

## Critical Review

# Methamphetamine and MDMA (Ecstasy) Neurotoxicity: 'of Mice and Men'

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### Summary

Methamphetamine (METH) and 3,4-methylendioxy-methamphetamine (MDMA; 'ecstasy') are currently major drugs of abuse. One of the major concerns of amphetamines abuse is their potential neurotoxic effect on dopaminergic and serotonergic neurons. Although data from human studies are somewhat limited, compelling evidence suggests that these drugs cause neurotoxicity in rodents and primates. Recent studies in transgenic and knockout mice identified the role of dopamine transporters, nitric oxide, apoptotic proteins, and inflammatory cytokines in amphetamines neurotoxicity. Further research into the mechanisms underlying the dopaminergic and serotonergic neurotoxicity and the behavioral corollaries of these neuronal insults could facilitate our understanding of the consequences of human abuse of METH and MDMA on cognition, drug-seeking behavior, extinction and relapse.

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### INTRODUCTION

Methamphetamine (METH) and 3,4-methylendioxy-methamphetamine (MDMA; 'ecstasy') are derivatives of amphetamine, which act as potent psychostimulants in the central nervous system (CNS), and in recent years they became major drugs of abuse. The recreational use of METH has increased particularly in the Midwest and the West Coast of the US. MDMA gained enormous popularity among adolescents and young adults in 'rave' parties throughout the world (known as a 'club drug'). For instance, in a survey of 70

attendees of a 'club rave' in the Baltimore-Washington DC area, 86% reported lifetime ecstasy use, 51% reported use within 30-days, and 30% reported having used ecstasy within the 48 h preceding the interview (1). A survey of 3500 visitors of 'techno parties' in seven European capital cities revealed substantial polydrug use of such diverse substances as ecstasy, amphetamine, cocaine and cannabis (2). A study of drug-using behavior of > 3000 10th graders in the US showed that 7% had lifetime ecstasy use, 5% had used within the past year and 2% within the previous 30 days (3). Repeated use of substituted amphetamines leads to severe addiction to the drugs, violent and psychotic behavior, anxiety and depression (4).

In addition to the physiological and psychological complications associated with amphetamines abuse, evidence from animal and human studies suggests that long-term and/or a high dose of amphetamines exposure cause neuronal damage. The intent of this brief review is to highlight the evidence supporting the development of amphetamines neurotoxicity in the mouse model and the implications of this model for better understanding of the mechanisms underlying neurotoxicity and the functional consequences of the neurotoxic insults. Yet, allusion is made to human studies which suggest that cognitive impairment in METH and MDMA abusers may be related to depletion of dopaminergic and serotonergic markers. Given the concise nature of this review, the reader is referred to several other recent reviews focused on METH (5–8) and MDMA (9) neurotoxicity in various species including, mice, rats and nonhuman primates. Throughout this manuscript the terms 'neurotoxicity' and 'depletion' of dopamine (DA) and 5-hydroxytryptamine (5-HT; serotonin) markers (neurotransmitters and transporters) are used interchangeably. However, it should be noted that 'neurotoxicity' is usually identified as cell death or loss of presynaptic nerve terminals, and an increase in the expression of glial fibrillary acidic protein (GFAP), which is a marker of gliosis. 'Depletion' is related to reversible or partially reversible, albeit long lasting, decline of

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monoamines and their transporters. Currently, it remains inconclusive whether the toxic effects of METH and MDMA are permanent or merely long lasting. The term *amphetamines* is used to denote a group of amphetamine analogs.

