# Neurotoxicity of Substituted Amphetamines: Molecular and Cellular Mechanisms

JEAN LUD CADET[*], IRINA N. KRASNOVA, SUBRAMANIAM JAYANTHI and JOHNALYN LYLES

*Molecular Neuropsychiatry Branch, DHHS/NIH/NIDA, Intramural Research Program, 5500 Nathan Shock Drive, Baltimore, Maryland 21224, USA. jcadet@intra.nida.nih.gov*

**The amphetamines, including amphetamine (AMPH), methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA), are among abused drugs in the US and throughout the world. Their abuse is associated with severe neurologic and psychiatric adverse events including the development of psychotic states. These neuropsychiatric complications might, in part, be related to drug-induced neurotoxic effects, which include damage to dopaminergic and serotonergic terminals, neuronal apoptosis, as well as activated astroglial and microglial cells in the brain. The purpose of the present review is to summarize the toxic effects of AMPH, METH and MDMA. The paper also presents some of the factors that are thought to underlie this toxicity. These include oxidative stress, hyperthermia, excitotoxicity and various apoptotic pathways. Better understanding of the cellular and molecular mechanisms involved in their toxicity should help to generate modern therapeutic approaches to prevent or attenuate the long-term consequences of amphetamine use disorders in humans.**

## AMPHETAMINE

Amphetamine (AMPH) is a psychostimulant that belongs to widely used illegal drugs in the world. AMPH is a popular drug of abuse in Australia (Bartu *et al.*, 2004), Belgium (Raes and Verstraete, 2005), Brazil (Silva and Yonamine, 2004), Switzerland (Augsburger *et al.*, 2005) and UK (Wylie *et al.*, 2005). AMPH is a common drug of abuse in Sweden and other northern European countries (Jones, 2005; Gustavsen *et al.*, 2006). In the USA, non-medical use of medications prescribed for ADHD treatment, including those that contain AMPH, is high among high school and college students (McCabe *et al.*, 2004; 2005). It has been reported that the abuse of these drugs is second only to marijuana (Brown *et al.*, 2001).

AMPH abuse is associated with very serious harms. These include increased psychological morbidity, dependence and health problems. For example, acute AMPH side-effects include tachycardia, hypertension, hyperthermia, increased muscle tention, liver and renal failure, nausea, blurred vision, ataxia, anxiety, psychosis and seizures (Kalant and Kalant, 1975; Janowsky and Risch, 1979; Alldredge *et al.*, 1989; Murray, 1998). Other severe and fatal AMPH intoxications have also been reported (Ginsberg *et al.*, 1970; Kalant and Kalant, 1975; Salanova and Taubner, 1984; De

Letter *et al.*, 2006; Steentoft *et al.*, 2006). Chronic AMPH abuse is associated with impairments in attention and memory, problems with learning, as well as compromised decision making (McKetin and Mattick, 1997; Rogers *et al.*, 1999; Ornstein *et al.*, 2000). Some of these neuropsychiatric complications are thought to be related to AMPH-induced neurotoxic effects which consist of decreases in tyrosine hydroxylase (TH) activity (Ellison *et al.*, 1978), long-term dopamine (DA) depletion (Wagner *et al.*, 1980a), loss of dopamine transporters (DAT) (Scheffel *et al.*, 1996; Krasnova *et al.*, 2001), as well as decreases in vesicular monoamine transporter proteins (Krasnova *et al.*, 2001). In addition to its effects on monoaminergic terminals, AMPH can cause cell death of primary cortical cells, TH-positive mesencephalic neurons, and of PC12 cells *in vitro* (Stumm *et al.*, 1999; Lotharius and O'Malley, 2001; Oliveira *et al.*, 2002) as well as degeneration of cell bodies in the cortex of AMPH-treated rodents (Jakab and Bowyer, 2002). The drug can also cause the activation of caspase-3 and appearance of TUNEL-positive cells in the striatum (Krasnova *et al.*, 2005). Calbindin- and DA- and cAMP-regulated phosphoprotein, Mr 32 kD (DARPP-32)-positive medium spiny projection neurons, but not choline acetyltransferase (ChAT)-, parvalbumin- or somatostatin-positive interneurons undergo AMPH-induced apoptosis (Krasnova *et al.*, 2005). Although the mechanisms for AMPH-mediated toxicity are not completely clear, they appear to include uptake into DA terminals, DA release, oxidative stress and the activation of p53-dependent and mitochondria-mediated cell death pathways. Herein, the data supporting these mechanisms in AMPH toxicity are reviewed.

## AMPH Toxicity Involves ROS Formation and ROS-mediated Transcriptional Changes.

AMPH-induced redistribution of DA from synaptic vesicles to the cytosol followed by its release to the extracellular space by reverse transport through DAT causes increased DA levels in the synaptic cleft (Sulzer *et al.*, 1995). DA metabolism is accompanied by the production of hydroxyl (Huang *et al.*, 1997) and superoxide (Krasnova *et al.*, 2001) radicals that participate in the toxic effects of the drug via free radical-mediated destruction of monoaminergic terminals (Huang *et al.*, 1997; Cadet

and Brannock, 1998; Wan *et al.*, 2000; Krasnova *et al.*, 2001). This occurs because reactive oxygen species (ROS) induced by AMPH administration can exceed the compensating abilities of anti-oxidant enzymes such as superoxide dismutases (SODs), catalase and glutathione peroxidase (Cadet and Brannock, 1998). The possible involvement of superoxide radicals in AMPH toxicity is also supported by the findings that transgenic mice that overexpress CuZnSOD are partially protected against the toxic effects of the drug on dopaminergic systems (Krasnova *et al.*, 2001).

