurotoxic doses of the drug can increase the expression of proteins, such as caspase-12, GRP78/BiP and CHOP/GADD153 (Jayanthi et al., 2004) that participate in ER-induced apoptosis (Marciniak and Ron, 2006). This METH-related ER stress might be secondary to oxidative stress (Cadet et al., 1994a; Jayanthi et al., 1998) and to increases in BAX/Bcl-2 ratios caused by this illicit drug (Jayanthi et al., 2001).

Role of Fas Ligand (FasL)/Fas Cell Death Pathway in METH-induced Apoptosis

In addition to the ER- and mitochondria-dependent death pathways, METH-induced neuronal apoptosis has been linked to stimulation of the FasL/Fas-mediated cell death pathway (Cadet and Krasnova, 2007; Cadet et al., 2007; Jayanthi et al., 2005). FasL is a member of the tumor necrosis factor (TNF) superfamily of cytokines that is involved in mechanisms of neuronal apoptosis observed in various models of brain injury (Choi and Benveniste, 2004). FasL expression is regulated by transcription factors AP-1, Egr and Nurr77 (Droin et al., 2003; Toth et al., 2001), all of which are induced by toxic doses of METH in the rat striatum (Jayanthi et al., 2005). Accordingly, METH was shown to elicit the expression of FasL in striatal neurons (Jayanthi et al., 2005). METH-induced activation of FasL/Fas apoptotic pathway in the striatum depends on upregulation of calcenurin activity as well as dephosphorylation and nuclear translocation of nuclear factor of activated T cells (NFAT) (Jayanthi et al., 2005), that are known to be involved in FasL regulation (Luoma and Zirpel, 2008; Shioda et al., 2007). In addition, METH injections caused cleavage of caspases 8 and 3, both of which are mediators of FasL/Fas apoptosis pathway (Thorburn, 2004). These changes in the FasL/Fas pathway and drug-induced apoptosis were attenuated by pretreatment with DA D1 receptor antagonist, SCH23390 (Jayanthi et al., 2005), suggesting a role for DA system in the activation of Fas-mediated cell death pathway. Because NFATs are known to participate in the regulation of Ca2+ and calcineurin-mediated transcriptional activity in the nervous system (Hogan et al., 2003) and because pretreatment with SCH23390 also blocked METH-induced increase in calcineurin expression and NFAT nuclear translocation (Jayanthi et al., 2005), it is possible to suggest that DA system is involved in the regulation of FasL/Fas apoptotic pathway via calcineurin-NFAT-dependent mechanism. METH treatment caused increase in FasL protein expression and apoptosis in striatal GABA- and enkephalin-positive neurons without inducing damage to substance P-expressing medium spiny neurons or somatostatin- and choline acetyltransferase-positive interneurons (Jayanthi et al., 2005).

Role of Autophagy and Ubiquitin/Proteasome System in METH Toxicity

Autophagy is the process through which abnormal protein aggregates and damaged cellular organelles are enwrapped within an endoplasmic reticulum-derived double membrane vesicle called autophagosome and then delivered to lysosomes for degradation (Yorimitsu and Klionsky, 2005). Several studies have shown that neurotoxic doses of METH can cause autophagy in vitro and in vivo (Castino et al., 2008; Fornai et al., 2004b; Kanthasamy et al., 2006; Larsen et al., 2002; Lazzeri et al., 2006). For example, midbrain neuronal cells exposed to METH develop vacuolation of endocytic compartments and formation of autophagic

granules within their cytoplasm (Cubells et al., 1994; Larsen et al., 2002). Kanthasamy et al. (2006) have also reported drug-related autophagic changes in mesencephalic DA cell cultures. Immortalized mesencephalic cells treated with METH also show characteristic vacuoles in their cytoplasm (Cadet et al., 1997). METH-induced accumulation of cytoplasmic inclusions resembling autophagic vacuoles has also been reported in PC12 cells, in nigrostriatal DA neurons and in striatal GABAergic neurons (Fornai et al., 2004b; Lazzeri et al., 2006). The formation of these inclusions appears to be related to inhibition of the ubiquitin-proteasome system, which is a major pathway for degradation of abnormal or nonfunctional proteins within cells (Lazzeri et al., 2006, 2007).