## EVIDENCE FOR NEUROTOXICITY

Amphetamines act as ‘false neurotransmitters’; they are transported into the cytoplasm by presynaptic transporters and then occupy the vesicular monoamine transporter (VMAT2) causing an increase in extra-vesicular cytosolic DA/5-HT levels. This increase in transmitter’s concentration reverses the transport of the transmitter into the extracellular space (10). It is likely that the rewarding effect of amphetamines is dependent on the balance between their influence on DA and 5-HT transmission; increase in synaptic DA but not 5-HT is apparently responsible for the incentive value of the drug. Thus, while most amphetamines cause neurotoxicity not all amphetamine analogs have the potential for abuse. For instance, fenfluramine (FEN) is an anorectic agent that was used in combination with phentermine (PHEN) to treat obesity (i.e., FEN/PHEN), and par-chloroamphetamine (PCA) has neither therapeutic use nor abuse potential. Both drugs, however, influence primarily 5-HT transmission and are known to cause loss of 5-HT axon terminals in forebrain regions of rodents (11). Given that increase in GFAP expression is considered a marker of gliosis, most studies suggest that toxic doses of METH and MDMA, but not FEN, increase GFAP expression (e.g., (12)). This review is primarily focused on the toxic effects of METH and MDMA as they represent two of the most popular abused psychostimulants.

### Human studies

Several lines of evidence suggest that depletion of dopaminergic and serotonergic markers are associated with cognitive impairments in human amphetamine abusers. Positron emission tomography (PET) studies in METH abusers showed a significant reduction in the density of the DA transporter (DAT) in the caudate (28%) and putamen (21%); this reduction was associated with motor slowing and memory impairment (13). A study that recruited 8-month-abstinent METH users found deficits in working memory tasks compared to matched controls. Perfusion magnetic resonance imaging (pMRI) studies of these subjects showed an increase in regional cerebral blood flow (rCBF) in several parietal regions and a decrease in rCBF in putamen regions, changes which are indicative of neuronal damage (14). Depletion of serotonergic markers in human MDMA users was correlated with the degree of drug use and cognitive impairments (15). Cognitive deficits were identified in 19, 52 and 73% of novice, moderate and heavy ecstasy users, respectively; these deficits were attributed to hippocampal and pre-frontal cortex dysfunction as a result of drug use (16),

although in this study there was no evidence for serotonergic neurotoxicity due to MDMA abuse.

It appears that there is relatively more evidence to support METH-induced neurotoxicity than MDMA-induced neurotoxicity in humans. While this disparity could arise from the diverse pharmacological effects of METH and MDMA on monoamines, it could also be a result of the different patterns of METH and MDMA abuse. METH is frequently abused by individuals in their familiar environment, and in somewhat regularly spaced intervals, similar to the abuse pattern of cocaine. Ecstasy is usually taken by individuals in large groups and in a novel environment (e.g., dance parties). The context of drug administration (familiar vs. novel) and the stimuli associated with a specific context may weaken or potentiate the pharmacological effects of the drug. For instance, a stressful environment, such as in ‘rave’ parties, may weaken MDMA neurotoxicity, while elevated ambient temperature due to a crowded environment may potentiate the neurotoxic effect of MDMA. Studies in rodents have demonstrated that stress may reduce amphetamines neurotoxicity (12), whereas elevated ambient temperature is known to facilitate amphetamines neurotoxicity (12, 17). Furthermore, many ecstasy pills contain other substances in addition to MDMA, some of which may cause neuroprotection and therefore reduce the neurotoxic effect of MDMA ((18), see below). Thus, there are multiple explanations why MDMA neurotoxicity may be less apparent than METH neurotoxicity in humans.

While serotonergic depletion may cause depression, the major concern of dopaminergic neurotoxicity is the potential development of Parkinsonism in humans abusing MDMA/METH. The latter issue remains particularly controversial with regard to ecstasy abuse; it was argued that there is no direct evidence linking MDMA abuse to Parkinson’s disease, and that some of the methods and criteria employed to determine monoamines’ depletion in human studies were inadequate (19). Regardless, it is important to note that the depletion of monoamines caused by amphetamines is usually significantly lower than the depletion of DA observed in Parkinson’s disease (e.g., 90–95%). Therefore, a reasonable concern with human METH and/or MDMA abuse is whether *subtle neurotoxicity* might render the organism more susceptible to future neurodegenerative disorders, such as Parkinson’s disease.