Because ROS play a role in cellular signaling processes, including the regulation of transcriptional factors (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 AMPH-induced cascades of toxic events. These ideas are supported by the demonstration that administration of AMPH causes activation of AP-1 transcription factors (Persico *et al.*, 1995; Ferguson *et al.*, 2003; Milanovic *et al.*, 2006). The possibility that superoxide radicals might be involved in AMPH-induced transcriptional responses has been tested using microarray analyses (Krasnova *et al.*, 2002). This allowed the identification of 37 genes that show superoxide-mediated responses. Among these are genes that belong to classes of transcription factors, growth factors, heat shock proteins (HSPs), and xenobiotic metabolism. In response to neuronal damage, organisms initiate and elaborate events that trigger neuroprotective pathways that serve to minimize or prevent damage; they also function to increase the chance of functional recovery (Wieloch and Nikolich, 2006). These pathways include the increased synthesis and release of growth factors and cytokines such as the neuronal protein, activin A (Werner and Alzheimer, 2006), which is activated by AMPH in a superoxide-responsive manner (Krasnova *et al.*, 2002). The participation of activin A in protective mechanisms is illustrated by the reports that it reduces MPP+-induced cellular damage to DA neurons *in vitro* (Krieglstein *et al.*, 1995) and rescues striatal neurons from excitotoxic lesioning with quinolic acid (Hughes *et al.*, 1999). Another AMPH-responsive superoxide-mediated gene is macrophage colony-stimulating factor which is involved in the pro-
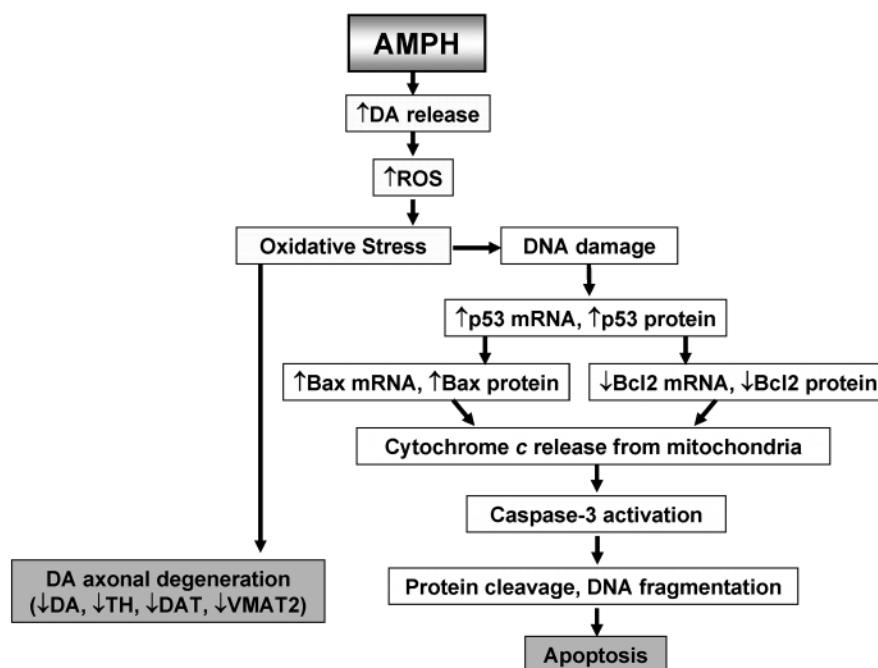
FIGURE 1   Overview of the molecular mechanisms involved in AMPH neurotoxicity. Oxidative stress, p53 and mito-
chondrial pathway play an essential role in the AMPH-induced neuronal apotosis and DA terminal degeneration.

liferation and migration of activated microglia into injured sites of the brain (Imai and Kohsaka, 2002). Additional genes whose transcript levels are induced by AMPH code for HSPs such as HSP110 and HSC70. HSPs have been shown to protect cells against oxidative damage (Papp *et al.*, 2003; Macario and Conway de Macario, 2005).

**AMPH Toxicity Involves Activation
of the p53-mediated Cell Death Pathway.**
ROS-induced stresses are known to be associated with DNA damage and p53 accumulation *in vitro* (Lombard *et al.*, 2005). P53 activation has been shown to participate in events that cause neuronal apoptosis (Culmsee and Mattson, 2005). This is thought to be related to the influence exerted by p53 on the expression of the Bcl-2 family of proteins which include the pro-apoptotic protein, Bax and the anti-apoptotic protein, Bcl-2 (Moll *et al.*, 2005; Chowdhury *et al.*, 2006). Specifically, p53 causes upregulation of Bax and downregulation of Bcl-2 (Moll *et al.*, 2005; Chowdhury *et al.*, 2006). As reported above, AMPH has been shown to cause neuronal cell death in various brain regions (Jakab and Bowyer, 2002; Krasnova *et al.*, 2005). The AMPH-induced neuronal apoptosis has been

recently shown to involve the activation of the p53 pathway with secondary increases in Bax levels and decreases in Bcl-2 levels in the mouse striatum (Krasnova *et al.*, 2005). The role of Bax activation in AMPH-related apoptosis was further supported by experiments showing that Bax-deficient mice were partially resistant to drug-induced cell death (Krasnova *et al.*, 2005). Figure 1 shows a schematic representation  of the mechanisms that may underlie AMPH-related apoptosis and DA terminal degeneration.

**AMPH Treatment and Temperature Regulation**
Temperature regulation appears to be also an important factor in the toxic responses to AMPH. In rodents, the psychostimulant was shown to produce biphasic effects with low doses ($\leq 2.5$ mg/kg) inducing hypothermia and higher doses ($\geq$ 5 mg/kg) causing hyperthermia at ambient temperature above 20ºC (Seale *et al.*, 1985; Krasnova *et al.*, 2001; Baker and Meert, 2003). This effect was found to be dose-dependent, with the degree of hyperthermia correlating to AMPH and DA levels in rat striatal microdialysate (Clausing and Bowyer, 1999). Several studies have also hinted to connections between hyperthermic and neurotoxic

actions of AMPH (Clausing *et al.*, 1995; Miller and O'Callaghan, 1996). Conditions that reduce or prevent AMPH-induced increases in core body temperature are, at least, partially neuroprotective (Clausing *et al.*, 1995; Miller and O'Callaghan, 1996). In contrast, hyperthermia could exacerbate AMPH toxicity because the formation of free radicals in the brain is elevated by temperature increase (Kil *et al.*, 1996) and because hyperthermia also potentiates the cytotoxic effects of ROS (Lin *et al.*, 1991). These ideas are also supported by the report that hyperthermia significantly increases DA quinone formation (LaVoie and Hastings, 1999) since quinones derived from DA have the ability to inhibit proteasome (Zafar *et al.*, 2006) which is involved in detoxification mechanisms.

