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REVIEW

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Acute and long-term effects of MDMA on cerebral dopamine biochemistry and function

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Abstract *Rationale and objectives:* The majority of experimental and clinical studies on the pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) tend to focus on its action on 5-HT biochemistry and function. However, there is considerable evidence for MDMA having marked acute effects on dopamine release. Furthermore, while MDMA produces long-term effects on 5-HT neurones in most species examined, in mice its long-term effects appear to be restricted to the dopamine system. The objective of this review is to examine the actions of MDMA on dopamine biochemistry and function in mice, rats, guinea pigs, monkeys and humans. *Results and discussion:* MDMA appears to produce a major release of dopamine from its nerve endings in all species investigated. This release plays a significant role in the expression of many of the behaviours that occur, including behavioural changes, alterations of the mental state in humans and the potentially life-threatening hyperthermia that can occur. While MDMA appears to be a selective 5-HT neurotoxin in most species examined (rats, guinea pigs and primates), it is a selective dopamine neurotoxin in mice. Selectivity may be a consequence of what neurotoxic metabolites are produced (which may depend on dosing schedules), their selectivity for monoamine nerve endings, or the endogenous free radical trapping ability of specific nerve endings, or both. We suggest more focus be made on the actions of MDMA on dopamine neurochemistry and function to provide a better understanding of the acute and long-term consequences of using this popular recreational drug.

Keywords MDMA · Dopamine · Hyperthermia · Behaviour · Neurotoxicity · Oxidative stress · Metabolism · Rodents · Non-human primates · Humans

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Introduction

It is now approaching 20 years since 3,4-methylenedioxyamphetamine (MDA) was first reported to be neurotoxic to 5-HT nerve endings in the brains of rats (Ricaurte et al. 1985), a paper followed shortly thereafter by confirmation of this finding and the observation that administration of the related compound 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) had a similar effect (Stone et al. 1986). The damage to 5-HT neurones was suggested to be "selective" in that the nerve endings of other neurotransmitters were not damaged (Gibb et al. 1990). Specifically, the lack of damage to dopamine nerve endings was emphasised when comparing the action of MDMA with methamphetamine that produces neurotoxic damage to both dopamine and 5-HT neurones in rat brain (Schmidt and Kehne 1990; Green et al. 1992).

Consequently, the focus of the majority of research on MDMA has been on the acute and long-term effects of the drug on 5-HT function, despite the fact that MDMA administration was shown to produce acute changes in both dopamine and 5-HT release in cerebral tissue many years ago, and was reported to be neurotoxic to dopamine neurones in the brain of mice (see later). The purpose of this review, therefore, is to outline the action of MDMA on cerebral dopamine biochemistry and function of several species, including humans and examine recent work which suggests that more attention should be paid to the role of dopamine in both the acute and long-term effects of MDMA.

Acute effects of MDMA on cerebral dopamine neurochemistry

Rats

MDMA administration rapidly induces the release of dopamine from cerebral tissue. This has been shown in vitro by the use of tissue slices (Johnson et al. 1986; Schmidt 1987; Crespi et al. 1997). Crespi et al. (1997) showed that the MDMA-induced [^{3}H]-dopamine release in a striatal synaptosomal preparation was calcium-dependent and that the potency was, in descending order of potency: amphetamine>*p*-chloroamphetamine>MDMA>fenfluramine. O'Loinsigh et al. (2001) found the order of potency to be MDA>MDMA>methylenedioxyethylamphetamine>methylenedioxybutylamphetamine.

MDMA has also been shown to enhance dopamine release in vivo with the use of microdialysis techniques (Yamamoto and Spanos 1988; Gough et al. 1991; Nash and Brodkin 1991; Nash and Yamamoto 1992; Gudelsky et al. 1994; Yamamoto et al. 1995; Koch and Galloway 1997; Sabol and Seiden 1998; Colado et al. 1999; Nixdorf et al. 2001). In the caudate, the MDMA-induced increase in extracellular dopamine is greater than that of 5-HT (Gough et al. 1991). Systemic injection of MDMA also increases the extracellular concentration of dopamine in the nucleus accumbens (Yamamoto and Spanos 1988). The results of White et al. (1994) were consistent with this observation, since they observed an increase in extracellular 5-HT and dopamine when MDMA was infused into the nucleus accumbens of awake rats. Again the magnitude of the dopamine increase was greater than that of the 5-HT increase. A similar rapid increase in dopamine was reported to occur in the striatum, together with a decrease in homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) (Fig. 1).

When MDMA was administered in vivo, with subsequent in vitro analysis of striatal tissue, it has been reported to either increase or leave unchanged the extracellular dopamine content and lower DOPAC metabolite content in the first few hours (Schmidt et al. 1987, 1991a; Logan et al. 1988; Yamamoto and Spanos 1988; Gough et al. 1991; Colado and Green 1994).

The role of the dopamine uptake site in the induction of dopamine release by MDMA is controversial, probably due to specific methodological differences related to the administration pathway, the ambient room temperature or the strain of rats used in different studies. Koch and Galloway (1997) found that the dopamine uptake inhibitor GBR12909 prevented MDMA-induced dopamine release from a brain slice preparation. This is consistent with the observation that GBR12909 antagonised the dopamine release produced by injection of MDMA into the brain (Nash and Brodkin 1991). Similar results were obtained when mazindol and MDMA were co-administered systemically (Shankaran et al. 1999). However, Mechan et al. (2002), using in vivo microdialysis, observed that GBR12909 did not inhibit the dopamine release in the striatum induced by peripheral injection of MDMA. Similar data were obtained in mice (Camarero et al. 2002). These data would suggest that MDMA enters the dopamine nerve ending by diffusion rather than the uptake carrier. It is also noteworthy that the dopamine uptake inhibitor mazindol fails to antagonise the dopamine

