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Brain Research Reviews 42 (2003) 155–168
BRAIN RESEARCH REVIEWS
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Review

Methylenedioxymethamphetamine (MDMA, Ecstasy) neurotoxicity: cellular and molecular mechanisms

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Accepted 12 March 2003

Abstract

Methylenedioxymethamphetamine (MDMA, Ecstasy) is a very popular drug of abuse. This has led to new intense concerns relevant to its nefarious neuropsychiatric effects. These adverse events might be related to the neurotoxic effects of the drug. Although the mechanisms of MDMA-induced neurotoxicity remain to be fully characterized, exposure to the drug can cause acute and long-term neurotoxic effects in animals and nonhuman primates. Recent studies have also documented possible toxic effects in the developing fetus. Nevertheless, there is still much debate concerning the effects of the drug in humans and how to best extrapolate animal and nonhuman primate data to the human condition. Herein, we review the evidence documenting the adverse effects of the drug in some animal models. We also discuss possible mechanisms for the development of MDMA neurotoxicity. Data supporting deleterious effects of this drug on the developing fetus are also described. Much remains to be done in order to clarify the molecular and biochemical pathways involved in the long-term neuroplastic changes associated with MDMA abuse.
Published by Elsevier Science B.V.

Theme: Neural basis of behavior

Topic: Drugs of abuse: amphetamine and other stimulants

Keywords: Methylenedioxymethamphetamine; MDMA; Ecstasy; Neurotoxicity

Contents

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0165-0173/03/$ – see front matter Published by Elsevier Science B.V.
doi:10.1016/S0165-0173(03)00173-5

1. Introduction

3,4-Methylenedioxy-*N*-methamphetamine (MDMA, Ecstasy) is a semi-synthetic compound that can be derived from an essential oil of plants including nutmeg, mace, sassafras, saffron, parsley, dill, and vanilla beans. MDMA was first synthesized by Merck Pharmaceuticals and patented in 1914 [19]. MDMA is a ring-substituted derivative of phenylisopropylamine, structurally similar to methamphetamine and the hallucinogen, mescaline (Fig. 1) [19,61,103]. MDMA affects peripheral and central nervous system (CNS) functions by acting mainly on the serotonergic system. The drug is reported to have sympathomimetic properties [161], and to modulate psychomotor [6] and neuroendocrine functions [45,115]. MDMA acts as an indirect monoaminergic agonist [155] and displays relatively high, similar affinities for α_2-adrenoceptors, 5-HT_2 serotonin (5-HT) receptors, M-1 muscarinic receptors, and H-1 histamine receptors. MDMA binds with less affinity to dopamine (DA) and norepinephrine (NE) uptake sites, M-2 muscarinic receptors, α_1-adrenoceptors, β-adrenoceptors, 5-HT_1 receptors, and D1 and D2 DA receptors [7]. Neurochemical studies performed in vitro [102,117,155] and/or in laboratory animals [37,50,78,155,165,167] demonstrate that MDMA blocks 5-HT reuptake and induces 5-HT release and, to a lesser extent, also causes DA [38,102] and NE [52] release. MDMA releases 5-HT from striatal slices at concentrations that are ~10-fold lower than concentrations required for stimulating DA release [144,155]. The calcium-independent 5-HT release appears to be related to MDMA action on the 5-HT transporter (5-HTT) as demonstrated by in vitro studies in which the release is blocked by fluoxetine or imipramine, drugs that inhibit the 5-HTT [5,188]. In addition to its inhibition of monoamine re-uptake, MDMA might also increase extracellular levels of monoamines by inhibiting brain monoamine oxidase activity [187,193].

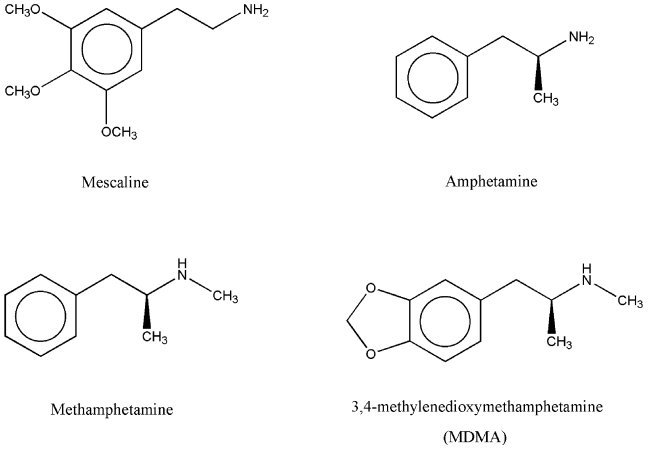

Fig. 1. Structural similarity of MDMA to stimulants and the hallucinogen, mescaline.