There are at least two inherent problems with clinical studies on the effects of amphetamines on brain neurochemistry and function that should be pointed out. First, human ecstasy users frequently practice poly-drug abuse (alcohol, cannabis, cocaine), and it is difficult to delineate the specific effects of MDMA. Second, most ecstasy pills contain a mixture of various drugs, and the quantity of MDMA in a pill may range from 19 to 140 mg. Other drugs mixed into the ecstasy pills may include ketamine, dextromethorphan, amphetamine, METH, ephedrine and salicylates (18). While the combination of MDMA and other amphetamine analogs

may exacerbate neurotoxicity, ketamine and dextromethorphan can attenuate neurotoxicity by blockade of N-methyl-D-aspartate (NMDA) type of glutamate receptors which is known to afford neuroprotection. Given the limitations of clinical studies, animal models of METH- and MDMA-induced neurotoxicity in laboratory-controlled conditions are necessary in order to eliminate the influence of poly-drug use and social environment on the pharmacological effects of amphetamines. Furthermore, the animal model of amphetamine-induced neurotoxicity enables selective DA and 5-HT lesions, thereby isolating the consequences of injury to individual monoamine systems.

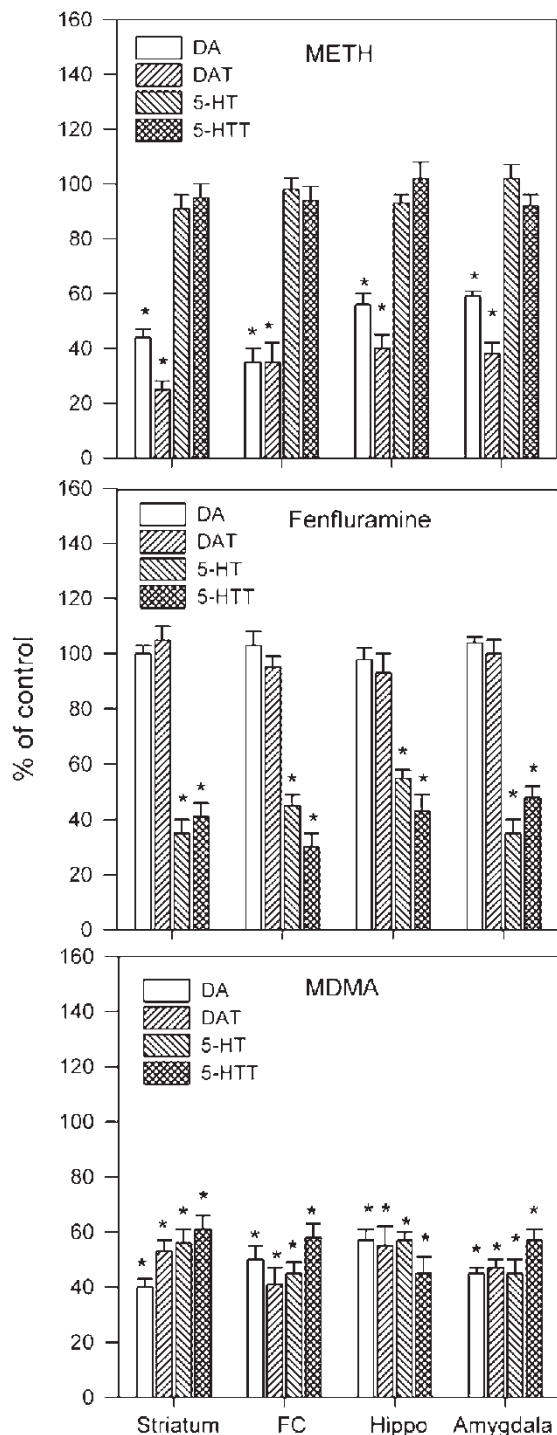
### **Animal studies**

Frequently, there are two major concerns about the clinical relevance of animal studies on amphetamines neurotoxicity, as often there is a disparity between rodent and human exposure to these drugs. The first concern is that most rodent studies employ an acute regimen of a high dose of amphetamine that is given within a period of 8–72 h, whereas the human pattern of drug use extends over weeks, months and years. However, the use of the ‘acute’ model of neurotoxicity in rodents is relevant to the final outcome – the neurotoxic insult that may occur following drug exposure, although the pattern of drug abuse may influence the *degree* of neurotoxic damage. Nevertheless, the ‘acute’ model of rodents may resemble to some extent the binge pattern of drug use by human. The second concern is that the dosage of amphetamines given to rodents may exceed the dosage abused by humans. This practice may be due to the differential ‘sensitivity’ of rodents and humans to various psychoactive drugs. For instance, physiologically effective doses of opiate analgesics (e.g., morphine) and sedative hypnotics (e.g., benzodiazepines) in mice and rats could be 10–20-fold higher than the effective dose in humans. Likewise, the psychomotor stimulating and rewarding effect of cocaine in mice and rats is observed at doses far above that abused by humans. These differences may be due to diverse pharmacokinetics and pharmacodynamics of the drug in rodents and humans. One noticeable example is the pharmacokinetics of METH: the  $t_{1/2}$  of METH in rats is  $\sim 70$  min and in humans it is  $\sim 70$  h. Thus, it is not unusual that the regimen of amphetamines required to attain neurotoxicity in rodents is different than that which might cause neurotoxicity in humans. It is difficult to directly compare the rodent and human dosages that cause neurotoxicity because consideration should be given to the contributions of poly-drug use and environmental stimuli that might modulate the pharmacological effects of the drug in human but not in rodents in a controlled laboratory environment.