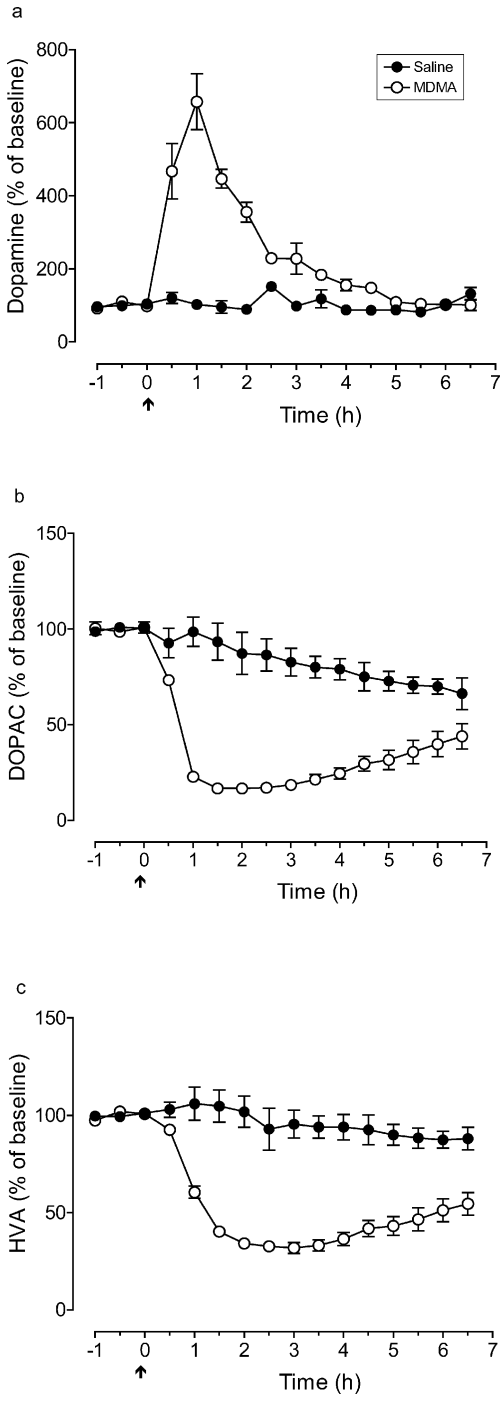

Fig. 1 Changes in the levels of **a** dopamine, **b** 3,4-dihydroxyphenylacetic acid (*DOPAC*) and **c** homovanillic acid (*HVA*) in the striatal dialysate of Dark Agouti rats treated with MDMA (15 mg/kg, IP, marked by the *arrow*). Values are expressed as a percentage of the mean of three measurements before drug administration. Each value is the mean±SEM of five to seven experiments. The basal concentrations in saline-treated rats were: dopamine (0.83±15 pg/µl), DOPAC (252±23 pg/µl) and HVA (246±16 pg/µl). Reproduced from Colado et al. (1999) by permission of Stockton Press

releasing action of methamphetamine (Marek et al. 1990), which suggests that this related amphetamine compound also enters nerve endings by diffusion.

Following multiple doses of MDMA, there is a significant reduction of [^{3}H]-dopamine uptake into synaptosomes prepared from the brains of treated animals, an effect observed 1 h after the last dose, but not 24 h later (Hansen et al. 2002). A similar reduction occurs if striatal synptosomes are incubated with MDMA, an effect which is prevented by pre-treatment with protein kinase C inhibitors, suggesting the possible involvement of this enzyme in the response (Hansen et al. 2002).

There is good evidence to suggest that 5-HT is involved in the mechanisms associated with MDMA-induced dopamine release in the striatum. The release is markedly inhibited by pre-treatment of the rats with fluoxetine (Koch and Galloway 1997). Furthermore, pre-treatment with the 5-HT$_2$ receptor agonists 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) or 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) potentiates MDMA-induced dopamine release (Gudelsky et al. 1994). Consistent with these data, which suggest that 5-HT$_2$ receptors enhance MDMA-induced dopamine release, is the observation that the release was inhibited in both substantia nigra and striatum by the 5-HT$_{2A/2C}$ antagonist ritanserin (Yamamoto et al. 1995). It is certainly possible that the greater magnitude of MDMA-induced acute dopamine release compared to that of 5-HT (Gough et al. 1991; White et al. 1994) results from the MDMA-induced release of 5-HT acting to further enhance dopamine release. The fact that tetrodotoxin attenuated the MDMA-induced dopamine release indicates that release may be an impulse-mediated response (Yamamoto et al. 1995).

Dopamine release in the hippocampus is inhibited by the noradrenaline uptake inhibitor desipramine and the selective noradrenaline depleting drug DSP4 [N-(2-chloroethyl)-N-ethyl-2-bromo benzylamine], which indicates that MDMA is releasing dopamine from noradrenergic terminals in this brain region (Shankaran and Gudelsky 1998).

Mice

MDMA administration produces an acute release of dopamine in mouse brain. Following three injections of MDMA the striatal concentration of dopamine, HVA and DOPAC has been found to be reduced 3 h later (O'Shea et al. 2001). Further evidence for MDMA inducing dopamine release was provided by in vivo microdialysis studies which found a marked increase in extracellular dopamine in the striatum following MDMA administration (Colado et al. 2001; Camarero et al. 2002). A single dose of MDMA produced only a modest rise in dopamine concentration, but the rise was both magnified and sustained by further doses of MDMA (Fig. 2).

Administration of GBR12909 enhanced the MDMA-induced rise in extracellular dopamine (Camarero et al. 2002), a result, which mirrors the observation in rats by Mechan et al. (2002) and indicates that MDMA may enter the nerve terminal by diffusion rather than via the dopamine uptake site.

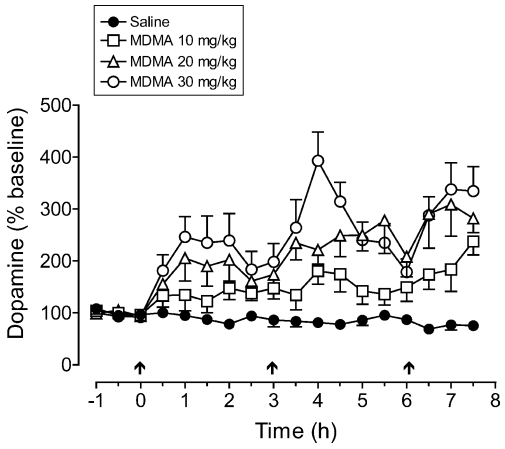

Fig. 2 Changes in the levels of dopamine in the striatal dialysate of Swiss Webster mice treated with repeated injections of MDMA (10, 20 or 30 mg/kg, IP, marked by the *arrows*). Animals received three injections at 3-h intervals. Values are expressed as a percentage of the mean of three measurements before drug administration. Each value is the mean±SEM of five to nine experiments. The basal dopamine concentration in saline-treated rats was 0.93±0.2 pg/µl. Reproduced partially from Camarero et al. (2002) by permission of Blackwell Publishing

Finally, it should be noted that MDMA has a low affinity for dopamine receptors (Battaglia et al. 1988a), which allows the proposition that any dopamine-mediated effects of MDMA are a consequence of the dopamine releasing action of the compound rather than any direct action on dopamine receptors.