Although AMPH-induced increases in temperature are thought to be involved in the toxicity of the drug, the manner by which the temperature is induced remains to be determined. DA release (Clausing and Bowyer, 1999) and $D_1$ receptor stimulation (Sanchez, 1989; Zarrindast and Tabatabai, 1992; Verma and Kulkarni, 1993) have been implicated. The observations that animals with severe hyperthermia released more DA in the striatal extracellular space provide partial support for this contention (Clausing and Bowyer, 1999). Moreover, the idea is also supported by the reports that hyperthermia is induced by administration of the $D_1$ agonist SKF 38393 in mice (Sanchez, 1989; Zarrindast and Tabatabai, 1992; Verma and Kulkarni, 1993), the effect that could be blocked by $D_1$ antagonist SCH 23390 (Sanchez, 1989; Zarrindast and Tabatabai, 1992). It has to be pointed out that since AMPH can cause release of other monoamines (Seiden *et al.*, 1993), their possible involvement also needs to be considered. For example, lesions of ventral norepinephrine bundle innervating the hypothalamus and limbic system cause attenuation of AMPH-induced hyperthermia in rats (Kostowski *et al.*, 1982).

In addition to DA release, AMPH-induced production of free radicals might also contribute to thermal instability (Krasnova *et al.*, 2001). Mice that overexpress the antioxidant enzyme, CuZnSOD, in the brain show no hyperthermic responses after AMPH treatment and are protected against long-term neurotoxic drug effects (Krasnova *et al.*, 2001). Thus, the possibility of complex interactions between thermoregulation and free radical load in

the long-term neurotoxicity induced by this illicit drug needs to be considered.

It is also of interest to note that various strains of mice show different hyperthermic responses to AMPH. Specifically, psychostimulants caused substantial hyperthermia in CD-1 (Krasnova *et al.*, 2001), Swiss-Webster (Craig and Kupferberg, 1972), DBA/2 (Seale *et al.*, 1985), and BALB/c mice (Jori and Rutczynski, 1978), while C57BL/6 (Seale *et al.*, 1985; Krasnova *et al.*, 2001) and $C_3H$ animals (Jori and Rutczynski, 1978) had low to moderate transient temperature increase. These differences in temperature responses may help to further dissect the role of hyperthermia in AMPH toxicity. For example, it seems there is no simple algorithm to predict toxicity based on temperature responses because CD-1 mice are more resistant to AMPH neurotoxicity than C57BL/6 mice in spite of showing greater and longer-lasting hyperthermia than C57BL/6 mice (Krasnova *et al.*, 2001).

Finally, the issues of temperature regulation have major clinical implications because AMPH can cause fatal hyperpyrexia in humans (Ginsberg *et al.*, 1970; Kalant and Kalant, 1975; Callaway and Clark, 1994; De Letter *et al.*, 2006). Thus, understanding of the root causes of AMPH-induced hyperthermia might help to develop therapeutic approaches that can prevent or attenuate the disastrous effects of this drug when taken in high doses.

## METHAMPHETAMINE

Metamphetamine (METH, Speed, crank) is abused worldwide due to its powerful stimulant properies that cause the user to feel "high" and to have increased energy (McCann *et al.*, 1998b; Sekine *et al.*, 2001; Farrell *et al.*, 2002). METH is easily available because it can be synthesized cheaply and distributed to various communities throughout the world. Presently, there is widespread abuse in the United States where it has migrated from the West Coast to other states (Puder *et al.*, 1988; Derlet *et al.*, 1989; Cho and Melega, 2002). METH can be abused via multiple routes which include oral, intravenous and smoking administration. In addition to its euphorigenic effects, METH can also cause anxiety, increased agitation, delirium, psychotic states, cognitive and psychomotor impairments, seizures, and death (Wilson *et al.*, 1996;

Lan *et al.*, 1998; Buffenstein *et al.*, 1999; Yui *et al.*, 1999; Simon *et al.*, 2000; Volkow *et al.*, 2001a; London *et al.*, 2004; Dore and Sweeting, 2006). Cerebral vasculitis, cerebrovascular accidents due to hemorrhage or vasospasm, and cerebral edema have also been reported in METH abusers (Chynn, 1968; Salanova and Taubner, 1984). The drug can also cause neurodegenerative changes in the brains of human addicts. These pathological changes include loss of striatal DAT observed in positron emission tomographic (PET) studies (Volkow *et al.*, 2001b; Sekine *et al.*, 2003) and in post-mortem investigations, loss of serotonin transporters (5-HTT) (Sekine *et al.*, 2006), decrease in the levels of DA, serotonin (5-HT) and their metabolites (Wilson *et al.*, 1996). A number of studies have documented that METH can cause long-term damage to presynaptic dopaminergic and serotonergic terminals in rodents (Ricaurte *et al.*, 1980; Wagner *et al.*, 1980b). More recently, it has also been shown that the drug can cause death of cell bodies both *in vitro* (Cadet *et al.*, 1997; Stumm *et al.*, 1999) and *in vivo* (Eisch and Marshall, 1998; Deng *et al.*, 1999; Deng and Cadet, 2000; O'Dell and Marshall, 2000). In what follows, we discuss some of the mechanisms that have been implicated in METH-induced neurodegenerative effects.

**Role of Oxidative Stress in METH-induced Toxicity**
The biochemical actions of the drug depend on its entry into monoaminergic terminals (Berger *et al.*, 1992; Iversen, 2006), followed by entry into monoaminergic vesicle consequent to its interaction with vesicular monoamine transporters (Sulzer *et al.*, 1995). This is followed by displacement of monoamines into the cytoplasm of the terminals and METH-induced monoamine release into respective synaptic clefts (Baldwin *et al.*, 1993; Marshall *et al.*, 1993; Cubells *et al.*, 1994; Sulzer *et al.*, 1995; Schwartz *et al.*, 2006). METH neurotoxicity appears to depend on both, DA released within terminals and on DA released in synaptic clefts (Cadet and Brannock, 1998). These suggestions are supported by reports that DAT knockout mice are resistant to METH-induced degeneration of DA axons (Fumagalli *et al.*, 1998) and by observations that psychostimulant toxicity depends on quinone forma-