Initial reports on the neurotoxic potential of METH on dopaminergic neurons came from studies in rats (20) and monkeys (21). Anatomical evidence supporting the neurotoxic effects of METH stems from studies showing that a high dose of METH given to rats caused degeneration of DA nerve

fibers, loss of tyrosine hydroxylase, DA transporter, tryptophan hydroxylase, and loss of 5-HT-immunoreactive axons and axon terminals (5, 6, 22). Most studies agree that METH is damaging striatal DA nerve terminals but is sparing DA cell bodies in substantia nigra, pars compacta, and ventral tegmental area (6). METH neurotoxicity is long lasting; dopaminergic deficits were observed for up to 52 weeks in rats, and serotonergic deficits persisted for several years in monkeys following administration of high doses of METH (23). While METH causes dual dopaminergic/serotonergic neurotoxicity in rats and primates, MDMA causes primarily serotonergic neurotoxicity in rats (9) and monkeys (6). However, in mice, MDMA causes primarily dopaminergic neurotoxicity (12, 24). The extent of dopaminergic and serotonergic neurotoxicity caused by amphetamine analogs depends on several factors including: (a) specific amphetamine analogs, (b) animal species (24), (c) mouse strain (8), (d) dosage and frequency of drug administration (e.g., (25)), and (e) the ambient temperature of drug administration and the thermoregulatory effect of the drug (12, 17).

In our laboratory, we aimed to develop a mouse model of selective DA and 5-HT neurotoxicity, and found that Swiss Webster mice are particularly useful for this purpose. For instance, administration of METH ( $5 \text{ mg kg}^{-1} \times 3$ ; 3 h apart) to Swiss Webster mice caused selective depletion of striatal DA, DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and DAT binding sites, with no evidence of 5-HT depletion (26). Administration of fenfluramine ( $25 \text{ mg kg}^{-1} \times 2$ ; 6 h apart; for 2 days) caused selective depletion of 5-HT and 5-HT transporter (5-HTT) binding sites in striatum, frontal cortex and hippocampus with no evidence of dopaminergic neurotoxicity (27). However, administration of MDMA ( $15 \text{ mg kg}^{-1} \times 2$ ; 8 h apart, for 2 days) caused marked depletion of striatal DA and DAT binding sites as well as depletion of 5-HT in the striatum and hippocampus, and depletion of 5-HTT binding sites in the frontal cortex. The depletion of striatal DAT and frontocortical 5-HTT binding sites in mice was long-lasting as it was observed 82 days following exposure to MDMA (24). More recently, we found that administration of MDMA ( $15 \text{ mg kg}^{-1} \times 2$ ) for 3 days instead of 2 days caused a larger decrease in serotonergic markers in the striatum, frontal cortex, hippocampus and amygdala of Swiss Webster mice (Fig. 1). The results summarized in Fig. 1 show that selective dopaminergic and serotonergic neurotoxicity can be achieved with the appropriate doses of METH and fenfluramine, respectively, while dual dopaminergic/serotonergic neurotoxicity can be attained with the suitable regimen of MDMA administration to Swiss Webster mice. The significance of these models is two-fold. First, it allows investigation of mechanisms involved in each neurotoxic insult, and second, it could facilitate the study of the functional significance (e.g., behavioral outcome) of each insult. The dual dopaminergic/serotonergic injury caused by MDMA in mice is a practical