2. Acute effects of MDMA

The deleterious effects of MDMA on brain serotonergic systems have been studied extensively using rats [37,91,92,122,123], guinea pigs [7], dogs [54,118], nonhuman primates [53,70,76,136,137,139], chickens [18] as well as pigeons [83]. In mice, however, MDMA appears to affect mainly the nigrastriatal dopaminergic system [22,23]. MDMA toxicity is affected by doses [46,131], routes of administration, as well as by treatment regimens [7,103,124,136]. In addition, age [16,17,166], gender [86,98,131] and species [46,103,177] used can affect the manifestations of MDMA neurotoxicity.

MDMA causes both acute biochemical and long-term biochemical effects. The acute effects of the drug are thought to be responsible for the behavioral and psychological responses to MDMA [85,87,88,92,165]. These acute effects include: (1) rapid 5-HT release, followed by substantial decreases in the levels of 5-HT (Table 1) and 5-hydroxyindoleacetic acid (5-HIAA), the major 5-HT metabolite [150,156,158,180,181], with recovery occurring within 24 h; and (2) a marked decrease in tryptophan hydroxylase (TPH) activity which is reported to last for, at least, 2 weeks in various regions of the rodent brain

Table 1
Effects of MDMA on 5-HT levels in the mammalian brain

Species	Brain regions	Doses (mg/kg)	Time of sacrifice	% Control	Ref.
Rat	Striatum	10×1	3 h	45	[154]
		20×1		37	
Rat	Striatum	20×1	2 weeks	19	[37]
		40×1		24	
	Hippocampus	20×1		16	
		40×1		22	
	Cortex	20×1		30	
		40×1		40	
Monkey	Caudate	5×1	2 weeks	86	[138]
	Putamen	5×1		89	
	Hippocampus	5×1		77	
	Cortex	5×1		86	
	Hypothalamus	5×1		77	
	Thalamus	5×1		84	
Human	Caudate	N/A	N/A	77	[75]
	Putamen	N/A	N/A	77	

[150,156,180]. There is no evidence of loss of 5-HT uptake sites at the early time points after MDMA administration. On the other hand, the long-term neurotoxic effects of MDMA occur within 24 h to 1 week after drug administration [154]. These consist of: (1) decreases in the levels of 5-HT (Table 1) and 5-HIAA after 24 h; (2) loss of 5-HT transporters (5-HTT) after 7 days [10]; and (3) marked decreases in TPH activity [156,180,181]. In addition, histological studies have demonstrated that MDMA can produce neurodegeneration in the striatum and cortex of rats [37,134] and axonal loss in nonhuman primates [190].

2.1. Acute biochemical effects in animals

MDMA administration (10–20 mg/kg s.c.) results in a massive release of 5-HT from presynaptic vesicles [117,155] followed by a rapid decrease in 5-HT and 5-HIAA levels [150,155,156,158,180,181] and a decrease in TPH activity [150,156,180]. MDMA induces calcium-independent carrier-mediated 5-HT release [5,155,188] via its interactions with the 5-HT transporters. This is also supported by reports that inhibition of the transporter with fluoxetine and imipramine can block MDMA-induced 5-HT release [11,52,63,102,143]. In addition, MDMA has also been shown (in vitro and in vivo) to cause dose-dependent DA release [35,38,73,78,102,113,158] in the striatum [73,113], nucleus accumbens [193] caudate [59,193] and hippocampus [163] in rats. MDMA also causes NE release from slices obtained from rat brain [52]. Increases in the extracellular DA [11,59,63,74,82,158,175,192,193] and NE [72] levels have also been observed. For example, MDMA (10 mg/kg) has been reported to cause increases in the extracellular DA levels measured in dialysates obtained from the striata of awake-behaving rats [192,193]. Acute biochemical MDMA effects have also been reported in dogs [118]. Specifically, Nishisawa et al. [118] found that MDMA (2 mg/kg; i.v.), infused over 10 min, affects brain 5-HT synthesis measured 1 h after the injection, as determined by positron emission tomography (PET) with the tracer, α[^{11}C]-methyl-L-tryptophan in order to investigate the effect of the drug on the rate of 5-HT synthesis. The rate of synthesis was increased 1 h after the injection and decreased 5 h later [118].

2.2. Acute behavioral effects in animals

The acute behavioral effects of MDMA include hyperthermia [39–41,58,115,152], which is related to ambient temperature [39,57], hyperactivity [39,57], and the serotonin behavioral syndrome (SBS) [25,34,165,170]. The characteristics of SBS include enhanced locomotor activity, reciprocal forepaw treading, head weaving, piloerection, hind limb abduction, proptosis, ataxia, and subsequent dose-dependent convulsions and death [61]. Spanos and Yamamoto showed that behavioral sensitization occurred after repeated low doses of Ecstasy (1 ml/kg), with secondary increases in SBS duration and intensity [170]. MDMA-induced hyperactivity is thought to be the result of DA released in conjunction with 5-HT [92,100,193]. Using the antagonist, GR127935, which has high affinity for the 5-HT1B and 5-HT1D receptors, McCreary et al. [100] demonstrated that 5-HT1B/1D receptors participate in the acute hyperactivity response induced by a low dose (3 mg/kg) of the drug. Because 5-HT is involved in temperature regulation, MDMA-induced hyperthermia may also be related to MDMA-mediated increases in brain 5-HT concentration [91,170]. Administration of MDMA given at daily increasing doses of 10, 15, and 20 mg/kg to rats also causes significantly impaired performance on behavioral tests which measured spontaneous locomotor activity using a photo-cell cage system, skilled motor function assessed by performance on a skilled paw reach task, and cognition assessed by performance on an operant delayed non-match to place procedure [92].