It appears that DA may play role in METH-induced dysfunction of the ubiquitin-proteasome system and in the formation of cytplasmic inclusions because both are attenuated by inhibition of DA synthesis with the TH inhibitor, α-methyp-*p*-tyrosine (Fornai et al., 2004b) This effect was reversed with L-DOPA, which restored intracellular DA levels (Fornai et al., 2004b). Similarly, METH failed to produce cytoplasmic inclusions in primary striatal cell cultures which do not contain DA, while exposure of these cultures to DA led to the appearance of intracellular inclusions and cell death (Lazzeri et al., 2007). The DA D1 receptor agonist, SKF38393, also caused the appearance of cytoplasmic inclusions in striatal cultures in a fashion similar to those caused by DA (Lazzeri et al., 2007). These inclusions were blocked by the DA D1 receptor antagonist, SCH23390 (Lazzeri et al., 2007). METH-induced formation of cytoplasmic inclusions appears to depend on ROS production because it is prevented by treatment with the antioxidant, *S*-apomorphine (Fornai et al., 2004b).

Further investigations of signaling pathways underlying METH-induced formation of cytplasmic inclusions using PC12 cells have revealed a potential role for β-arrestin, which is involved in ubiquitination and degradation of G-protein coupled receptors (Fornai et al., 2008). Exposure to the DA receptor agonist, apomorphine, caused rapid ubiquitination of β-arrestin in PC12 cells similar to that induced by METH whereas treatment with the DA D2 receptor antagonist, eticlopride and to the non-selective DA receptor antagonist, flufenazine, reduced both METH-induced β-arrestin ubiquitination and cytoplasmic inclusion formation, thus providing further support for the involvement of DA receptors in these effects (Fornai et al., 2008). The role for β-arrestin in mediating the appearance of intracellular inclusions is also supported by findings that the number of METH-induced cytplasmic bodies was reduced in cells transfected with β-arrestin dominant-negative mutant and increased by the persistently ubiquitinated β-arrestin-ubiquitin fusion protein (Fornai et al., 2008). It is interesting to note that DA receptor antagonists inhibited the formation of 50% of cytoplasmic bodies, which is in contrast with the full protection observed after DA depletion (Fornai et al., 2004b, 2008). Together, these data suggest that DA receptors play only a partial role in the formation of cytplasmic inclusions caused by METH in PC12 cells and point to additional pathways that might be triggered by DA. Indeed, prevous studies have shown that cytosolic DA causes inhibition of ubiquitin-proteasome system (Keller et al., 2000) and formation of nigrostriatal inclusions (Fornai et al., 2003). This DA-dependent mechanism might apply to the formation of cytplasmic bodies in both nigrostriatal DA neurons and striatal GABA neurons expressing DA receptors. Indeed, METH-induced activation of DA receptors may be involved in causing the appearance of cytplasmic inclusions in striatal postsynaptic GABA neurons, while drug-related increases of free cytosolic DA levels in nigrostriatal terminals might account for the formation of intracellular bodies in nigrostriatal DA neurons (Fornai et al., 2008).

Interestingly, METH-induced cytplasmic inclusions that are positive for protein markers of autophagy-lysosomal sysem Rab24, microtubule-associated protein light chain 3 (LC3) and belcin 1 also stain for α-synuclein, parkin and proteins that belong to the ubiquitin-proteasome pathway (Castino et al., 2008; Fornai et al., 2004a, 2004b, 2005; Lazzeri et al., 2007), suggesting morphological and functional identity of autophagic vacuoles with α-synuclein-