**Figure 1.** Levels of dopamine (DA), DA transporter (DAT), 5-hydroxytryptamine (5-HT) and 5-HT transporter (5-HTT) in striatum, frontal cortex (FC), hippocampus (Hippo) and amygdala of Swiss Webster mice. Animals were treated with either saline, METH ( $5 \text{ mg kg}^{-1} \times 3$ ), fenfluramine ( $25 \text{ mg kg}^{-1} \times 2$ , for 2 days) or MDMA ( $15 \text{ mg kg}^{-1} \times 2$ , for 3 days) and were sacrificed 3 days later for the assessment

model of dopaminergic and serotonergic depletion that might develop in humans abusing both METH and MDMA.

### MECHANISMS OF NEUROTOXICITY

Numerous studies have focused on elucidating the mechanism(s) underlying the neurotoxicity of substituted amphetamines. It appears that multiple neurotransmitters, free radicals, apoptotic proteins and inflammatory cytokines all contribute to the development of neurotoxicity. Evidence suggested that the massive increase in synaptic concentration of DA and 5-HT following amphetamines administration to rats produces toxic metabolites, such as 6-hydroxydopamine (6-OHDA) and 5,7-dihydroxytryptamine (5,7-DHT), respectively (23), which are known to abrogate DA and 5-HT neurons, respectively. However, there are two curiosities with this hypothesis. First, 6-OHDA and 5,7-DHT are known to cause damage to both nerve terminals and cell bodies, while most studies reported that amphetamines do not destroy cell bodies. Second, recent studies showed that severe depletion ( $\sim 95\%$ ) of vesicular and cytoplasmic DA from mouse brain did not prevent METH-induced dopaminergic neurotoxicity (28). Other studies suggest that the expression of the DAT is essential for the development of dopaminergic neurotoxicity, while the absence of the vesicular monoamine transporter (VMAT2) exacerbates dopaminergic neurotoxicity. Homozygote DAT ( $-/-$ ) mice were protected against METH neurotoxicity (29), and heterozygous VMAT2 ( $+/-$ ) mice were more sensitive to METH neurotoxicity than wild-type mice (30). These findings imply that (a) DAT is required for the reuptake of DA and/or a specific 'neurotoxin' from extracellular space into the cytoplasm for the expression of neurotoxicity, and (b) VMAT2 is required to eliminate DA from the cytoplasm and to 'protect' against neurotoxicity.

The involvement of the excitatory amino acid glutamate in METH neurotoxicity stems from studies showing the protective effects of the noncompetitive NMDA receptor antagonist, MK-801 (31) as well as the noncompetitive metabotropic glutamate (mGlu5) receptor antagonist (32) against METH-induced dopaminergic neurotoxicity in mice. While the protective effect of MK-801 may be partially due to its ability to reduce METH-induced hyperthermia (12), the protective effect of the mGlu5 receptor antagonist was independent of thermoregulation.