2.3. Acute pharmacological effects in humans

Initial studies on the behavioral and psychological effects of MDMA in humans had reported that Ecstasy users experienced a peaceful, emotional experience with enhanced insight, feelings of increased closeness to others, euphoria, heightened sensory awareness, and symptoms of sympathetic arousal including tremors, and tachycardia [30–32,47,62,169]. A more recent study [184] in healthy volunteers also found that MDMA (1.7 mg/kg) produces a state of enhanced mood and well-being associated with slight-to-moderate depersonalization, moderate thought disorder without delusional thinking or paranoia, little or no anxiety, and no apparent increases in psychomotor drive, findings which confirmed those of previous investigations.

Acute adverse physical effects of MDMA have also been reported [30–32]. These include bruxism or jaw clenching, suppressed appetite, concentration difficulties, impaired gait (ataxia) and motor restlessness and muscle aches [89]. There are also reports of fatigue, lack of energy and appetite, feelings of restlessness, and brooding [184]. Subjects also exhibit sweating, tachycardia, and hyperthermia [128]. Following cases of severe hyperthermia, death may occur due to cardiac arrhythmias, acute renal failure, rhabdomyolysis and disseminated intravascular coagulation (DIC) [26,48,91,160].

3. Neurotoxicity

3.1. Neurotoxicity in rats

Neurotoxic effects of MDMA appear between 24 h and 1 week following MDMA administration [150]. Neuro-

chemical and anatomical studies initially reported long-term reductions in markers of 5-HT systems in rats [37,107,122,150,158,181]. These include decreased levels of 5-HT and of its major metabolite, 5-HIAA [37,107,149,155], decreased number of 5-HT transporters [10,37,46], and decreased activity of the rate-limiting enzyme of 5-HT synthesis, TPH [46,107]. Other studies confirmed that the most severe reductions in 5-HT and 5-HIAA levels occurred in the rat neocortex, striatum, and hippocampus [10,46,107,167]. These abnormalities are reported to last for months or even years after drug administration [9,51,66,84,145,146]. De Souza et al. [46] reported that 5-HT tissue concentrations, hippocampal 5-HT uptake sites, and functional 5-HT uptake might partially recover after exposure to high doses of MDMA (20 mg/kg, 2× daily, 4 days). There are long-term decreases in TPH activity in the neostriatum, hippocampus, hypothalamus and cortex [156,181]. Histological studies using the Fink–Heimer staining method have also provided evidence for the degeneration of nerve terminals in the striatum and somatosensory cortex after chronic exposure to MDMA (80 mg/kg, 2× daily, 2 days) [37]. Using 5-HT-specific antibodies, loss of serotonergic axons in the neocortex, striatum, and thalamus have also been found in rats treated with MDMA (20 mg/kg, 2× daily, 4 days) [122]. These were associated with increased axon calibre, large swollen varicosities, and dilated proximal axon stumps [107,122]. Ricaurte et al. [142] and Callahan et al. [24] have also provided evidence that MDMA can cause reduction of the anterograde transport of [^{3}H]proline in ascending axons originating in the dorsal raphe nuclei, a subset of which comprise ascending 5-HT axons that project to various forebrain regions.

3.2. Neurotoxicity in nonhuman primates

Long lasting effects similar to those observed in rats have also been reported in nonhuman primates [70,95,137,139,148,167]. Nonhuman primates have been shown to be more sensitive to the neurotoxic effects of MDMA than rats [46,135]. In nonhuman primates, MDMA (2.5, 3.75 or 5.0 mg/kg) causes dose-dependent reductions in 5-HT in the cortex, caudate nucleus, putamen, hippocampus, hypothalamus and the thalamus [139]. Reduced 5-HT levels were evident for up to 7 years following exposure to the drug [66,148]. The MDMA-induced deficits in nonhuman primates are also reflected in the levels of 5-HIAA in the cerebrospinal fluid (CSF) [70,137]. In one study [70], MDMA given at 2.5 or 10 mg/kg, twice daily for 4 days to rhesus monkeys produced selective and significant decreases in CSF levels of 5-HIAA and brain 5-HT and 5-HIAA concentrations. The higher dose of MDMA (10 mg/kg) also produced a selective decrease in 5-HT uptake sites [70]. Living baboons treated with MDMA (5 mg/kg s.c., 2× daily, 4 days) also show marked and prolonged decreases in 5-HT transporter density measured by PET imaging of (+)[^{11}C]McN-5652, a radioligand that selectively binds to the 5-HT transporter [148]. 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 [148]. The density of the striatal vesicular monoamine transporters (VMAT2) measured with [^{3}H]dihydrotetrabenzine (DTBZ) was also reduced in these baboons [142]. Immunohistochemical studies have also revealed marked decreases in axon density in the forebrain of nonhuman primates treated with MDMA (2–10 mg/kg) [107,139]. Hatzidimitriou et al. [66] showed reductions in 5-HT axon density 2 weeks and 7 years after MDMA treatment (5 mg/kg s.c., 2× daily, 4 days) in all areas of the cerebral cortex. Reorganization of 5-HT projections has been reported to occur in the brains of nonhuman primates treated with MDMA [51,66,142,148]. For example, in one study, squirrel monkeys, previously lesioned with MDMA, showed substantial serotonergic axonal sprouting and a highly abnormal reinnervation pattern 18 months after MDMA treatment [51]. The dorsal neocortex remained denervated, whereas the amygdala and hypothalamus were reinnervated or hyperinnervated, in these MDMA-treated animals [51].