and ubiquitin-proteasome-positive inclusions (Castino et al., 2008). In line with these findings, recent studies employing proteomic approaches to identify pathways involved in METH toxicity have reported increases in the expression of autophagy-linked LC3, α-synuclein, ubiquitin-conjugating enzyme E2N, and ubiquitin carboxy-terminal hydrohylase-L1 in the striatum and cortex of drug-treated rats (Kobeissy et al., 2008; Li et al., 2008; Liao et al., 2005). Because autophagy plays a critical role in the degradation of oxidatively damaged proteins (Yorimitsu and Klionsky, 2005), it is possible that METH-induced DA-dependent production of ROS promotes protein misfolding and aggregation, resulting in the upregulation of autophagic degradation in DA neurons as a part of the protective mechanism against drug toxicity (Castino et al., 2008). This idea is supported by findings showing that suppression of autophagy with 3-methyladenine caused Bax oligomerization, mitochondria permeabilization and apoptosis in METH-treated PC12 cells, the toxic effects which were prevented by caspase inhibitor ZVAD-fmk (Castino et al., 2008).

Concluding Remarks

In summary, the brains of human METH addicts, who abuse large doses of the drug, are characterized by a variety of neuropathological changes. These include degeneration of monoaminergic terminals, dysregulation of energy metabolism, evidence of oxidative stress, as well as microgliosis and reactive astrogliosis. The deleterious effects of the drug have been consistently replicated in animal models. These studies have helped to identify some of the pathways that form the mechanistic substrates for METH-induced damage to monoaminergic terminals. Similarly, recent investigations have clarified the bases for neuronal apoptosis caused by METH exposure in various regions of the mammalian brain. This knowledge is just beginning to impact on the thinking regarding how to best approach the development of potentially effective therapeutic strategies that will address the neurological and psychiatric deterioration observed in some METH addicts. The use of therapeutic agents that address solely the addictive properties of METH might not be sufficient to attenuate the varied neuropathological end-points caused by the use of the drug. One possibility might be the need to combine therapeutic anti-addictive drugs with neuroprotective agents within the same clinical setting where these patients are being treated. The combination of anti-addictive agents with the anti-manic drug, lithium, that has been shown to have neuroprotective properties (Chuang, 2004), might be a fruitful approach to the treatment of METH abusers. In any case, more studies are needed in order to further clarify strategies that might serve to promote recovery of monoaminergic systems in models of METH toxicity.