Increasing evidence now suggests the involvement of free radicals and specifically reactive oxygen species (ROS) in the

of neurotoxicity. METH and fenfluramine caused selective depletion of DA/DAT and 5-HT/5-HTT, respectively; MDMA caused depletion of DA, DAT, 5-HT and 5-HTT.  $*P < 0.05$  compared to control values (100%). Data depict representative results from references (24, 26 and 27).

neurotoxic effects of METH (5, 7) and MDMA (9). Peroxynitrite ( $\text{ONOO}^-$ ) is formed from the interaction between nitric oxide (NO) and superoxide radicals, and is considered a major neurotoxin (33). Inactivation of tyrosine hydroxylase and the DAT by peroxynitrite are thought to be involved in METH-induced dopaminergic neurotoxicity (34). Evidence for the role of NO in dopaminergic neurotoxicity arises from several *in vivo* studies. First, METH-induced dopaminergic neurotoxicity in mice caused a marked increase in striatal peroxynitrite and 3-nitrotyrosine, which is a marker of peroxynitrite formation *in vivo* (35). Second, selective neuronal nitric oxide synthase (nNOS) inhibitors such as 7-nitroindazole (7-NI), 3-bromo 7-nitroindazole and S-methylthiocitrulline blocked METH-induced dopaminergic neurotoxicity in mice with no effect on METH-induced hyperthermia (26,36). Third, mice deficient in the nNOS gene (nNOS knockout; KO) were resistant to METH-induced dopaminergic neurotoxicity compared to wild type mice (37).

Based on these observations and the findings that nNOS KO mice are resistant to the psychomotor stimulating and rewarding effects of psychostimulants (36), we hypothesized that NO has a specific role in DA- but not 5-HT-mediated effects of psychostimulants. To test this hypothesis we investigated whether blockade of nNOS or ablation of nNOS (KO mice) provides protection against serotonergic neurotoxicity induced by the amphetamine analog fenfluramine (27). We found that neither inhibition of nNOS by 7-NI in Swiss Webster mice nor the absence of the nNOS gene in the nNOS ( $-/-$ ) mice afforded protection against serotonergic neurotoxicity caused by high doses of fenfluramine ( $25 \text{ mg kg}^{-1} \times 2$ ; for 2 days). In more recent experiments we found that the dual dopaminergic/serotonergic neurotoxicity caused by a high dose of MDMA ( $15 \text{ mg kg}^{-1} \times 2$  for 2 days) was only partially attenuated in nNOS ( $-/-$ ) mice (unpublished observations). Together, these findings support the hypothesis that NO generated by nNOS and peroxynitrite are mediators of dopaminergic but not serotonergic neurotoxicity. Thus, it is likely that different mechanisms underlie dopaminergic and serotonergic neurotoxicity, at least in mice.

There is increasing evidence that exposure to METH is associated with activation of apoptotic biochemical cascades

involving caspases, pro-apoptotic Bcl-2 family genes and the tumor suppressor gene p53 that are all recruited during cell death. A toxic regimen of METH administered to mice caused an increase in the pro-death Bcl-2 family genes BAD, BAX and BID, which was accompanied by a decrease in the anti-death genes Bcl-2 and Bcl-XL. Subsequently, reduction of mitochondrial respiration and membrane potential, the release of mitochondrial cytochrome c and activation of caspases 3 and 9 were proposed to contribute to programmed cell death caused by METH (38).

The role of p53 in METH-induced 5-HT neurotoxicity is suggested by the finding that mice deficient in the p53 gene (p53 KO) were protected from depletion of serotonergic markers (5). Interestingly, the authors achieved serotonergic neurotoxicity in mice only following the administration of a relatively high dose of METH ( $10 \text{ mg kg}^{-1} \times 4$ ) whereas a lower dose ( $5 \text{ mg kg}^{-1} \times 4$ ) did not produce 5-HT neurotoxicity, a finding which is in agreement with our studies in mice (Fig. 1). It remains unresolved however, whether p53 has role in dopaminergic neurotoxicity caused by METH.

Inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and cyclooxygenase-2 (COX-2) have a major role in processes underlying neuronal injury, and recent studies suggest their involvement in METH neurotoxicity. Mice deficient in the IL-6 gene (IL-6 KO) were protected from METH-induced dopaminergic neurotoxicity (5). METH neurotoxicity in mice deficient in TNF- $\alpha$  (TNF- $\alpha$  KO) was markedly increased compared to wild type mice, suggesting that TNF- $\alpha$  has a neuroprotective role (39). Administration of a toxic dose of METH to mice caused marked increase in COX-2 in the striatum but not the hippocampus, suggesting that the neurotoxic damage in the striatum is associated with inflammation and oxidative stress (40). Table 1 summarizes the major elements found to participate in METH neurotoxicity.