Does the acute effect of MDMA on dopamine release have functional consequences?

Some of the behavioural consequences of MDMA administration to rats are similar to those seen after injection of other 5-HT releasing drugs such as *p*-chloroamphetamine (PCA) and fenfluramine, and there has therefore been substantial investigation on the involvement of 5-HT in the functional consequences of MDMA administration. However, there is also good evidence for a role of dopamine.

Given the evidence for the marked release of dopamine from its terminals following MDMA administration to rats, it is not surprising that the drug induces hyperlocomotion (Gold and Koob 1988; Gold et al. 1989; Spanos and Yamamoto 1989; Callaway et al. 1990; Callaway and Geyer 1992; Dafters 1995). However, MDMA administration can also induce the appearance of the 5-HT syndrome (see Grahame-Smith 1971a; Green and Heal 1985; Colado et al. 1993), presumably as a consequence of the major release of 5-HT that is occurring (Slikker et al. 1989; Spanos and Yamamoto 1989; Colado et al. 1993; Shankaran and Gudelsky 1999). Because MDMA induces the release of both these major neurotransmitters, any

analysis of the various components of the behavioural changes seen is complex (Bankson and Cunningham 2001, 2002) and this simultaneous release presumably contributes to the differences in overt behaviour seen when comparing amphetamine with MDMA. For example, while amphetamine administration resulted in rats showing increased activity over the whole activity chamber, MDMA-induced activity was predominately in the periphery of the chamber (Gold et al. 1989; Callaway et al. 1990; McCreary et al. 1999). Furthermore, fluoxetine pretreatment inhibits the locomotor activity induced by MDMA but not that induced by amphetamine (Callaway et al. 1990) and studies have shown that multiple subtypes of 5-HT receptors contribute to this behavioural effect of MDMA (Fletcher et al. 2002). Thus, 5-HT_{2A} and 5-$HT_{1B/D}$ receptors appear to have a facilitatory role while that played by 5-HT_{2C} receptors appears to be inhibitory (McCreary et al. 1999; Bankson and Cunningham 2001; Fletcher et al. 2002).

Similarly, MDMA induces an increase in locomotor activity in mice (Miller and O'Callaghan 1994; Bengel et al. 1998; Scearce-Levie et al. 1999; Itzhak et al. 2003), which also appears to be regulated, at least in part, by the 5-HT transporter (Bengel et al. 1998) and the 5-HT_{1B} receptor (Scearce-Levie et al. 1999; Compan et al. 2003).

Sensitization to repeated low doses of MDMA has been reported in rats (Spanos and Yamamoto 1989; Kalivas et al. 1998), and the increased size of the response appeared to be associated with an elevation in the extracellular content of dopamine which occurs after each administration (Kalivas et al. 1998). In mice, MDMA appears to induce sensitization to subsequent doses of MDMA or cocaine, although maintenance of this sensitization is related to the enduring neurotoxicity induced by the drug (Itzhak et al. 2003).

Dopamine release in the striatum is also associated with some of the functional effects of MDMA. Schmidt et al. (2002) found that MDMA produced a dose-dependent inhibition of haloperidol-induced catalepsy, the activity being present in the [RS]- and [S]-enantiomer of MDMA. This is in accord with the observation that it is [S]-MDMA, which is the potent releaser of dopamine (Johnson et al. 1986). MDMA also induces ipsilateral circling in rats with a unilateral lesion of the striatum (Lebsanft et al. 2003), which demonstrates that rotation is primarily due to dopamine release from the intact side of striatum. These authors also reported an attenuation of the response by citalopram and *p*-chlorophenylalanine (PCPA). However, since MDMA-induced dopamine release is attenuated by fluoxetine (Koch and Galloway 1997) and 5-HT agonists enhance striatal dopamine release (Gudelsky et al. 1994), this result is not surprising. Whether these observations on the effect of MDMA on striatal dopamine release can in any way be linked to the anecdotal reports of the drug having a beneficial effect in human subjects suffering from Parkinson's disease (Margolis 2001) remains unclear. In fact, in MPTP-treated marmosets, MDMA administration causes an initial and transient improvement in motor disability, but a subsequent worsening and the appearance of a much longer lasting reduction of motor activity (Iravani et al. 2003).

One major clinical problem that can occur in recreational users of MDMA is hyperthermia with body temperatures as high as 43°C having been reported (Henry et al. 1992). Under "normal" ambient room temperature conditions (20–22°C), MDMA usually produces a marked hyperthermic response of approximately 1–2°C in rats, with a peak at about 40–60 min post-injection (Nash et al. 1988; Schmidt et al. 1990a; Colado et al. 1993; Dafters 1994; Broening et al. 1995; Che et al. 1995; Malberg et al. 1996; O'Shea et al. 1998). Data suggest that MDMA and methamphetamine interfere with normal heat loss mechanisms, which probably explains the hyperthermic action of these two compounds (Mechan et al. 2002; Mohaghegh et al. 1997). However, an acute decrease in temperature has also been reported in some studies with MDMA (Malberg and Seiden 1998; Marston et al. 1999). In mice, the effect of MDMA on body temperature is much more variable than that observed in rats depending on the dose and strain examined, nevertheless most studies show hyperthermia (Miller and O'Callaghan 1994; Johnson et al. 2000, 2002a; Colado et al. 2001; O'Shea et al. 2001; Fantegrossi et al. 2003; Sanchez et al. 2003). The hyperthermic response is directly related to the conditions at which animals are housed during drug administration, the rise in temperature being greater the higher the ambient temperature and the number of animals per cage (Carvalho et al. 2002; Fantegrossi et al. 2003). These data are particularly relevant given the typical rave environment (hot and crowded) in which the drug is usually taken.