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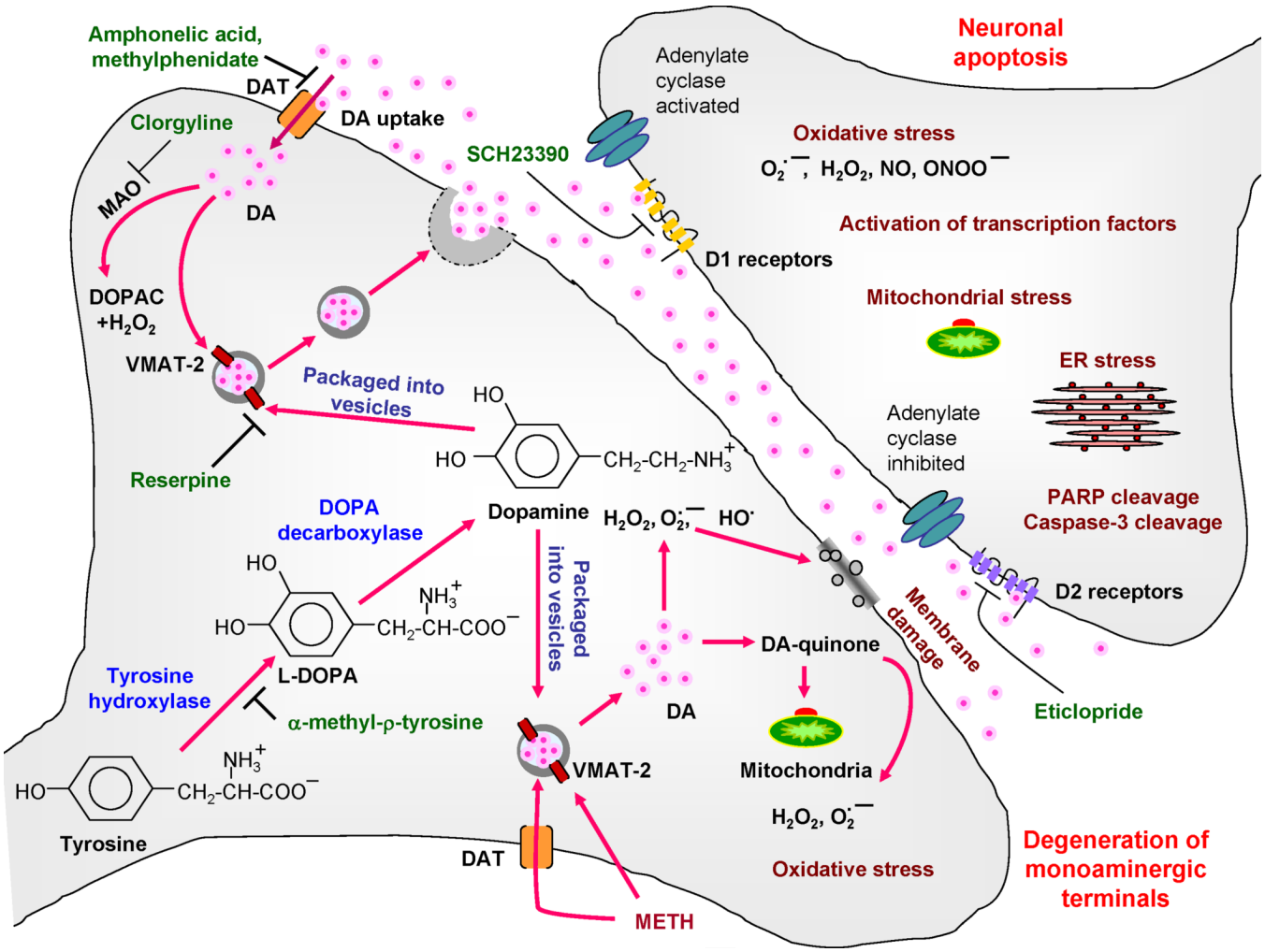

Figure 1.

Schematic rendering of cellular and molecular events involved in METH-induced DA terminal degeneration and neuronal apoptosis within the striatum. The figure summarizes findings of various studies that have addressed the role of DA, oxidative stress, and other mechanisms in METH toxicity. METH enters dopaminergic neurons via DAT and passive diffusion. Within these neurons, METH enters synaptic vesicles through VMAT-2 and causes DA release into the cytoplasm via changes in pH balance. In the cytoplasm, DA auto-oxidizes to form toxic DA quinones with generation of superoxide radicals and hydrogen peroxides via quinone cycling. Subsequent formation of hydroxyl radicals through interactions of superoxides and hydrogen peroxide with transition metals leads to oxidative stress, mitochondrial dysfunctions and peroxidative damage to presynaptic membranes. The involvement of endogenous DA in METH neurotoxicity is supported by findings that the TH inhibitor, α-methyl-*p*-tyrosine, which blocks DA synthesis, affords protection against METH toxicity. In addition, the role of DA is supported by observations that use of the MAO inhibitor, clorgyline, and of the irreversible inhibitor of vesicular transport, reserpine, which results in increases in cytoplasmic DA levels can exacerbate METH-induced toxicity. Together, these events are thought to be partly responsible for the loss of DA terminals. DA release from the terminals is also involved because the DAT inhibitor, amphonelic acid, which blocks METH-induced DA release from DA terminals can also prevent damage to DA axons. The toxic effects of released DA might occur through activation of DA receptors because DA receptor antagonists block degeneration of DA

terminals. Interactions of DA with D1 receptors on post-synaptic membrane cause activation of various transcription factors and subsequent upregulation of death cascades in postsynaptic neurons. These death cascades can be inhibited, in part, by the DA D1 antagonist, SCH23390.