tion consequent to increased DA levels within nerve terminals (LaVoie and Hastings, 1999). METH-related quinone formation is thought to be associated with the generation of superoxide radicals and hydrogen peroxide during quinone redox cycling (Stokes *et al.*, 1999; Miyazaki *et al.*, 2006). A role for oxidative mechanisms in the neurotoxic effects of the drug is supported by observations that administration of *N*-acetyl-L-cysteine, ascorbic acid or vitamin E was able to protect against METH-induced destruction of monoaminergic terminals (Wagner *et al.*, 1985; De Vito and Wagner, 1989; Fukami *et al.*, 2004). In addition, selenium and melatonin can also provide protection against METH toxicity (Ali *et al.*, 1999; Imam and Ali, 2000). The participation of superoxide radicals in the neurotoxic effects of METH on DA nerve terminals was tested by injecting METH to transgenic mice that overexpress the human CuZnSOD gene (Cadet *et al.*, 1994a; Hirata *et al.*, 1996; Jayanthi *et al.*, 1998). These mice have much higher CuZnSOD activity than wild-type animals from similar backgrounds (Jayanthi *et al.*, 1998; Jayanthi *et al.*, 1999) and were indeed protected against the toxic effects of the drug. In contrast, inhibition of SOD by diethyldithiocarbamate potentiates the nefarious effects of METH (De Vito and Wagner, 1989). Furthermore, bromocriptine, which scavenges hydroxyl radicals, was also able to attenuate METH-induced DA depletion in mice (Kondo *et al.*, 1994). When taken together, these observations support the notion that DA release caused by METH is accompanied by redox cycling of dopaquinone and consequent formation of oxygen-based radicals such as superoxide radicals. Reports that METH can induce changes in the levels of glutathione (Harold *et al.*, 2000) and of antioxidant enzymes (Jayanthi *et al.*, 1998), increase lipid peroxidation (Jayanthi *et al.*, 1998; Gluck *et al.*, 2001), and induce the formation of protein carbonyls (Gluck *et al.*, 2001) provide further support for the thesis that oxygen-based radicals are involved in METH-induced toxicity (Cadet and Brannock, 1998).

**METH Toxicity and Excitotoxicity**
METH-induced neurotoxicity also appears to occur via excitotoxic damage secondary to glutamate

release and activation of glutamate receptors. Glutamate toxicity is dependent, in part, on the production of nitric oxide (NO) (Dawson and Dawson, 1998; Chung *et al.*, 2005). The idea of the involvement of glutamate in METH toxicity is supported by observations that METH can cause glutamate release in the brain (Nash *et al.*, 1988; Baldwin *et al.*, 1993; Marshall *et al.*, 1993; Abekawa *et al.*, 1994; Mark *et al.*, 2004). In addition, some glutamate antagonists have been shown to attenuate METH-induced dopaminergic toxicity (Sonsalla *et al.*, 1989; Battaglia *et al.*, 2002) (see later discussion on temperature). Glutamate-mediated NO formation appears to also be involved in METH toxicity because knockout mice that are deficient in either neuronal (nNOS) or inducible (iNOS) nitric oxide synthase (NOS) are resistant to drug-induced toxic damage to monoaminergic terminals (Itzhak *et al.*, 1998). These data have solidified the argument for a role of the glutamate/NO pathway in METH neurotoxicity (Itzhak *et al.*, 1998; Imam *et al.*, 2001; Itzhak and Ali, 2006). Finally, various nNOS inhibitors, which do not affect hyperthermia, can also protect against destruction of monoaminergic axons caused by METH administration (Itzhak *et al.*, 2000; Sanchez *et al.*, 2003). In addition to their roles in the damage of monoaminergic terminals, oxygen-based radicals and NO appear to be involved in METH-related cell death because CuZnSOD transgenic mice show partial protection against drug-induced apoptosis (Deng and Cadet, 2000). Moreover, death of rat fetal mesencephalic cells caused by METH treatment was abrogated by the use of NOS inhibitors (Sheng *et al.*, 1996).

**Role of Thermal Instability in METH Toxicity**
There is substantial evidence that hyperthermia participates in METH-induced toxicity on monoaminergic systems. Manipulations that result in higher temperatures cause increases in METH toxicity, whereas those that decrease temperatures have been shown to provide some degree of protection (Bowyer *et al.*, 1994; Miller and O'Callaghan, 1994; Albers and Sonsalla, 1995; Farfel and Seiden, 1995). The potentiative effects of hyperthermia might occur through increased formation of DA-dependent reactive oxygen species. In contrast, there are pharmacological agents that block METH toxicity without influencing the thermal responses in animals. For example, inhibition of nNOS blocks METH toxicity without altering the hyperthermic response (Itzhak *et al.*, 2000; Sanchez *et al.*, 2003). DA uptake blockers also protect in a fashion that appear to be independent of any effects on temperature (Callahan *et al.*, 2001).

In addition to its effects on monoaminergic terminals, METH can also cause cell death. Potential protective effects of various genetic and pharmacological manipulations have been tested in that model. For example, knockout mice that are partially deficient of c-Jun show protection against METH-induced neuronal apoptosis, an effect that is independent of hyperthermia (Deng *et al.*, 2002b). Intracerebral injection of neuropeptide Y (NPY) has recently been shown to cause attenuation of the apoptotic effects of the drug in mice (Thiriet *et al.*, 2005). Because NPY is involved in thermoregulation (Richard, 1995; Levine *et al.*, 2004) and because METH-related increases in body temperature are thought to participate in METH toxicity (Cadet *et al.*, 2003, for review), the possibility that NPY might have prevented drug-induced hyperthermia was tested (Thiriet *et al.*, 2005). NPY was found to attenuate body temperature increases after the second of the four METH injections but not during the later phases of hyperthermia (Thiriet *et al.*, 2005). These observations suggest that NPY-induced protection is, in part, dependent on its effects on body temperature. It appears that METH-related changes in body temperature participate, but are not essential in the manifestations of drug toxicity.