Since increasing 5-HT function can produce hyperthermia (Grahame-Smith 1971a, 1971b; Yamawaki et al. 1983; Colado et al. 1993), there has tended to be an assumption that MDMA-induced hyperthermia is 5-HT receptor mediated (Shankaran and Gudelsky 1999). However, a recent study has indicated that MDMA-induced hyperthermia is a consequence of dopamine release. Several 5-HT antagonists failed to block MDMA-induced hyperthermia (Mechan et al. 2002), and administration of the selective 5-HT uptake inhibitor fluoxetine almost totally inhibited the increase in extracellular 5-HT but had no effect on the hyperthermic response in the same animals, confirming earlier studies (Schmidt et al. 1990b; Berger et al. 1992; Malberg et al. 1996), which indicates that 5-HT release and hyperthermia are separable. The observation that the dopamine D_1 receptor antagonist SCH 23390 dose-dependently inhibited MDMA-induced hyperthermia suggests that MDMA probably induces hyperthermia by enhancing the release of dopamine, which then acts on D_1 receptors (Mechan et al. 2002). This interpretation is supported by the work of Sugimoto et al. (2001), who found that PCA-induced hyperthermia was also unaltered by fluoxetine or the 5-HT depleting drug PCPA, but was antagonized by the dopamine D_1 receptor antagonist SCH 23390.

With regard to the acute consequences of MDMA on body temperature, it is worth mentioning the pharmaco-

logical interactions between MDMA and cocaine, another recreational drug which is reported to be taken by 75% of heavy ecstasy users (Parrott et al. 2000). In rodents, both of these drugs induce hyperthermia and increase dopamine concentration in the synaptic cleft; MDMA by increasing dopamine release (Yamamoto and Spanos 1988; Colado et al. 1999) and cocaine by inhibiting dopamine uptake through an action at the dopamine transporter (Kennedy and Hanbauer 1983; Bradberry et al. 1993). Ingestion of cocaine with MDMA may therefore exacerbate any MDMA-induced hyperthermia.

Crucial to our understanding of the psychological consequences of MDMA use in humans, there have been several studies on the rewarding properties of MDMA and these studies generally implicate dopamine in the actions of the drug. Systemic MDMA administration results in substantial increase in dopamine release in the nucleus accumbens (Yamamato and Spanos 1988; White et al. 1994). Behavioural sensitization to cocaine is associated with enhanced dopamine release in the nucleus accumbers (Pettit et al. 1990; Kalivas and Duffy 1993; Heidbreder et al. 1996) and Kalivas et al. (1998) found behavioural cross sensitization to cocaine in rats repeatedly treated with MDMA. However, this is a complex area and made more so by the release by MDMA of 5-HT with its own effects on reward. This is discussed in more detail elsewhere (White et al. 1996; Cole and Sumnall 2003).

It is also possible that previous exposure to MDMA may increase the reinforcing effects of other psychostimulants such as cocaine and amphetamine. There is strong experimental evidence indicating that rats treated with MDMA subsequently develop enhanced behavioural and biochemical responses to psychomotor stimulants. Recent studies have shown that, in animals pretreated with MDMA, cocaine produces a higher increase in the extracellular levels of dopamine in the nucleus accumbens than in control rats (Morgan et al. 1997). If the reinforcing effect of cocaine is dependent, in part, upon increased dopamine release in the nucleus accumbens, these data suggest that MDMA may increase vulnerability to cocaine abuse. Subsequently, using the appropriate paradigms, it has been shown that rats pretreated with MDMA show a significantly greater conditioned place preference (CPP) response to cocaine than vehicle-treated animals (Horan et al. 2000), although this may depend on the protocol of MDMA administration, since another study failed to confirm this (Cole et al 2003). In mice, adolescent exposure to MDMA increased hyperlocomotion and CPP to a priming injection of cocaine after a 14-day drug-free period (Achat-Mendes et al. 2003).

Since CPP is believed to be a measure of appetitive behaviour, these results provide direct evidence of an increase in the rewarding properties of cocaine in rats pre-exposed to MDMA and suggest that MDMA abuse leads to increased vulnerability to cocaine addiction and dependence. In fact, pre-exposure to a high dose of MDMA facilitates acquisition of cocaine self-administration in rats (Fletcher et al. 2001) which again confirms that MDMA pre-exposure sensitizes rats to the reinforcing effects of cocaine. Consequently, and although we must be extremely cautious when extrapolating results from animals to humans, it would be reasonable to propose that MDMA users may be at risk of developing addiction and dependence to other psychomotor stimulants.

MDMA and dopamine neurotoxicity

Introduction

There is such a large body of evidence that MDMA produces neurotoxic degeneration of 5-HT nerve endings in the brain of experimental animals (for review, see Green et al. 2003) that the long-term effects of MDMA on dopamine neurones in several species tends to be overlooked. This may be, in part, because the majority of studies on MDMA use rats and the dopamine neurones of this species appear to be particularly resistant to MDMA-induced damage.

Rats

There are many publications which report solid evidence to support the contention that MDMA administration results in neurotoxic degeneration of 5-HT nerve endings in the forebrain of rats. This evidence is both neurochemical (loss of 5-HT and 5-HIAA, decrease in [^{3}H]-paroxetine binding to the nerve endings, decrease in [^{3}H]-5HT uptake into synaptosomes) and histological (for review, see Green et al. 2003). There is also compelling evidence against MDMA producing neurotoxic damage to dopamine nerve endings (Stone et al. 1986; Battaglia et al. 1987; Schmidt and Kehne 1990; Lew et al. 1996; Sabol et al. 1996; Colado et al. 1997, 1999). Recently Shankaran and Gudelsky (1999) also demonstrated that MDMA-induced striatal 5-HT release was inhibited by a prior neurotoxic dose of MDMA but that MDMA-induced dopamine release was unaltered.

The apparent resistance of the rat dopaminergic system to MDMA-induced neurotoxicity was recently emphasised by the study of Sanchez et al. (2003). This group depleted the antioxidant activity of the brain by feeding rats with a selenium-deficient diet. However, this procedure still failed to result in MDMA producing damage to dopamine neurones, even though it resulted in a marked decrease in glutathione peroxidase activity, one of the main cellular antioxidant systems against free radical formation. This contrasts with a similar study in mice (see later). However, dopamine toxicity has occasionally been observed in rats (Commins et al. 1987; Yuan et al. 2002). In the first report, MDMA was given repeatedly at very high doses and in the second, MDMA-treated rats were kept at high ambient temperature. In both cases animals presumably experienced a larger and more sustained hyperthermic response, which could have produced the modest dopamine loss in the striatum.