3.3. Neurotoxicity in humans

A major concern regarding these toxicity studies in animals has to do with relating these findings to the human condition. It has been suggested that because the doses used in the animal studies are much higher than the doses of Ecstasy taken by humans, these observations might not reflect the effects of MDMA on the human brain. A few studies have been conducted in human MDMA abusers [13,20,56,75,96,98,99,129,137,138,162] to address some of these issues. There is a growing consensus that MDMA might indeed be toxic to humans. For example, measurement of lumbar CSF 5-HIAA levels in MDMA abusers revealed that CSF 5-HIAA is significantly reduced in these subjects compared to subjects that never used MDMA [13,96,98,137,138]. There were no changes in the levels of the DA metabolite, homovanillic acid (HVA), nor in the concentration of the NE metabolite, 3-methoxy 4-hydroxyphenylglycol (MHPG) [98].

Additionally, human PET imaging techniques using [^{11}C]McN-5652 to selectively label 5-HT transporters of 14 previous MDMA abusers found significant differences in 5-HTT binding in MDMA abusers compared to non-MDMA users [99]. 5-HTT sites were decreased in a manner that correlated with the extent of abuse [99,141]. The status of 5-HT markers in MDMA abusers has also been assessed with single photon emission computed tomography (SPECT) using [^{123}I]R91150, a radioligand, which binds with high affinity to 5-HT2A receptors [132]. The availability of the postsynaptic 5-HT2A receptor was lower in recent MDMA abusers but higher in ex-MDMA

abusers. Acute effects of MDMA were associated with decreased 5HT2A receptor densities possibly due to receptor occupancy by high levels of MDMA-induced 5-HT release. In contrast, the long-term effects, consisting of increased 5-HT2A receptor densities, might be due to compensatory increased receptor synthesis in response to MDMA-induced 5-HT depletion. In another SPECT study, Semple et al. [162] reported reduced cortical transporter binding in Ecstasy abusers using [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl) tropane ([^{123}I]β-CIT), a radioligand that binds with high affinity to 5-HTTs. The 10 Ecstasy users in this study showed reduced cortical 5-HTT binding, which was prominent in the primary motor cortex. The subjects had taken a minimum of 50 tablets, used the drug for 1 year or more, and were currently taking Ecstasy on a regular basis [162]. In a similar study, using [^{123}I]β-CIT, Reneman et al. investigated the effects of ecstasy abuse on the density of cortical 5-HT transporters and long-term memory function. They also found decreases in cortical 5-HTT in recent MDMA abusers. However, there were no significant reductions in Ecstasy abusers who had not used Ecstasy in the past year or longer [133]. Both short- and long-term abstinent Ecstasy abusers displayed deficits in verbal memory that correlated with MDMA doses used over their lifetime [133]. Whether SPECT analysis with [^{123}I]β-CIT is sensitive enough to measure the density of 5-HT transporters [67,140] and the less than 1.5:1 signal to noise ratio even in regions with a high density of 5-HT transporters with SPECT and [^{123}I]β-CIT [140] are technical controversies associated with these studies.

PET imaging with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) has also been performed on seven previous Ecstasy abusers and seven controls who had not used illicit drugs in order to investigate the effects of Ecstasy use on glucose metabolism in the human brain [120]. Glucose metabolic uptake in the MDMA abusers was altered in several brain regions with reductions observed in the hippocampus, amygdala and cingulate and increases found in Brodmann's areas 10 and 11, the putamen and caudate nucleus. The hippocampus and Brodmann's area 11 were the most affected [120]. In a similar study by Buchert et al. [20], FDG was also used to detect the long-term alterations in regional cerebral glucose metabolism. The investigators reported that FDG uptake in ecstasy users was significantly reduced in the cingulate, Brodmann's area 11, putamen, caudate, amygdala and hippocampus but increased in Brodmann's area 10. In addition, the reductions were more severe in individuals that begin abusing Ecstasy before age 18 [20].