**Microglial Reactions and METH Toxicity**
Microglial cells are the major immunocompetent cells in the brain. They express chemokines, cytokines and their receptors. Under normal conditions, these cells provide extensive and continuous surveillance of their cellular environment (Raivich, 2005). Microglial cells are activated by various types of pathological states including infectious processes (Rock *et al.*, 2004) and neural injuries (Ladeby *et al.*, 2005). This activation includes dramatic changes in appearance, migration to the site of the damage, and phagocytosis of dying and dead cells. Microglia can also produce small signaling molecules, called cytokines, to trigger astrocytes to respond to the injury site. Recently,

reactive microgliosis has been implicated in a number of neurological disorders including Alzheimer's (Xiang *et al.*, 2006) and Huntington's (Sapp *et al.*, 2001) diseases.

Evidence accumulating from several laboratories has recently implicated reactive microglial cells as culprits in the manifestation of METH toxicity. Asanuma *et al.* (2003) reported that the non-steroidal anti-inflammatory drug, ketoprofen, caused protection against METH-induced dopaminergic toxicity and suppressed drug-mediated microgliosis. Thomas and colleagues (2004) subsequently reported that METH caused dose-dependent microglial activation which coincided with DA terminal degeneration. LaVoie *et al.* (2004) have also provided evidence that microgliosis precedes METH-induced pathological states in striatal dopaminergic terminals. More importantly, manipulations such as the use of MK-801 and dextromethorphan which protect against METH toxicity also inhibit microglial activation (Thomas and Kuhn, 2005). In contrast, minocycline has been reported to block microglial activation without providing protection against METH-induced damage (Sriram *et al.*, 2006). Microglial cells might potentiate drug-related damage by releasing toxic substances such superoxide radicals and NO which have already been implicated in METH neurotoxicity (see discussion above). When taken together, these observations suggest that identifying the specific role that microglial cells play in DA terminal degeneration might help to develop specific therapeutic approaches for patients who have been exposed to METH.

## Involvement of AP-1 Related Transcription Factors in METH-induced Neurotoxicity

The accumulated evidence had suggested that some effects of oxygen-based radicals might be mediated by activation of AP-1 transcription factors (Dalton *et al.*, 1999). Tests for the possibility that METH toxicity might also be associated with variations in the expression of these proteins have revealed changes in the expression of a number of AP-1 related genes within 2 hours after drug administration (Cadet *et al.*, 2001). These include up-regulation of c-jun, c-fos, jun B, as well as jun D (Cadet *et al.*, 2001). These changes are probably related to METH-induced generation of free radi-

cals. ROS such as hydroxyl and superoxide radicals can induce the expression of many genes via their regulation of AP-1 transcription factors (Dalton *et al.*, 1999). The role for c-fos in METH-induced neuropathological changes has been confirmed by using c-fos +/- mice which show increased degeneration of DA terminals and increased cell death after psychostimulant treatment (Deng *et al.*, 1999). These observations suggest a protective role for c-fos against METH damage. Some of the factors that might be involved in causing this partial protection include integrins that belong to cell adhesion receptors and are also involved in the regulation of signal transduction (Gilcrease, 2006). This idea is supported by the evidence of decreased basal levels of integrin expression in c-fos +/- mice and the further reduction of these receptors in response to toxic doses of METH (Betts *et al.*, 2002). This conclusion is further supported by the observations that integrins can promote cell survival after injury and apoptotic insults via signaling through the PI3K-Akt pathway which leads to BAD phosphorylation, therefore reducing BAD ability to block the anti-apoptotic effects of Bcl-2 (Martin and Vuori, 2004; Gilcrease, 2006). In contrast, inhibition of integrins increases apoptotic cell death (Martin and Vuori, 2004; Gilcrease, 2006).

Because c-jun knockout mice show partial protection against the adverse effects of METH (Deng *et al.*, 2002b), it is likely that c-jun is involved in the pro-death effects of the drug. Moreover, because the c-jun knockout mice and their wild-type counterparts show similar degree of METH-induced dopaminergic toxicity, c-jun appears to only be involved in the mediation of neuronal apoptosis in cells postsynaptic to DA terminals.

## Role of DNA Damage in METH-induced Toxicity

As mentioned above, METH has been shown to cause neuronal apoptosis in several brain regions (Deng *et al.*, 2001). Because apoptosis is associated with DNA damage, it was thought possible that administration of the drug might trigger responses meant to repair the METH-induced DNA damage. Microarray analyses have indeed revealed that METH administration caused changes in the expression of several genes that participate in DNA repair processes (Cadet *et al.*, 2002). These changes

are probably related to METH-induced prooxidant states because oxidative stress can cause single and double DNA strand breaks (Li and Trush, 1993). These breaks can be repaired via base excision repair (BER), nucleotide excision repairs (NER), mismatch repair (MMR), and DNA damage reversal (Petit and Sancar, 1999; Hsieh, 2001; Nilsen and Krokan, 2001). Thus, the observations that METH treatment can cause upregulation of APEX, PolB, and LIG1 suggest that these changes might be compensatory increases aimed at counteracting METH-mediated ROS-induced DNA damage through the BER pathway. If the psychostimulant can cause similar DNA damage in humans, these observations might offer a partial explanation for the developmental abnormalities observed in babies born of METH abusing mothers (Smith *et al.*, 2006).

## Involvement of Mitochondrial Death Pathway in METH-induced Apoptosis

Another interesting group of proteins that are differentially regulated by METH includes Bcl-2 family (Stumm *et al.*, 1999; Cadet *et al.*, 2001; Jayanthi *et al.*, 2001). Specifically, METH caused upregulation of pro-apoptotic proteins, BAX and BID, and downregulation of the anti-death proteins, Bcl-2 and Bcl-X$_L$. The changes in pro-death proteins are consistent with observations that METH administration is associated with release of mitochondrial contents into the cytosol (Deng *et al.*, 2002a; Jayanthi *et al.*, 2004). These include cytochrome *c* and apoptosis inducing factor (AIF). When taken together with the recent *in vitro* demonstration that METH can cause release of cytochrome *c* from mitochondria, activation of caspases 9 and 3, as well as activation of DFF40 and its transit to the nucleus (Deng *et al.*, 2002a), the *in vivo* data implicate a formal role of mitochondria in METH-induced neuronal degeneration. Other factors released from mitochondria such as Smac/DIABLO, endonuclease G, and AIF also participate in dismantling cells during apoptosis (Ravagnan *et al.*, 2002). These proteins, including AIF and Smac/DIABLO, have now been shown to be involved in METH-induced apoptosis (Jayanthi *et al.*, 2004). Their release is followed by activation of caspase 3 and the breakdown of several structural cellular proteins (Jayanthi *et al.*, 2004). Thus, these observations implicate the mitochondrial death pathway as a major player in METH-

related cell death in the rodent brain (Cadet *et al.*, 2005). This suggestion is supported by the fact that overexpression of Bcl-2 can protect against drug-induced apoptosis (Cadet *et al.*, 1997).