What has been suggested in a series of studies is that dopamine does play a role in the neurodegenerative process that results in MDMA-induced damage to 5-HT nerve endings. This contention, however, remains controversial and has been questioned in some recent publications. Early studies demonstrated that altering dopamine function also altered the degree of MDMA-induced damage to 5-HT neurones. Drugs used in these studies to alter dopamine function included the dopamine synthesis inhibitor α-methyl-*p*-tyrosine, the depleting drug reserpine (Stone et al. 1988), the dopamine uptake inhibitors, GBR12909 (Stone et al. 1988) and mazindol (Shankaran et al. 1999), and the dopamine antagonist haloperidol (Schmidt et al. 1990c; Hewitt and Green 1994), as well as lesioning of dopamine terminals with 6-hydroxydopamine (Stone et al. 1988). All these pretreatments attenuated MDMA-induced dopamine loss in the striatum, and Sprague et al. (1998) proposed an integrated hypothesis linking MDMA-induced dopamine release (see earlier) with neurotoxic damage to 5-HT nerve endings. Supporting the hypothesis was the report of Schmidt et al. (1991b) that L-dopa potentiated MDMA-induced damage to 5-HT neurones.

Shankaran et al. (1999) reported that the MDMA-induced dopamine release in the striatum was suppressed by mazindol, a compound that also attenuates the MDMA-induced increase in free radical formation (measured by conversion of salicylate to 2,3-dihydroxybenzoic acid). The authors therefore concluded that the enhanced dopamine release increased free radical formation thereby contributing to MDMA-induced damage to 5-HT nerve endings. Consistent with these findings is the fact that MAO-B inhibitors are neuroprotective (Sprague and Nichols 1995) and an antisense oligonucleotide targeted at the MAO-B enzyme also attenuated the long-term MDMA-induced 5-HT loss (Falk et al. 2002).

In contrast, Colado et al. (1999) argued that the protective effect of reserpine, α-methyl-*p*-tyrosine and haloperidol was the result of the hypothermic action of compounds. The protective effect of reserpine is not seen when MDMA is administered 24 h later, even though dopamine stores are still depleted, possibly because the hypothermic effect of reserpine has been lost (Hekmatpanah et al. 1989). Colado et al. (1999) also failed to find a potentiating effect of L-dopa on MDMA-induced neurotoxicity.

More direct evidence against the role of dopamine in MDMA-induced damage to 5-HT neurones has recently come from the report of Yuan et al. (2002). This group were unable to detect a protective action of α-methyl-*p*-tyrosine or reserpine when the body temperature of the treated animals was kept elevated to match that of the MDMA-alone group. These data suggest that hypothermia may have played a key neuroprotective role in some earlier studies.

Mice

MDMA has a very different neurotoxic profile in the mouse in comparison to that seen in the rat. This was first demonstrated many years ago, but has been relatively little investigated. Basically, MDMA is a relatively selective dopaminergic neurotoxin in mice leaving 5-HT concentrations unaffected (Stone et al. 1987; Logan et al. 1988; O'Callaghan and Miller 1994), which is exactly opposite to the effect of MDMA in rats. Long-lasting effects of MDMA in the striatal dopamine neurones are reflected by a loss of dopamine concentration, a reduction in the density of dopamine uptake sites, a decrease in tyrosine hydroxylase activity and an elevation in the levels of glial fibrillary acidic protein, a marker of astrogliosis (Mann et al. 1997; Jayanthi et al. 1999; Johnson et al. 2002a). However, this general point ignores the fact that one of the original investigating groups reporting on this phenomenon (Logan et al. 1988) subsequently also noted that there were strain differences in mice. Their original study (Logan et al. 1988) used random-bred mice. Zheng and Laverty (1993) reported that CBA mice were more sensitive to the neurotoxic effect of multiple doses of MDMA than either BALB/C or C57BL/6 strains. However, they also detected a neurotoxic loss in 5-HT in addition to dopamine loss in the CBA mice. O'Shea et al. (2001) using Swiss Webster mice confirmed the selective dopamine loss in this strain and also reported that fluoxetine administration had no effect on the neurotoxicity. The dopamine uptake inhibitor GBR12909 is neuroprotective against damage to dopamine neurones (O'Shea et al. 2001; Camarero et al. 2002), even though it does not inhibit the MDMA-induced release of dopamine when measured by microdialysis (Camarero et al. 2002). Since GBR12909 did inhibit the MDMA-induced rise in free radical formation in the striatum, these data suggest that GBR12909 is not protecting via an action in blocking MDMA uptake into the nerve ending but rather that the compound may prevent the entry of neurotoxic metabolites via the uptake carrier.

The role of free radicals in MDMA-induced damage to dopamine neurones in mouse brain has been demonstrated by several different approaches. Recently, using intracerebral microdialysis in vivo, it has been demonstrated that MDMA increases the formation of 2,3-dihydroxybenzoic acid (2,3-DHBA) from salicylic acid perfused through a probe implanted in the striatum, indicating increased hydroxyl radical formation (Colado et al. 2001; Camarero et al. 2002). In this line, Cadet et al. (1994, 1995, 2001) observed that Cu-Zn-superoxide dismutase transgenic mice are resistant to MDMA-induced neurotoxicity. In addition to increased free radical production, MDMA decreases the activity of the main brain antioxidant enzymes such as glutathione peroxidase, catalase and Cu-Zn-superoxide dismutase and increases lipid peroxidation in several brain areas of the mouse, which may be reflecting the existence of an oxidative stress process (Jayanthi et al. 1999; Camarero et al. 2002). Furthermore, MDMA has been reported to produce a greater striatal

dopamine loss in animals that are vitamin E-deficient compared with replete mice (Johnson et al. 2002b). Lowering cerebral antioxidant defences of mice by feeding them a selenium-deficient diet also increases the size of MDMA induced dopamine loss (Fig. 3). Interestingly, selenium deficiency also results in MDMA inducing neurotoxic damage to 5-HT nerve endings, in contrast to selenium-replete mice (Table 1). Supporting all this evidence is the fact that the antioxidant enzyme capacity in the brain is compromised by glucocorticoids (McIntosh et al. 1998), and corticosterone increases the vulnerability of the striatum to the damage induced by MDMA (Johnson et al. 2002a).

The exact role of free radicals in producing the damage remains unclear. However, recent investigations indicate the possible involvement of peroxynitrites. Administration of either of the nitric oxide synthase inhibitors S-methyl-thiocitrulline and AR-R17477AR was found to attenuate the MDMA-induced damage. AR-R17477AR also inhibited the MDMA-induced rise in free radical formation in vivo which indicates that it was either MDMA or dopamine metabolic breakdown products that were producing radicals which were combining with nitric oxide to produce tissue damaging peroxynitrites (Colado et al. 2001; Camarero et al. 2002). Such an interpretation would be consistent with recent data which suggest that NOS and peroxynitrites are involved in methamphetamine-induced neurotoxicity (Ali and Itzhak 1998; Itzhak et al. 1998, 2000; Imam et al. 1999).