Table 1

Summary of studies showing evidences of METH neurotoxicity in monkeys

METH treatment regimen	Time-points after METH injections	Tissue	Data obtained	Reference
Escalating dose treatment for 2 weeks, final dose 16–24 mg/kg/day;	24 h	Pons-medulla, midbrain, frontal cortex	↑ NE levels,	Seiden et al., 1976
		Caudate	↓ DA levels	
	2 weeks	Caudate	↓ DA levels	
escalating dose treatment for 3–6 months, final dose 24–52 mg/kg/day	24 h	Pons-medulla, midbrain, hypothalamus, frontal cortex	↓ NE levels	
		Caudate	↓ DA levels	
	3–6 months	Midbrain, frontal cortex	↓ NE levels	
		Caudate	↓ DA levels	
Initial dose 0.5 mg/kg/day gradually increased to final dose 32 mg/kg/day	3–6 months	Caudate, pons-medulla	↓ DA levels	Finnegan et al., 1982
		Frontal cortex	↓ NE levels	
Initial dose 4 mg/kg/day increased over 14 days to 40 mg/kg/day	2 months	Caudate Frontal cortex	↓ DA levels, ↓ 5-HT levels	Ando et al., 1985
Initial dose 8 mg/kg/day increased over 14 days to 40 mg/kg/day	2 months	Caudate	↓ DA levels	Preston et al., 1985a
		Cortex, hippocampus	↓ 5-HT levels	
Initial dose 8 mg/kg/day increased over 15 days to 40 mg/kg/day	38–50 days	Caudate	↓ DA levels, ↓ DA uptake sites	Preston et al., 1985b
		Cortex,thalamus	↓5-HT levels	
Initial dose 4 mg/kg/day increased over 14 days to 40 mg/kg/day	4 years	Caudate	↓ DA levels, ↓ 5-HT levels	Woolverton et al., 1989
		Hippocampus, frontal cortex, somatosensory cortex	↓ 5-HT levels	
2 mg/kg, 2 times, 4 h apart	1–2 weeks	Striatum	↓ DA synthesis	Melega et al., 1997
	3–4 weeks and 10–12 weeks	Striatum	↓ DA synthesis, ↓DA levels	
2 mg/kg, 4 times, every 2 h	2–3 weeks	Striatum	↓ DA levels, ↓ 5-HT levels ↓ DAT binding sites	Villemagne et al., 1998
		Frontal, parietal and temporal cortices	↓ 5-HT levels	
2 mg/kg, 2 times, 24 h apart	1 week	Striatum	↓ DAT binding sites	Melega et al., 2000
Escalating dose treatment for 33 weeks, to final plasma drug concentration 1–3 μM	3 weeks	Striatum	↓ DA levels, ↓ DAT binding	Melega et al., 2008