## Involvement of the Endoplasmic Reticulum (ER)-dependent Death Pathway in METH-induced Apoptosis

In addition to its effects on mitochondria, METH-induced oxidative stress appears to also cause dysfunctions of other organelles such as the endoplasmic reticulum (ER) (McCullough *et al.*, 2001). The ER helps to maintain cellular homeostasis by regulating calcium signaling (Ferri and Kroemer, 2001). Dysregulation of intracellular calcium homeostasis can cause ER stress and ER-mediated apoptosis (Paschen, 2001). ER stress and calcium dysregulation appear to participate in METH-induced cell death because apoptotic doses of the drug can cause activation of calpain, a calcium-responsive cytosolic cysteine protease (Murachi *et al.*, 1980), which is involved in ER-dependent cell death (Nakagawa and Yuan, 2000). A role for the ER in METH toxicity is supported by the fact that apoptotic doses of METH (Jayanthi *et al.*, 2004) also influence the expression of proteins, such as caspase-12, GRP78/BiP (glucose-regulated protein/immuno-globulin heavy chain binding protein) and CHOP/GADD153 (C/EBP homology protein/ growth arrest and DNA damage 153) that participate in ER-induced apoptosis (Zinszner *et al.*, 1998). The observed ER stress in METH-induced neurotoxicity might be secondary, in part, to direct effects of the psychostimulant (Asanuma *et al.*, 2000), to METH-mediated oxidative stress (Cadet *et al.*, 1994a; Cadet and Brannock, 1998; Jayanthi *et al.*, 1998), and to shifts in BAX/Bcl-2 ratios induced by the drug (Jayanthi *et al.*, 2001).

## Involvement of the Fas/Fas Ligand Death Pathway in METH-induced Apoptosis

In addition to the mitochondrial death pathway, cell death can occur consequent to activation of Fas receptors by Fas ligand (FasL) (Barnhart *et al.*, 2003; Choi and Benveniste, 2004). FasL (TNFSF6) (Li-Weber *et al.*, 1999; Li-Weber and Krammer, 2002; Droin *et al.*, 2003) is a member of the TNF superfamily of cytokines (Locksley *et al.*, 2001) and is involved in causing apoptosis in various models
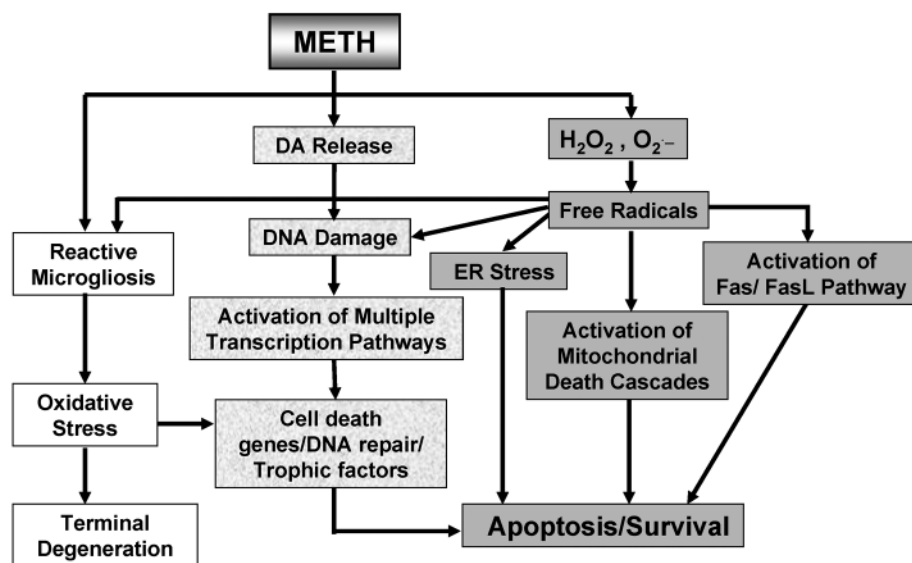
FIGURE 2    METH-regulated molecular events that lead to neuronal apoptosis and terminal degeneration in the striatum. This figure summarizes findings of the various papers that have addressed the issue of METH-induced neurotoxicity in the mammalian brain. The data indicate that oxidative mechanisms and cell death pathways are involved in the manifestation of METH toxicity.

of neuronal injury (Qiu *et al.*, 2002). METH was shown to increase the expression of FasL (Jayanthi *et al.*, 2005; reviewed in Cadet *et al.*, 2005). It was also shown that METH can induce cleavage of caspase 8, which is a known participatant in the Fas death pathway (Nagata, 1999).

We have summarized these molecular mechanisms in a theoretical scheme that represents the sequence of events leading to METH-induced neuronal apoptosis and terminal degeneration (Fig. 2).

## METHYLENEDIOXYMETHAMPHETAMINE (MDMA, Ecstasy)

3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy) is an abused ring-substituted phenyl-iso-propylamine that is related to both amphetamines and hallucinogens (McKenna and Peroutka, 1990). MDMA effects which include increased locomotor activity (Matthews *et al.*, 1989) are thought to be mediated, in part, by the release of 5-HT (Liechti *et al.*, 2000) and subsequent stimulation of its receptors (Bankson and Cunningham, 2001). In addition to MDMA behavioral effects, the drug is known to cause marked decreases in markers of 5-HT terminals (White *et al.*, 1996). Specifically, levels of 5-HT and its metabolite, 5-hydroxyindoleacetic acid

(5-HIAA) (Colado and Green, 1994), tryptophan hydroxylase (TPH) activity (Stone *et al.*, 1987) and the number of 5-HT uptake sites (see Lyles and Cadet, 2003) are all decreased after MDMA administration. MDMA can also cause cell death in some *in vitro* models (Simantov and Tauber, 1997; Stumm *et al.*, 1999).