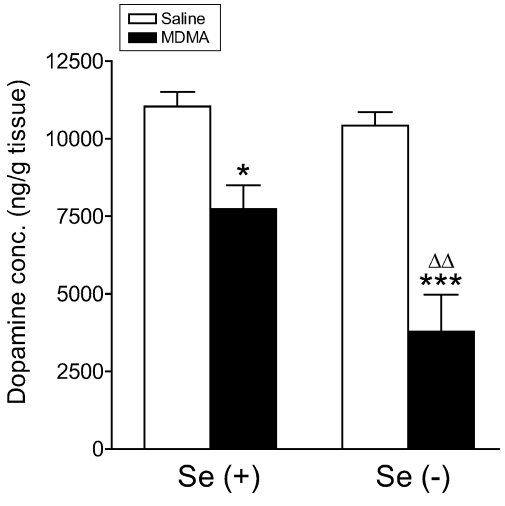

Fig. 3 Dopamine concentration in the striatum of C57BL/6J mice fed either a selenium-replete (*Se+*) or selenium deficient (*Se−*) diet and given three injections of MDMA (15 mg/kg, IP) at 3 h intervals. Animals were maintained on dietary treatment for 7 weeks before receiving MDMA and for 1 week after. Results shown as mean ±SEM (n=5–9). Different from the corresponding saline-group: *P<0.05, ***P<0.001. Different from Se-replete+MDMA group: $^{\Delta\Delta}P$<0.01. Dopamine concentration (ng/g tissue) in mice fed a standard diet was as follows: saline=10,398±339, MDMA=6638 ±538). Reproduced from Sanchez et al. (2003) by permission of Elsevier Science Ltd

Table 1 Concentrations of 5-HT (ng/g tissue) in cortex, hippocampus and striatum of mice fed either a Se-replete (*Se+*) or Se-deficient (*Se−*) diet and given three injections of MDMA (15 mg/kg, IP) at 3-h intervals. Animals were maintained on dietary treatment for 7 weeks before receiving MDMA and for 1 further week. The figure between parenthesis is the percentage of change versus the respective control group. Reproduced from Sanchez et al. (2003) by permission of Elsevier Science Ltd

	Diet	Saline	MDMA
Cortex	Se (+)	315±24	279±23 (11↓)
	Se (−)	287±21	196±8[a,b] (32↓)
	Standard	344±11	285±22 (17↓)
Hippocampus	Se (+)	503±10	518±29 (1↑)
	Se (−)	526±26	425±19[a,b] (29↓)
	Standard	476±27	441±11 (7↓)
Striatum	Se (+)	475±31	444±25 (7↓)
	Se (−)	450±8	372±13[a,b] (17↓)
	Standard	338±31	319±33 (6↓)

Results shown as mean±SEM (n=5–9). Different from the corresponding saline-group: [a]P<0.05. Different from Se-replete +MDMA group: [b]P<0.05

Guinea pigs

MDMA was found to be neurotoxic to 5-HT nerve terminals in guinea pig brain by Commins et al. (1987). This group reported that the compound also produced a significant loss in striatal dopamine concentration. The 5-HT loss was confirmed by Battaglia et al. (1988b), but no examination of dopamine biochemistry was performed. Recently, Saadat et al. (2004) attempted to confirm the Commins et al. (1987) report. However, despite administration of doses of MDMA that produced a greater than 70% loss in striatal 5-HT content, no decrease in dopamine concentration was observed. MDMA thus appears to be a selective 5-HT neurotoxin in guinea pigs.

Primates

A series of studies on primates over the last 15 years all reported significant damage to 5-HT nerve terminals following MDMA administration (Ricaurte et al. 1988a, 1988b, 1988c; Slikker et al. 1988, 1989; Insel et al. 1989; Kleven et al. 1989; Wilson et al. 1989; Ricaurte and McCann 1992; Fischer et al. 1995; Scheffel et al. 1998; Hatzidimitriou et al. 1999, 2002), but none reported evidence of damage to dopaminergic terminals when this had also been studied (Ricaurte et al. 1988a; Slikker et al. 1988; Insel et al. 1989; Ricaurte and McCann 1992; Hatzidimitriou et al. 1999). Even high doses of MDMA producing almost total loss (90%) of 5-HT in the caudate nucleus of squirrel monkeys left dopamine and noradrenaline levels unaffected (Ricaurte et al. 1988a).

It was therefore of particular surprise when one of the major groups involved in primate research recently reported that MDMA could produce damage to dopaminergic terminals in the brains of squirrel monkeys and

baboons following a binge dosing schedule (Ricaurte et al. 2002). The recent retraction of this report in the light of evidence that the laboratory had been erroneously supplied with methamphetamine instead of MDMA (Ricaurte et al. 2003) perhaps re-emphasises the fact that MDMA is probably a selective 5-HT neurotoxin in monkeys

Human studies

A major problem in assessing physiological or psychological changes produced by MDMA in human recreational users is that few clinically based controlled studies have been performed and most studies are conducted retrospectively on subjects who have used illicit tablets. There is therefore no knowledge of purity or doses of the ingested MDMA. This is discussed elsewhere (Green et al. 2003). However, a recent review has indicated that the majority of "ecstasy" tablets contain either MDMA or a closely related substance (Parrott 2004). However, to separate studies that examined the effect of MDMA of known purity and dose from those in which the "street drug" has been used, we will use the term "ecstasy" for the latter.

Dopamine is known to be involved in the mediation of euphoria in humans when induced not only by ingestion of classical psychostimulants such as d-amphetamine, cocaine or methylphenidate (Lieberman et al. 1990; Laruelle et al. 1995; Schlaepfer et al. 1997; Volkow et al. 1997) but also following MDMA administration. Liechti and Vollenweider (2000) observed that administration of the relatively selective dopamine D_2 receptor selective antagonist haloperidol (1.4 mg/kg, IV) to volunteers 10 min before MDMA (1.5 mg/kg, PO) changed the pattern of subjective MDMA effects from a pleasurable state of well-being and euphoria to a dysphoric state with slightly increased anxiety. In contrast, haloperidol failed to antagonise cardiovascular effects of MDMA such as blood pressure and heart rate. These findings indicate a role for dopamine in mediating the psychological, but not cardiovascular, effects of MDMA.