Other methods used to assess the status of the serotonergic system include determination of homeostatic regulatory mechanisms of prolactin, cortisol, and growth hormone via pharmacological challenges since 5-HT is thought to be involved in the normal regulation of secretion of these hormones [95]. For example, administration of L-tryptophan [98,129], D-fenfluramine [55,56], or *meta*-chlorophenylpiperazine (*m*-CPP) [95] to MDMA abusers results in altered hormonal responses in these patients. The results with fenfluramine are consistent with observations obtained in rats treated with MDMA [115]. A few studies have shown increased plasma cortisol and prolactin concentrations following MDMA use. In one study, 125 or 75 mg of MDMA were given to 14 male subjects who were tested to determine the neuroendocrine effects of MDMA in healthy volunteers [93]. They found that MDMA significantly increases plasma cortisol and prolactin concentrations following the 125 mg dose [93]. This was further confirmed in a later study [45] in which MDMA, in doses ranging from 50 to 150 mg, was given to 27 male recreational MDMA abusers who had abused Ecstasy between five and 50 times in their lives. MDMA produced a marked increase in plasma cortisol concentrations with less than 75 mg of MDMA and in prolactin concentrations with less than 100 mg MDMA. In addition, at all doses except 50 mg, MDMA produced dose-dependent increases in blood pressure, heart rate, and pupilary diameter [45]. These data support activation of serotonergic transmission even though the role of other neurotransmitter systems cannot be ruled out.

Because CSF 5-HIAA levels are decreased in individuals that are impulsive and hostile [28,29,68,81,168] and because MDMA abusers also show decreased CSF 5-HIAA levels [96], it was thought likely that MDMA abusers might demonstrate impulsive-like behavioral patterns [98]. In one study [98], MDMA abusers did not show any increases in impulsiveness or hostility. These findings are not consistent with those of others who have found that MDMA abusers do show more impulsivity than control individuals [55,56,111,127]. It is still possible, nevertheless, that increased impulsivity is not a result of MDMA abuse, but that MDMA abusers might suffer from a primary disorder of impulse control that might have led them to the use of the drug. Further studies are needed to determine if a disruption in the serotonergic system from MDMA abuse is responsible for these observations.

Neuropsychological studies [60,77,108,110,183,185] of MDMA abuse have also shown that MDMA abuse can negatively impact the performance of memory [13,80,97,109–111,126] and of psychomotor tasks [96]. For example, McCann et al. assessed the ability to perform psychomotor tasks, which required sustained attention to complete arithmetic calculations, visual discrimination and working memory, short-term memory, or semantic recognition and verbal reasoning. Both the cognitive deficits on certain tasks and the decrements in CSF 5-HIAA appear to correlate with the extent of abuse by these patients [13]. There also appears to be a direct effect of MDMA on memory performance because administration of the drug causes a dose-dependent impairment of psychomotor tasks [45].

MDMA abusers have also been reported to suffer from sleep disturbances [127,189] although only a few studies

have analyzed the effects of MDMA on sleep patterns in humans [3] and animals [12] in a very controlled fashion. The sleep study in humans revealed that MDMA abuse caused significant decreases in total sleep time [3]. MDMA abusers have also been reported to show increased stage 3 and 4 sleep [95].

Approaches used to study the effects of MDMA in humans typically measure 5-HT, 5-HIAA, and 5-HTT binding. It is difficult to know if abnormalities preceded or are consequences of MDMA abuse. The MDMA-induced clinical signs and symptoms, because they can be compared to behaviors that anteceded drug use, might actually provide better indications that the drug does cause long-term neurological effects. Additionally, many of the studies conducted in humans utilize previous Ecstasy abusers compared to a control group of individuals who usually report no use of illicit drugs or use of select drugs known not to cause 5-HT effects. This might be a limitation since Ecstasy abusers also abuse other drugs and the purity of the Ecstasy consumed is quite unknown.

4. Mechanisms of toxicity

In spite of two decades of studies on MDMA toxicity, the mechanisms underlying its effects remain to be fully elucidated. In what follows, we provide an overview of some of the ideas that have been put forward to explain the neurotoxic effects of MDMA.