#### RELEVANCE OF THE MOUSE MODEL OF NEUROTOXICITY: MECHANISMS AND FUNCTIONAL CONSEQUENCES

Evidently, the utilization of various transgenic and knockout mouse strains allowed the identification of several genes that play an important role in dopaminergic and

**Table 1**  
Modulators of methamphetamine neurotoxicity in mice and rats

Transmitter/Transporter	Free radicals	Apoptotic proteins	Inflammatory cytokines
Dopamine (22)	ROS (5–9)	Bcl-2 (38)	IL-6 (5)
Glutamate (31, 32)	$\text{NO}^\bullet$ (nNOS) (36, 37)	p53 (5)	TNF- $\alpha$ (39)
DAT (29)/VMAT2 (30)	$\text{ONOO}^-$ (34, 35)	Caspases (5, 38)	COX-2 (40)

DAT, dopamine transporter; VMAT2, vesicular monoamine transporter 2; ROS, reactive oxygen species;  $\text{NO}^\bullet$ , nitric oxide; nNOS, neuronal nitric oxide synthase;  $\text{ONOO}^-$  peroxynitrite; IL-6, interleukin-6, TNF- $\alpha$ , tumor necrosis factor  $\alpha$ , COX-2, cyclooxygenase-2. Numbers in parentheses are references.

serotonergic neurotoxicity caused by amphetamines. Results from such studies and future investigations should facilitate the elucidation of the distinct mechanisms involved in dopaminergic and serotonergic neurotoxicity. As summarized, one example is the finding that the nNOS gene is likely to play a role in dopaminergic but not serotonergic neurotoxicity caused by amphetamines. The results from this type of studies should also assist the development of pharmacotherapies to ameliorate potential neuronal damage and cognitive impairments due to amphetamines abuse. A major question that needs to be addressed concerns the functional significance of these three mouse models of amphetamine-induced neurotoxicity (Fig. 1). It is important to note that amphetamines, unlike other neurotoxins used as models of dopaminergic and serotonergic neurotoxicity (e.g., 6-OHDA and 5,7-DHT, respectively), cause degeneration at the nerve terminals rather than at cell bodies. Accordingly, the functional outcome of amphetamines neurotoxicity may be different from that of 6-OH and 5,7-DHT neurotoxicity.

The mouse model of amphetamines-induced neurotoxicity is however a useful tool that can be applied to isolate the consequences of dopaminergic and serotonergic neurotoxicity and to investigate dual dopaminergic/serotonergic neurotoxicity. The latter model of neurotoxicity caused by MDMA as we identified in the mouse brain (Fig. 1) is relevant to dopaminergic and serotonergic depletion that might occur in humans abusing both METH and MDMA. Elucidation of the behavioral outcomes of these insults would allow better understanding of the consequences of human exposure to METH and MDMA on cognition, drug-seeking behavior, extinction and relapse.

## CONCLUSIONS AND FUTURE DIRECTIONS

Despite the fact that there is more compelling evidence for amphetamines-induced neurotoxicity in rodents than in humans, it is unlikely that the human brain is less vulnerable than the rodent brain to neurotoxic insult. It remains a challenge to directly compare amphetamines neurotoxicity in rodents and humans, given that (a) the pattern of animal drug exposure and human drug abuse are different, and (b) the methods for assessment of neurotoxicity in rodents and humans are not always alike. Nevertheless, it is now clear that METH and MDMA cause serious cognitive impairments in humans and neurotoxicity to dopaminergic and serotonergic neurons in rodents. It appears that different mechanisms underlie the development of dopaminergic and serotonergic neurotoxicity, and further studies in mice should advance our knowledge of these mechanisms. Likewise, investigation of the behavioral outcome of the neurotoxic insults caused by amphetamines in mice is essential for better understanding the consequences of human abuse of amphetamines.

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