Table 2

Summary of studies showing evidences of METH toxicity in rats

METH treatment regimen	Time-points after METH injections	Tissue	Data obtained	Reference
15 mg/kg, 9 times, every 6 h	36 h – 13 days	Striatum	↓TH activity, ↓DA levels	Kogan et al., 1976
	36 h – 3 days	Substantia nigra	↓TH activity	
15 mg/kg, 5 times, 6 h apart	1 – 30 days	Striatum	↓TH activity	Hotchkiss et al., 1979
	1 – 7 days		↓TPH activity	
12.5 or 25 mg/kg, 2 times/ day for 30 days	2 weeks	Caudate	↓DA levels	Wagner et al., 1979
15 mg/kg, 4 times, every 2 h	2, 4, 15 and 30 days	Striatum	↓TH activity	Hotchkiss and Gibb, 1980
		Striatum, hippocampus	↓TPH activity	
15 mg/kg, 5 times, 6 h apart	7 days	Striatum, olfactory tubercle	↓DA levels	Morgan and Gibb, 1980
	12 h – 30 days		↓TH activity	
	12 h – 30 days	Striatum, nucleus accumbens olfactory tubercle	↓TPH activity	
50 mg/kg, 2 times/day for 4 days	3 weeks	Striatum, cortex, substantia nigra, mesolimbic area	↓DA levels	Ricaurte et al., 1980
		Striatum, cortex, septum, amygdala, hypothalamus, substantia nigra	↓5-HT levels	
25 or 50 mg/kg, 2 times/day for 4 days	2 weeks	Caudate	↓DA levels, ↓DA uptake sites	Wagner et al., 1980
50 mg/kg/day for 30 days	2 – 8 weeks	Caudate	↓DA levels	
15 mg/kg, 6 times, 6 h apart	36 h and 110 days	Striatum	↓TH activity	Bakhit et al., 1981
		Striatum, hippocampus, cortex, nucleus accumbens	↓5-HT levels, ↓TPH activity	
50 mg/kg, 2 times/day for 4 days	6 months	Caudate	↓DA levels	Bittner et al., 1981
15 mg/kg, 5 times, every 6 h	6 and 11 days	Striatum	↑Swollen nerve fibers	Lorez, 1981
50 mg/kg, 3 times, 8 h apart	4 days	Striatum, nucleus accumbens	Degeneration of nerve fibers	Ricaurte et al., 1982
	3 weeks	Striatum	↓TH activity	
15 mg/kg, 5 times, every 6 h or	18 h after last challenge dose	Striatum	↓DA levels, ↓5-HT levels, ↓TH activity, ↓TPH activity	Schmidt et al., 1985b
pretreatment with 2.5 mg/kg 5 times, every 6 h; then with 5 and 7.5 mg/kg, 5 times, every 6 h followed by high-dose challenge 15 mg/kg, 5 times, every 6 h			↓DA levels, ↓5-HT levels, ↓TPH activity	
100 mg/kg, single dose	2 days	Somatosensory cortex	Neuronal degeneration	Commins and Seiden, 1986
	2 weeks		↓5-HT levels	
15 mg/kg, 4 times, every 3 h	3 days	Striatum	↓DA levels, ↓TH activity	Green et al., 1992
		Cortex, hippocampus	↓5-HT levels	
50 mg/kg, 3 times, 8 h apart	12 weeks	Caudate-putamen, nucleus accumbens/olfactory tubercle	↓DA levels, ↓5-HT levels	Richards et al., 1993
		Somatosensory cortex, amygdala, hippocampus	↓5-HT levels	
7.5 mg/kg, 3 times, 2 h apart or 2 mg/kg for 7 days	4 days	Striatum, prefrontal cortex	↓DA levels, ↓5-HT levels	Stephans and
		Striatum	↓DA levels	