4.1. Formation of a toxic MDMA metabolite

MDMA metabolites, which generate free radicals and associated oxidative stress and membrane damage, have been proposed as causal agents for the long-term MDMA-induced neurodegeneration [33,125]. Metabolism of MDMA results in the formation of methylenedioxyamphetamine (MDA) by N-demethylation and 3,4-dihydroxymethamphetamine (HHMA), the major metabolite, by O-demethylation. O-demethylation of MDA results in 3,4-dihydroxyamphetamine (HHA). HHMA and HHA are metabolized by catechol-*O*-methyltransferase (COMT) to 4-hydroxy-3-methoxy-methamphetamine (HMMA) and 4-hydroxy-3-methoxy-amphetamine (HMA), respectively [44,45,94]. MDA is also converted to α-methyldopamine (α-MeDA), which might be involved in MDMA neurotoxicity because subcutaneous administration of MDA metabolites, α-MeDA and HMA can cause decreases in 5-HT concentrations in the frontal cortex [194]. In contrast, blocking the N-demethylation of MDMA, which leads to the formation of α-MeDA via MDA, did not prevent MDMA-induced reduction in TPH activity or in cortical 5-HT [156]. The possibility that N-demethylation of MDMA to MDA might constitute an intermediate step in the formation of a neurotoxic metabolite might be unlikely because pretreatment with the inhibitor did not provide protection [103,171]. It is important to note that systemic administration of the major metabolites of MDA, HHA and of MDMA, HHMA did not produce neurotoxicity [103]. The metabolite, HHMA is metabolized to quinone-like structures that were thought to be involved in MDMA-induced neurotoxicity [69]. The metabolites of MDMA generate reactive species through redox cycling. These reactive species might inactivate TPH and cause damage to protein and lipid components of the neuron terminal. Moreover, catechols, hydroquinones, and quinones can undergo spontaneous oxidation by oxygen, to generate superoxides and hydrogen peroxide that could lead to lipid peroxidation and damage to 5-HT terminals secondary to the production of hydroxyl radicals. These ideas are supported by the observations that the spin trap reagent and free radical scavenger, α-phenyl-*N*-*tert*-butyl nitrone (PBN), prevented MDMA-induced toxicity [33].

4.2. Role of inhibition of tryptophan hydroxylase

MDMA produces rapid inhibition of tryptophan hydroxylase, the rate-limiting enzyme in the pathway of 5-HT synthesis that lasts for 2 weeks or longer following a single dose of MDMA to rats. This is an irreversible inhibition because restoration of enzyme activity requires new enzyme synthesis [156]. Enzyme inhibition is not thought to be caused directly by MDMA because the drug has no effect on hydrolase activity in vitro [156]. Quinone by-products, by interacting with sulfhydryl groups in the enzyme, might actually be the culprits [69,130]. Support for this idea comes from the finding that, following MDMA administration, activity of the enzyme can be restored by reduction with sulphydryl reagents under anaerobic conditions [178].

4.3. Role of 5-HT or 5-HT metabolites

It has also been suggested that 5-HT or a metabolite of 5-HT may be responsible for MDMA neurotoxicity because blockade of 5-HT uptake by fluoxetine or citalopram antagonizes MDMA-induced 5-HT depletion [150] and facilitates the recovery of TPH activity [156]. These observations suggest that MDMA-induced neurotoxicity might involve 5-HT or the formation of a toxic 5-HT metabolite that can be taken up by the 5-HT uptake carrier. In addition, the reports that 5-HT_{2A} antagonists can attenuate MDMA-induced neurotoxicity [114,153] suggest that 5-HT_{2A} receptors also participate in the toxicity, possibly, through causing changes in calcium homeostasis or via translocation and activation of protein kinase C (PKC) [79]. The fact that L-type calcium channel blocker, nimipodine, can also protect against MDMA toxicity, does support a role for calcium uptake in MDMA's effects [49]. Because 5-HT2A antagonists can also attenuate MDMA-

induced DA release [112,153,157], the possibility also exists that DA mediated events might also participate in the effects of these substances.

4.4. Role of dopamine

MDMA is selectively neurotoxic to the serotonergic system with almost no deleterious effects on the dopaminergic systems of most species except for mice [21,23]. MDMA elicits DA release in vitro and in vivo. MDMA also induces DA release [155] and the subsequent increase in postsynaptic 5-HT amplifies the concentration of extracellular DA [64,175]. The 5-HT activates 5-HT2A receptors, which enhances dopamine synthesis and release [64]. Nevertheless, a linear relationship between acute DA release and the extent of long-term 5-HT terminal deficits has also been reported [116]. Moreover, prior administration of 6-hydroxydopamine, which destroys DA terminals also blocks MDMA neurotoxicity [153], while pretreatment with L-DOPA, a dopamine precursor increases MDMA neurotoxicity [153]. Furthermore, α-methyl-*p*-tyrosine has been shown to attenuate MDMA-induced DA efflux in the striatum and to prevent subsequent decreases in 5-HT uptake sites and in TPH activity [14,179,187].

5-HT2A antagonists attenuate increased L-DOPA utilization and MDMA-induced neurotoxicity [114,151]. In the absence of 5-HT2-mediated enhanced synthesis of DA, the DA neuron cannot sustain the carrier-mediated DA release, which is essential for the development of MDMA-induced neurotoxicity. 5-HT2 receptor agonists administered together with MDMA, potentiated MDMA-induced DA release and increased the toxic effect of MDMA on 5-HT levels 7 days following administration [65,187].

These findings led to the conclusion [114,153,173] that the excessive DA production and release following MDMA administration result in abnormally high levels of extracellular DA, which may be taken up into the depleted 5-HT terminals [154,172]. The oxidative processes within the terminal could produce toxic metabolites that damage the cell. One theory is that MDMA induced blockade of monoamine oxidase and thus normal metabolism could result in high concentrations of extracellular DA adjacent to 5-HT neurons that would enhance the carrier-mediated uptake of DA. 5-HT uptake inhibitors like fluoxetine blocked this effect [103]. Therefore, in addition to dopamine itself being toxic to the cell, studies suggested that monoamine oxidase B could metabolize DA in the 5-HT terminal to form hydrogen peroxide, which could lead to lipid peroxidation and oxidative stress [171].