Ecstasy ingestion not only appears to produce changes indicative of an acute effect on cerebral dopamine function but results also indicate that it may induce long-lasting changes in dopaminergic pathways that are apparent after drug use ceases. A recent study showed that 3 weeks after ecstasy discontinuation, the growth hormone (GH) response to bromocriptine was significantly reduced in ecstasy users in comparison with control subjects (Gerra et al. 2002). The authors suggested that the findings indicated a dysfunction of dopaminergic pathways that are involved in the regulation of GH-releasing hormone and consequently of pituitary GH release. Such a dysfunction need not be interpreted as evidence of neurotoxicity, however. In a post-mortem study from a single heavy user of ecstasy no evidence was found of a loss in the striatal concentration of dopamine (Kish et al. 2000) and more persuasively, the HVA levels in the cerebral spinal fluid of regular ecstasy users were within reported to be within the normal range (McCann et al. 1994, 1999). Semple et al. (1999), using single photon emission computed tomography (SPECT), also found no evidence of a reduction in dopamine transporter density in the brain of ecstasy users, but did detect a reduction in 5-HT transporter density. Reneman et al. (2001) undertook a similar study but only found a reduction in 5-HT transporter density in "heavy" ecstasy users and then only in female users, not males, perhaps indicating a greater susceptibility of female users. This group were, however, unable to detect any loss of nigrostriatal neurones using SPECT methodology (Reneman et al. 2002). Nevertheless, while exclusive ecstasy use does not appear to decrease the striatal dopamine transporter density, the combined use of amphetamine and MDMA may be associated with a reduction in striatal DA transporter density; that is, this combination might be neurotoxic to dopamine neurones (Reneman et al. 2002). These data may have substantial clinical significance, since ecstasy users are often polydrug users and a recent study carried out in Ireland reveals that 83% of heavy ecstasy users also take amphetamine (Parrott et al. 2000).

If ecstasy produces dopamine loss in the human brain then it can be predicted that it is likely, in the long-term, to increase the incidence of Parkinson's disease. However, this is likely to occur only in heavy and frequent users of the drug. Furthermore, any increase may not be seen for many years as substantial loss of dopamine must occur before parkinsonian symptoms appear and loss of cerebral dopamine content is a normal component of aging (O'Shea and Colado 2003). While there have been two anecdotal reports of Parkinson's disease occurring in recreational users of ecstasy (Mintzer et al. 1999a; Kuniyoshi and Jankovic 2003), the first report having been criticised by others (Baggott and Mendelson 1999; Sewell and Cozzi 1999; but see Mintzer et al. 1999b), two isolated case reports cannot, we feel, be used to support an argument that ecstasy carries this health risk. At present, therefore, there is no compelling evidence to suggest that MDMA use damages dopaminergic neurones in the human brain.

Metabolism and neurotoxic metabolites

Metabolism of MDMA

Studies on the metabolism of MDMA have centered almost exclusively on the rat with a small number of studies in humans. In the rat, MDMA is metabolised by three major pathways, demethylenation, demethylation and aromatic hydroxylation, as well as by a number of minor routes such as deamination and various conjugations, including glucuronidation and sulfation (Lim and Foltz 1988, 1991a, 1991b). Demethylenation of MDMA, via a cytochrome P450 monooxygenase system, has been demonstrated to occur in vitro in rat liver (Hiramatsu et al. 1990) and to a lesser extent, brain (Lin et al. 1992). CYP2D6 or debrisoquine hydroxylase, an enzyme that is

absent in 5–9% of the Caucasian population ("poor metabolisers"; Gonzalez and Meyer 1991), was identified as the main responsible isoenzyme in humans (Tucker et al. 1994), although CYP1A2 and CYP3A4 may also play a lesser role (Maurer et al. 2000). The equivalent isoform in rat was found to be CYP2D1 (Kumagai et al. 1994). Studies in female Dark Agouti rats, which are deficient in this enzyme and therefore a model of "poor metabolisers", revealed higher plasma levels of MDMA after administration of the drug and a larger hyperthermic response to MDMA (Colado et al. 1995). This led to the hypothesis that "poor metabolisers" would be at a greater risk of the acute effects of the parent drug, including the hyperthermic response (Colado et al. 1995). Consequently, they would also be at a reduced risk of the metabolite-induced neurotoxic effects; however, this failed to be observed in the same studies (Colado et al. 1995). These CYP2D enzyme isoforms catalyze the conversion of MDMA to 3,4-dihydroxymethamphetamine (HHMA; N-methyl-α-methyldopamine, N-Me-α-Me DA), an unstable reactive catechol derivative, in humans (Segura et al. 2001) and rats (Lim and Foltz 1988; Tucker et al. 1994). This compound has been shown to redox-cycle to the quinone in vitro (Kumagai et al. 1994; Tucker et al. 1994), which in the presence of glutathione (GSH) may form a GSH conjugate (Hiramatsu et al. 1990). HHMA has also been shown to undergo O-methylation by the action of catachol O-methyltransferase forming 4-hydroxy-3-methoxy-methamphetamine (HMMA; N-methyl-3-O-methyl-α-methyldopamine, N-Me-3-O-Me-α-Me DA) which appears to be a major metabolite in humans (Segura et al. 2001).

Demethylation, which takes place via CYP1A2 in both humans and rats (Maurer et al. 2000), gives rise to the similar, but more potent, neurotoxin MDA. This compound has been detected in vivo in both rat plasma and brain after the administration of MDMA (Chu et al. 1996), and plasma levels have recently been determined in rhesus monkeys after a repeated dosing neurotoxic regimen of MDMA (Bowyer et al. 2003). MDA has also been found in the plasma and urine of human volunteers given MDMA (de la Torre et al. 2000; Segura et al. 2001). MDA may in turn be demethylenated by CYP2D1/6, to the catechol 3,4-dihydroxyamphetamine (HHA; α-methyldopamine, α-Me DA) which may, in turn, form a quinone or be converted to 4-hydroxy-3-methoxyamphetamine (HMA; 3-O-methyl-α-methyldopamine, 3-O-Me-α-Me DA) (Segura et al. 2001).