METH treatment regimen	Time-points after METH injections	Tissue	Data obtained	Reference
followed by 7.5 mg/kg, 3 times, every 2 h				Yamamoto, 1996
12.5 mg/kg, 4 times, 2 h apart	48 and 237 days	Caudate	↓DA levels	Friedman et al., 1998
	48, 139 and 237 days	Caudate, hippocampus,	↓5-HT levels	
	48 and 139 days	Medial prefrontal cortex	↓5-HT levels	
40 mg/kg, single injection	12 h – 10 days	Caudate-putamen	↓TH protein levels, ↓DA levels, ↓5-HT levels	Cappon et al., 2000
	10 days		↑GFAP protein levels	
5–10 mg/kg, 4 times, 2 h apart	3 weeks	Striatum	↓DA contents	Chapman et al., 2001
		Substantia nigra	↓TH mRNA levels	
15 mg/kg, 4 times, every 2 h	3, 5 or 14 days	Striatum, nucleus accumbens	↓DAT binding	Guilarte et al., 2003
		Striatum, nucleus accumbens, cortex, anterior cingulate, hippocampus, amygdala, thalamus, central grey	↓5-HTT binding	
		Striatum, central grey	↓VMAT-2 binding	
10 mg/kg, 4 times, every 2 h or	7 days after last dose	Striatum	↓DA levels, ↓5-HT levels	Johnson-Davis et al., 2003
		Frontal cortex, hippocampus	↓5-HT levels	
2.5 mg/kg, 4 times, every 2 h; then 5 and 7.5 mg/kg, 4 times, every 2 h followed by high-dose challenge 10 mg/kg, 4 times, every 2 h		Hippocampus	↓5-HT levels	
6 mg/kg, 4 times, every 2 h or	3 days	Caudate-putamen	↓DA levels, ↓DAT binding	Segal et al., 2003
			↓VMAT-2 binding	
increasing doses (0.1–4.0 mg/kg) over 14 days, then acute binge 6 mg/kg, 4 times, every 2 h			↓DA levels, ↓VMAT-2 binding	
32 mg/kg/day for 5 days	2 days	Cortex, hippocampus, thalamus, septum, amygdala, hypothalamus	↓DA uptake sites	Armstrong and Noguchi, 2004
		Striatum, anterior cingulate, cortex, nucleus accumbens, hippocampus, septum, amygdala, hypothalamus	↓5-HT uptake sites	
8 mg/kg, 4 times, every 4 h or	7 days after last dose	Striatum	↓DA levels,	Johnson-Davis et al., 2004
	2 h		↓vesicular DA uptake,	
		Nonmembrane fraction of striatal synaptosomes	↓VMAT-2 immunoreactivity	
2 mg/kg, 4 times, every 4 h, 4 and 6 mg/kg, 4 times, every 4 h, then 8 mg/kg, 4 times, every 4 h	7 days	Striatum	↓DA levels	
	2 h		↓vesicular DA uptake	
5 mg/kg, once a day for 12 days	4–12 days or 6–19 days after first injection	Medial prefrontal cortex	↓TH immunoreactivity	Kadota and Kadota, 2004
			↑TUNEL-positive cells	
40 mg/kg, singe injection	24 and 48 h	Striatum	↑TUNEL-positive cells	Jayanthi et al., 2005
	3 days		↓DA levels	
Progressively more frequent injections (0.125 mg/kg/injection) for 2 weeks followed by 40 daily	15 min, 6 and 30 days after last dose 15 min and 6 days	Caudate-putamen	↓DAT binding,	Segal et al., 2005
			↓VMAT-2 binding	

METH treatment regimen	Time-points after METH injections	Tissue	Data obtained	Reference
injections (0.125-0.25 mg/kg per injection) for 40 days			↓D1 receptor binding	
			↓D2 receptor binding	
	6 and 30 days		↓DA levels	
5, 10 or 15 mg/kg, 4 times, 2 h apart	1 h	Striatum	↓vesicular DA uptake	Truong et al., 2005
	7 days		↓vesicular DA uptake	
			↓DA levels	
Escalating dose treatment for 14 days (starting with 0.1 mg/kg, increased to 4 mg/kg) followed by high-dose binge (6 mg/kg, 4 times/day, every 6 h) for 11 days	30 days	Frontal cortex, hippocampus	↓Number of pyramidal neurons	Kuczenski et al., 2007
	3 and 30 days		↓Calbindin-positive interneurons, microglial activation	
5 mg/kg, 6 times, 1 h apart or 10 mg/kg, 3 times, 2 h apart or	2 and 24 h	Striatum	↓DA levels, ↓5-HT levels, ↓NE levels	Graham et al., 2008
		Cortex, hippocampus	↓5-HT levels, ↓NE levels	
initial dose 0.5 mg/kg/day increased to 14 mg/kg/day over 14 days followed by 5 mg/kg, 6 times, 1 h apart or 10 mg/kg, 3 times, 2 h apart		Striatum	↓DA levels, ↓5-HT levels, ↓NE levels	
		Cortex, hippocampus	↓5-HT levels, ↓NE levels	