The DA theory alone does not account for the fact that 5-HT terminal damage is observed throughout the central nervous system in areas of the brain with very little DA innervation. Studies in mice also suggest oxidative insults mediate MDMA-induced neuronal toxicity [22,23]. MDMA is neurotoxic to DA axons rather than 5-HT axons in mice. Cadet et al. [22] showed that a high dose of MDMA (50 mg/kg) produced dopamine depletion in the striatum of non-transgenic mice. In homozygous transgenic mice that carried the complete sequence of the human copper–zinc superoxide dismutase (CuZnSOD) gene, MDMA did not produce dopamine depletion suggesting the CuZnSOD protected dopamine axons of the transgenic mice against damage by oxygen free radicals.

The GABAergic system is thought to serve as a modulator of dopaminergic activity. Colado et al. [34] demonstrated that chlormethiazole, a GABA agonist, attenuated the serotonergic toxicity induced by MDMA treatment in rats. In another study, Yamamoto et al. [192] conducted microdialysis studies and observed an MDMA-induced increase in extracellular dopamine coupled with a decrease in extracellular GABA levels in the rat striatum that can be reversed by the 5-HT2A receptor antagonist, ritanserin. It is possible that MDMA-mediated reduction in GABA might enhance its effects on DA synthesis and release [114,171], thus potentiating its neurotoxic effects in the long-term.

4.5. Role of glutamate and nitric oxide

Glutamate is known to cause neuronal damage and may be involved in MDMA-induced neurotoxicity [4,8,176]. One study [186] showed that MDMA applied locally decreased glutamate efflux in the nucleus accumbens of rodents due to interactions between the 5-HT and DA systems. According to Obradovic et al. [119], 5-HT2A receptor activation caused an increase in DA levels that effected a decrease in glutamate levels. In addition, a separate study [34,49] showed that blocking NMDA glutamate receptors with the antagonist, MK-801, protected against the decrease in 5-HT levels due to MDMA while another study [71] showed that MK-801 had no effect on reductions in TPH activity after MDMA treatment. Studies also showed that multiple doses of MDMA that led to an increase in the extracellular levels of dopamine in the striatum of rats had no effect on glutamate efflux (reviewed in Ref. [171]).

The role of nitric oxide (NO) in MDMA-induced toxicity also has been investigated in rats. For example, because the nitric oxide synthase (NOS) inhibitor, NG-nitro-L-arginine methyl ester (L-NAME), was the only NOS inhibitor that protected against the neurotoxic effects of MDMA, it has been suggested that L-NAME protective effects were the result of its ability to lower core body temperature since L-NAME also was the only NOS inhibitor to induce hypothermia [182]. However, other investigators observed that MDMA can cause death of human serotonergic cells and that these cells could be protected by using L-NAME in the culture [164]. Thus, much remains to be done to clarify the role, if any, of NO in MDMA toxicity.

4.6. Role of hyperthermia

MDMA causes acute dose-dependent hyperthermia in rats [40,41,58,115]. MDMA-induced hyperthermia in humans [26,42] also can be fatal [121]. Gordon et al. [58] suggested that MDMA might cause loss of thermoregulatory mechanisms because rats treated with MDMA at temperatures above 24 °C display hyperthermia whereas rats show hypothermia if treated at 10 °C. 5-HT2 receptor antagonists block the hyperthermic response and MDMA neurotoxicity although hyperthermia was observed when higher doses than 10 mg/kg were used [115]. Increasing the rat body temperature prevented the protective effects of ketanserin and of methyl-*p*-tyrosine [90]. Nevertheless, other agents that protect against MDMA neurotoxicity, including fluoxetine, did not prevent hyperthermia [104,115]. Recent studies by Mechan et al. [105], also provide evidence that a neurotoxic dose of MDMA can impair thermoregulatory processes in rats exposed to high ambient temperatures. Furthermore, these authors [104,105] have suggested that MDMA-induced hyperthermia might be the result of increased DA release through interactions with the DA D1 receptor [171]. Although MDMA does cause hyperthermia, the role of these hyperthermic responses in the causation of MDMA-induced serotonergic neurotoxicity remains to be further investigated.