## MDMA Neurotoxicity in Animals and Humans

Neurochemical and anatomical studies have shown that MDMA can cause long-term abnormalities in 5-HT systems of rodents (Schmidt *et al.*, 1986; Stone *et al.*, 1986; Commins *et al.*, 1987; Schmidt, 1987; O'Hearn *et al.*, 1988; Molliver *et al.*, 1990). These include decreased levels of 5-HT and its major metabolite, 5-HIAA (Commins *et al.*, 1987; Schmidt *et al.*, 1987; Schmidt, 1989; Molliver *et al.*, 1990), decreased number of 5-HTT (Battaglia *et al.*, 1987; Commins *et al.*, 1987; De Souza *et al.*, 1990), and decreased activity of the rate-limiting enzyme of 5-HT synthesis, TPH (De Souza *et al.*, 1990; Molliver *et al.*, 1990). These changes occur in the rodent neocortex, striatum, and hippocampus (Battaglia *et al.*, 1987; Slikker *et al.*, 1988; De Souza *et al.*, 1990; Molliver *et al.*, 1990). These abnormalities are reported to last for months or even years after drug administration (Battaglia

*et al.*, 1988; Scanzello *et al.*, 1993; Fischer *et al.*, 1995; Lew *et al.*, 1996; Sabol *et al.*, 1996; Hatzidimitriou *et al.*, 1999).

Similar adverse effects have been reported in non-human primates (Ricaurte *et al.*, 1988a,b; Slikker *et al.*, 1988; Insel *et al.*, 1989; Scheffel *et al.*, 1998; McCann *et al.*, 2000). There are dose-dependent reductions in 5-HT concentrations in the cortex, caudate nucleus, putamen, hippocampus, hypo-thalamus and the thalamus (Ricaurte *et al.*, 1988b). Reduced 5-HT levels were evident for up to seven years following exposure to the drug (Scheffel *et al.*, 1998; Hatzidimitriou *et al.*, 1999). The MDMA-induced deficits in nonhuman primates are also reflected in the levels of 5-HIAA in the cerebro-spinal fluid (CSF) (Ricaurte *et al.*, 1988a; Insel *et al.*, 1989). Living baboons treated with MDMA (5 mg/kg s.c., 2 X daily, 4 days) also show marked and prolonged decreases in 5-HTT density measured by PET imaging of (+)[$^{11}$C]McN-5652, a radioligand that selectively binds to the 5-HTT (Scheffel *et al.*, 1998). Brain tissues from these animals (sacrificed 3 weeks after the last PET and 13 months after MDMA administration) showed marked loss of 5-HT terminals (Scheffel *et al.*, 1998).

A number of investigators have also tested the pos-sibility that MDMA can cause degenerative effects in the human brain (Ricaurte *et al.*, 1988a; 1990; Price *et al.*, 1989; McCann *et al.*, 1994; 1998a; 1999; Bolla *et al.*, 1998; Semple *et al.*, 1999; Gerra *et al.*, 2000; Kish *et al.*, 2000; Buchert *et al.*, 2001). Some of these studies have concluded that MDMA is also toxic to humans because CSF 5-HIAA lev-els are reduced in MDMA abusers (Ricaurte *et al.*, 1988a; 1990; McCann *et al.*, 1994; 1999; Bolla *et al.*, 1998). PET imaging studies, using [$^{11}$C]McN-5652 to selectively label 5-HTT, have reported significant differences in 5-HTT binding in MDMA abusers compared to non-MDMA users (McCann *et al.*, 1998a). 5-HTT sites were decreased in a manner that correlated with the extent of abuse (McCann *et al.*, 1998a; Ricaurte *et al.*, 2000). In a similar study, using [$^{123}$I]β-CIT, Reneman *et al.* (2001) investigated the effects of ecstasy abuse on the density of cortical 5-HTT. They also found decreases in cortical 5-HTT in recent MDMA abus-ers. However, there were no significant reductions in ecstasy abusers who had not used the drug in the past year or longer (Reneman *et al.*, 2001).

The biochemical and molecular bases of MDMA-induced neurotoxicity are being actively investigat-ed. These pathways are thought to involve the for-mation of toxic MDMA metabolites, temperature dysregulation, dopamine-based quinone formation, and excitotoxic events.

**Formation of Toxic Metabolites**

MDMA metabolites, which generate free radicals, associated oxidative stress, and membrane dam-age, are thought to be involved in drug-induced neurodegeneration (Paris and Cunningham, 1992; Colado and Green, 1995). This idea is supported by observations that subcutaneous administration of MDMA metabolites, MeDA and HMA can cause decreases in 5-HT concentrations in the frontal cortex (Yeh and Hsu, 1991), although this line of research has remained controversial. The formation of hydroquinones, quinones and the subsequent generation of superoxides and hydrogen peroxide might be important to the manifestation of MDMA toxicity. These ideas are supported by the obser-vations that the spin trap reagent and free radical scavenger, α-phenyl-*N-tert*-butyl nitrone (PBN), prevented MDMA-induced toxicity (Colado and Green, 1995). In addition to MDMA metabolites, the participation of a toxic metabolite of 5-HT has also been invoked because the drug causes marked increases in 5-HT release (Gudelsky and Nash, 1996; O'Shea *et al.*, 2005; Amato *et al.*, 2006).