Table 3

Summary of studies showing evidences of METH toxicity in mice

METH treatment regimen	Time-points after METH injections	Tissue	Data obtained	Reference
5 mg/kg, 4 times, 2 h apart	3 days	Striatum	↓DA levels, ↓TH activity	Green et al., 1992
5 mg/kg, 2 times/day for 6 days followed by 10 mg/kg, 2 times/day for 1 day and 15 mg/kg, 2 times/day for 1 day	1 week after last injection	Striatum	↓DA levels	Cadet et al., 1994b
10 mg/kg, 4 times, 2 h apart	1 – 21 days	Striatum	↓DA levels, ↓TH protein levels	O'Callaghan and Miller, 1994
	1 – 14 days	Striatum, cortex	↑GFAP levels	
	48 h		Axonal degeneration	
2.5 or 5 mg/kg, 4 times, every 2 h	2 weeks	Striatum	↓DA uptake sites	Hirata et al., 1996
15 mg/kg, 4 times, every 2 h	5 days	Indusium griseum, tenia tecta, fasciola cinera	Neuronal degeneration	Schmued and Bowyer, 1997
4 mg/kg, 4 times, every 2 h	3 days	Striatum	↓DA levels	Kita et al., 1998
15 mg/kg, 4 times, every 2 h	48 h	Striatum	↓DA levels, ↓5-HT levels	Fumagalli et al., 1998
		Hippocampus	↓5-HT levels	
30 mg/kg, single injection	7 days	Striatum	↓DA levels, ↓5-HT levels	
10 mg/kg, 4 times, every 2 h	1 week	Striatum	↓DA uptake sites	Deng et al., 1999
			↓DAT protein levels	
			↓TH immunoreactivity	
			↑GFAP immunoreactivity	
	3 days and 1 week	Striatum, frontal cortex	↑TUNEL-positive cells	
15 mg/kg, 4 times, every 2 h	2 days	Striatum	↓DA levels	Fumagalli et al., 1999
15 mg/kg, single injection	7 days	Striatum	↓DAT protein levels	
5 mg/kg, 4 times, every 2 h	3, 7 and 14 days	Caudate-putamen	↓DA levels, ↓5-HT levels	Ladenheim et al., 2000
		Cortex	↓DA levels	
		Hippocampus	↓5-HT levels	
	14 days	Caudate-putamen, parietal cortex	↓DAT binding	
		Hippocampus	↓5-HTT binding	
	3 and 14 days	Caudate-putamen	Microglial activation	
	7 days	Parietal cortex	↑TUNEL-positive cells	
40 mg/kg, single injection	3 days	Striatum, hippocampus, cortex, indusium griseum, medial habenular nucleus	↑TUNEL-positive cells	Deng and Cadet, 2001
5 mg/kg, 4 times, every 2 h	48 h	Striatum	↓DA levels, Microglial activation	Thomas et al., 2004c
5 mg/kg, 3 times, every 4 h	17 days	Striatum, amygdala frontal cortex	↓DA levels, ↓DAT binding sites	Achat-Mendes et al., 2005
10 mg/kg, 4 times, every 2 h	3 days	Striatum	Death of enkephalin-positive projection neurons	Thiriet et al., 2005
30 mg/kg, single injection	24 h	Striatum	↑TUNEL-positive cells	Zhu et al., 2005
	24 h – 3 days		↓TH protein levels,	

METH treatment regimen	Time-points after METH injections	Tissue	Data obtained	Reference
			↓DAT binding sites	
	48 h and 3 days		↑GFAP immunoreactivity	
5 mg/kg, 3 times, every 3 h	72 h	Striatum, amygdala, frontal cortex	↓DA levels, ↓DAT binding sites	Anderson and Itzhak, 2006
30 mg/kg, single injection	24 h	Striatum	Apoptosis of projection neurons, cholinergic and parvalbumin-positive interneurons	Zhu et al., 2006a
5 mg/kg, 3 times, every 3 h	5 days	Striatum	↓TH immunoreactivity, ↑GFAP immunoreactivity	Achat-Mendes et al., 2007
40 mg/kg, single injection	24h	Olfactory bulb	↑TUNEL-positive cells	Deng et al., 2007
	1week		↓DA levels, ↓DAT binding sites, ↓TH immunoreactivity	
40 mg/kg, single injection	12 h – 3 days	Caudate-putamen	↓TH immunoreactivity	Bowyer et al., 2008
	12 h – 1 day		Axonal degeneration	
	1 – 3 days		Microglial activation	
	7 days		↓DA levels	
10 mg/kg, 4 times, 2 h apart	72 h	Striatum, cortex	↓DA levels	Fantegrossi et al., 2008
		Striatum	Microglial activation	