5. Toxicity in fetal development

In spite of the multiple reports of MDMA neurotoxicity in mature animals, studies on the effects of MDMA on the developing fetus are scarce. This is an area of great concern because MDMA abusers are young and of childbearing ages. In addition, the drug is known to produce a feeling of closeness towards others and sexual arousal [30–32]. Therefore, it is not far-fetched to presume that young MDMA abusers might be prone to get pregnant. It is thus of paramount importance to generate more detailed knowledge of the possible effects of the drug on fetal development. In fact, only two studies were found that assessed the effects on prenatal MDMA exposure [36,174]. Both reported that MDMA has no effect on prenatal neurochemical development of the serotonergic system in rats [36,174]. In the first study by St. Omer et al. [174], pregnant rats were gavaged with either 2.5 or 10 mg/kg of MDMA on alternating days during gestation (days 6–18). The study concluded that prenatal MDMA exposure produced subtle behavioral changes in the developing rats but did not affect the markers of 5-HT systems at the doses used in the study. Colado et al. [36] studied MDMA prenatal exposure by administering repeated high doses (20 mg/kg s.c. 2× daily) of MDMA to pregnant rats (days 14–17). This study also reported that MDMA did not produce damage to serotonin nerve terminals. Colado et al. [36] suggested that the fetal and neonate brain might be protected from damage caused by MDMA because either that it fails to form neurotoxic metabolites of MDMA or that the fetal brain has a much higher capacity to scavenge and inactivate free radicals compared to the adult brain. There is evidence that certain antioxidant enzymes are indeed increased in the developing mouse embryos, fetuses, and neonates [43] and in the perinatal rat lung [27] and rat cerebral microvessels [1]. Other studies [147,159] have also suggested an age-dependent different potential for free radical formation in rats. Broening et al. have reported that rats do not develop sensitivity to MDMA (10–40 mg/kg)-induced effects until PND40 [15]. This group has also suggested that a lack of MDMA-induced hyperthermia in neonates might account for the decreased sensitivity to MDMA-induced neurotoxicity [16]. However, Meyer and Ali [106] found no evidence that changes in body temperature contribute to differences in serotonergic neurotoxicity between neonate and adult rats. Another study by Aguirre et al. [2] suggested that low levels of MDMA might be responsible for perinatal insensitivity to MDMA-induced neurotoxicity. In this study, L-DOPA (80 mg/kg s.c.) followed by MDMA (20 mg/kg s.c.) administered at PND21 caused lasting decreases in 5-HT levels and 5-HT transporter density in the hippocampus and frontal cortex and significant hyperthermia [2]. The authors also gave pregnant rat dams MDMA (20 mg/kg s.c.) from embryonic day E6–E20 and sacrificed at PND15. The effects of MDMA on these pups were contrasted to that seen in rat pups given a single dose of 20 mg/kg postnatally at PND 14, 21, 28 or 35. MDMA did not affect the 5-HT content and 5-HT transporter density in pups exposed prenatally. Long-term reductions in 5-HT levels were observed only after PND35 in pups exposed to MDMA postnatally [2]. Others have reported that MDMA (10 mg/kg s.c. 2×/day) given to newborn rat pups can cause reductions in SERT binding in the hippocampus at PND 25 and 60 and neocortex at PND 60 and in 5HT levels in the hippocampus at PND 25 [106].

In contrast, the recent clinical literature suggests that prenatal MDMA exposure is toxic to the developing human fetus. One study reported that babies exposed to Ecstasy in utero show significantly increased risks for congenital defects, including cardiovascular and musculoskeletal anomalies [101]. In addition, several preclinical studies in animals and tissue culture suggest that in utero exposure to MDMA can cause damaging effects [17,18,191]. Bronson et al. [18] suggested that MDMA may have direct effects on the fetus based on their findings that MDMA (32 mg/kg) decreased embryonic motility in chicken embryos. Broening et al. [17] reported that MDMA exposure (5–20 mg/kg s.c., 2× daily) in 11–20-day-old neonatal rats caused dose-related impairments in sequential learning and spatial learning and memory. This time period in neonatal rats corresponds to late human third trimester brain development [17]. Finally, Won et al.

[191] observed that cultures prepared from MDMA exposed (40 mg/kg 2× daily, E6–E13) embryos of mice show long-term (up to 36 days of culture) increased reaggregate 5-HT levels and increased production and release of 5-HIAA. Due to the seemingly conflicting evidence, further studies are needed to evaluate the potential risks of MDMA to fetuses.

6. Conclusion

Ecstasy is a popular recreational drug among young adults and even teenagers. The evidence is overwhelming that MDMA produces acute and long-lasting neurotoxic effects in animals. There is a growing consensus that MDMA might also cause neurodegenerative effects in the human brain. Nevertheless, it is still not clear how the animal literature might completely relate to the human condition. Because of the pervasive abuse of MDMA among young people, who are of childbearing age, it is of paramount importance to identify possible deleterious effects of MDMA on the developing fetus. It will also be necessary to decipher the cellular and molecular mechanisms that are involved in causing these changes. These studies will be of clinical relevance because elucidation of these toxic cascades might help to plan future preventive and/or therapeutic interventions in that patient population.

Acknowledgements

Johnalyn Lyles is supported by the NIH/NIDA Intramural Research Program and the David and Lucille Packard Foundation. We thank Dr. Ning-sheng Cai for her helpful comments on the manuscript. We also wish to thank two anonymous reviewers for their constructive criticism and comments that helped to improve the manuscript.

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