DA-induced quinone formation is also one pos-sible cause of MDMA toxicity. This suggestion is supported by the fact that MDMA elicits DA release (Shankaran and Gudelsky, 1998; Amato *et al.*, 2006). In addition, destruction of DA terminals by injections of 6-hydroxydopamine protects against MDMA toxicity (Schmidt *et al.*, 1990). In contrast, pretreatment with L-DOPA, which increases DA levels, exacerbates MDMA toxicity (Schmidt *et al.*, 1990). Thus, DA, which is released by MDMA into synaptic clefts, might be taken up by 5-HT terminals where it is converted into quinone by-products that damage 5-HT terminals (Schmidt and Kehne, 1990; Sprague and Nichols, 1995). It is important to point out that the DA hypothesis does not account for the fact that MDMA can damage 5-HT terminals in areas of the brain such as the hippocampus (Shankaran and Gudelsky, 1998) that are almost devoid of DA terminals and for the fact
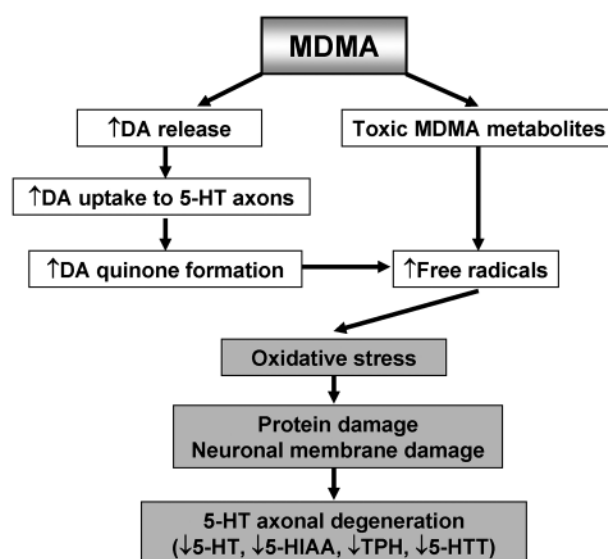
FIGURE 3   Mechanisms implicated in MDMA-induced 5-HT terminal degeneration. The schematic diagram shows that formation of toxic MDMA metabolites, DA quinones and oxidative stress may underlie MDMA toxicity towards 5-HT terminals in the brain.

that, in almost all animal species, except for mice (Cadet *et al.*, 1995), MDMA toxic effects appear to involve 5-HT systems. There is also molecular evidence for the involvement of a number of metabolic pathways in MDMA-induced neurotoxic damage to the brain. Using techniques of microarray analyses, it has been shown that MDMA administration influences the expression of several genes that code for proteins that are involved in metabolism and stress responses (Thiriet *et al.*, 2002). These changes in expression include increases in mRNA levels for Gpx-1 and heme oxygenase (Thiriet *et al.*, 2002). Because MDMA is metabolized via pathways that can induce the formation of superoxides and peroxides via redox-cycling (Cadet *et al.*, 1994b; 1995, Buchert *et al.*, 2001), the changes in these enzymes might constitute compensatory responses to incipient oxidative damage. A schematic diagram of MDMA-induced events that might cause degeneration of 5-HT terminals is presented in Fig. 3.

## Possible Role of Glutamate and Nitric Oxide in MDMA-induced Toxicity

Glutamate is a neurotransmitter that can cause cell death both *in vitro* and *in vivo* (Dawson and Dawson, 1998). It has been suggested that glutamate might also be involved in MDMA toxicity (Atlante *et al.*, 2001; Battaglia *et al.*, 2002; Stewart *et al.*, 2002). For example, blockade of NMDA receptors with the antagonist, MK-801, was able to provide some protection against MDMA-induced 5-HT depletion (Farfel *et al.*, 1992; Colado *et al.*, 1993; Atlante *et al.*, 2001; Battaglia *et al.*, 2002; Stewart *et al.*, 2002), although MK-801 had no effect on drug-related decreases in TPH activity (Johnson *et al.*, 1989). The role of NO in MDMA toxicity also has been investigated in rats. It has been reported that NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthase, protects against the neurotoxic effects of MDMA via a mechanism that involves temperature regulation *in vivo* (Taraska and Finnegan, 1997).

## Role of Hyperthermia in MDMA Neurotoxicity

The amphetamines, including MDMA, are known to cause hyperthermic responses (Nash *et al.*, 1988; Gordon *et al.*, 1991; Dafters, 1995; Dafters and Lynch, 1998). A number of drugs that attenuate MDMA toxicity also prevent the marked drug-induced hyperthermia. Specifically, 5-HT$_2$ receptor antagonists that block the hyperthermic response also protect from MDMA toxicity (Nash *et al.*, 1988). Morever, preventing the hypothermic responses produced by ketanserin also abolished its protective effects (Malberg *et al.*, 1996). In contrast, some agents, such as fluoxetine, that provide protection against MDMA neurotoxicity do not block the MDMA-induced temperature increase (Nash

*et al.*, 1988; Mechan *et al.*, 2002). The evidence suggests that hyperthermia might be a member of a complex set of events that paprticipate in the toxic cascades caused by the drug.

It is interesting to note that interactions between the hypothalamic-pituitary-thyroid axis and sympathetic nervous system might be involved in MDMA-related hyperthermic responses (Sprague *et al.*, 2003). For example, removal of either the pituitary or thyroid glands was shown to prevent hyperthermia produced by drug treatment (Sprague *et al.*, 2003). In addition, the use of antagonists of α1 and β3 adrenergic receptors was able to attenuate MDMA-induced temperature increase when used alone and could abolish the thermic response when the drugs were co-administered (Sprague *et al.*, 2003; 2005). Of further interest is the report that the skeletal muscle uncoupling mitochondrial protein 3 (UCP-3) is also involved in mediating MDMA-mediated hyperthermia because UCP-3-deficient mice treated with the drug showed blunted hyperthermic responses (Mills *et al.*, 2003).

## CONCLUDING REMARKS

The amphetamines have a long history of illicit use among the various classes in societies around the world. The abuse of these drugs has continued unabated inspite of the documentation of the clinical and basic toxicology. In this review, we have presented evidence that oxidative and excitotoxic mechanisms, hyperthermic responses, and other metabolic processes are involved in causing the neurodegenerative effects of AMPH, METH and MDMA. In addition, both AMPH and METH have now been shown to cause cell death in various regions of the rodent brain via mechanisms that involve mitochondrial pathways. Moreover, METH-induced neuronal apoptosis appears to also be dependent on the activation of caspase-12 through the endoplasmic reticulum (ER) death pathway. More recently the Fas/FaL receptor-mediated cell death mechanisms were also shown to be involved in METH toxicity. Microarray analyses have also documented the involvement of molecular pathways that were not initially thought to participate in mediating the effects of these drugs. Thus, modern neurobiological techniques are offering more information on the nefarious effects of

these drugs. It is hoped that this review will provide a substratum for other investigators to build upon.

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