Aromatic hydroxylation of MDMA has been shown to take place at position 6 of the aromatic ring, giving rise to 2-hydroxy-4,5-methylenedioxymethamphetamine or 6-hydroxy-MDMA (Lim and Foltz 1991a; Chu et al. 1996) which, via demethylenation by the CYP2D isoforms, yields 2,4,5-trihydroxymethamphetamine (2,4,5-THMA) (Lim and Foltz 1988, 1991b).

In all, 17 metabolites have been identified in the rat in vivo (Lim and Foltz 1988, 1991a, 1991b).

Role of metabolites in the neurotoxicity induced by MDMA

MDMA does not produce serotonergic toxicity when administered centrally to the rat (Molliver et al. 1986; Paris and Cunningham 1991; Esteban et al. 2001), in spite of producing similar acute neurochemical alterations (release of dopamine and 5-HT) (Esteban et al. 2001). This led to the proposal that peripheral metabolism of the drug is required in order to induce long-term depletions in the serotonergic system. Several metabolites of MDMA including MDA (Molliver et al. 1986), α-MeDA and 3-O-Me-α-MeDA (McCann and Ricaurte 1991), 6-hydroxy-MDMA and 2,4,5-THMA (Johnson et al. 1992; Zhao et al. 1992), have been tested for long-term neurotoxic effects after central (ICV and intracerebral) administration in the rat. Of the metabolites studied only 2,4,5-THMA exhibited toxicity on the serotonergic system. However, this compound also produced dose-dependent reductions in the content of dopamine, DOPAC and HVA in the striatum. Therefore, the neurotoxic profile does not match that observed after systemic administration of MDMA in the rat.

Recent studies have suggested a possible role for GSH conjugates of the reactive catechol metabolites of MDMA in the neurotoxicity induced by the drug. Due to their structure, these catechols would not be expected to cross the blood–brain barrier. However, the rapidly formed quinones (α-MeDA and N-Me-α-MeDA) may conjugate with GSH to form adducts such as 5-(glutathion-S-yl)-α-methyldopamine (5-GSyl-α-MeDA) and 5-(glutathion-S-yl)-N-methyl-α-MeDA (Hiramatsu et al. 1990; Miller et al. 1995) that may cross the blood–brain barrier using a GSH transporter. Indeed, the brain uptake index (BUI) of 5-GSyl-α-MeDA is reduced by GSH co-administration, indicating a competitive uptake mechanism (Miller et al. 1996). 5-GSyl-α-MeDA produces selective 5-HT loss in the striatum and cortex 7 days after repeated intrastriatal or intracortical administration but not after ICV administration in spite of producing the neurobehavioural and acute neurochemical effects characteristic of systemic MDMA and MDA (Miller et al. 1997; Bai et al. 1999). Once in the brain, 5-GSyl-α-MeDA is rapidly metabolised to 5-(cystein-S-yl)-α-methyldopamine which is further metabolised to 5-(N-acetyl-L-cystein-S-yl)-α-methyldopamine (Miller et al. 1995). This latter compound is cleared at a much slower rate than its precursors and is a more potent toxin, possibly due to the conservation of a quinone structure that allows further redox cycling (Miller et al. 1997; Bai et al. 1999), although it too required intracerebral rather than ICV administration to produce neurotoxic effects.

5-GSyl-α-MeDA may also undergo further addition of a GSH molecule yielding the di-conjugate 2,5-bis-(glutathion-S-yl)-α-methyldopamine. This compound has been shown to be neurotoxic in the 5-HT terminal fields following ICV, intrastriatal and intracortical administration (Miller et al. 1997; Bai et al. 1999). Thus, it appears that the thioether conjugates of α-MeDA do produce neuro-

toxic profiles that match those produced by systemic administration of MDMA.

Further evidence of the possible role of these compounds arose from the observation that treatment with acivicin, a γ-glutamyl transpeptidase (enzyme involved in the breakdown of GSH and GSH S-conjugates) inhibitor, not only increased the BUI of 5-GSyl-α-MeDA but also increased the neurotoxicity of systemically administered MDA and MDMA, presumably due to increased levels of the metabolite in the brain (Bai et al. 2001). To date, however, 5-GSyl-α-MeDA has only been recovered in bile after the administration of systemic MDA (Bai et al. 1999); therefore the important step of identification of this metabolite (or downstream metabolites) in the brain after systemic administration of MDMA is still required to fully determine the role of these thioether derivatives in the neurotoxicity induced by the drug in rats. It is also clear that comprehensive studies, such as those described above, are required in mice to try and evaluate why MDMA produces dopaminergic damage in this species.

General discussion

There are a now a large number of studies indicating that single or repeated administration of MDMA to experimental animals causes acute (in rats and mice) and long-term (in mice) dysfunction of the dopaminergic system. However, the major focus of attention still seems to fall on 5-HT as the major neurotransmitter involved in both the physiological and psychological consequences of MDMA ingestion.

With regard to the acute consequences of MDMA recreational use, there are two major consequences which follows its ingestion. One is the psychological changes that occur, and these changes are the main reason for taking the drug. Data reviewed in this paper suggest that these changes are primarily a consequence of dopamine release, although the effects of 5-HT release must also play a role in the total response detected by the individual. The second consequence can be an acute hyperthermic response, although this only occurs in some individuals and is probably related to the dose and subsequent metabolism of the drug. However, when it does occur it can be life-threatening. There is now compelling evidence to suggest that MDMA-induced hyperthermia also results primarily from enhanced dopamine release (Mechan et al. 2002). Since there are substantial data indicating that hyperthermia is a key component in producing MDMA-induced neurotoxicity in rats (Broening et al. 1995; Malberg and Seiden 1998), it can reasonably be claimed that acute dopamine release can indirectly impact on the subsequent loss of 5-HT nerve terminals. It should also be noted that although cocaine does not produce any long-term loss of 5-HT and dopamine, even when hyperthermia is potentiated (Cappon et al. 1998), its co-administration with MDMA may enhance hyperthermia and thus also enhance the neurodegeneration caused by MDMA.

The ability of MDMA to produce neurodegeneration of dopamine nerve endings is contentious. The compound has generally been considered to be a selective 5-HT neurotoxin, although this is primarily based on studies in rats. However, studies on both primates and humans appeared to support the notion. Nevertheless, it is a relatively selective dopamine neurotoxin in mice. This review has outlined the metabolic fate of MDMA and it seems likely to us that what appears to be selectivity may be primarily a consequence of what neurotoxic metabolites are produced (and this may depend on dosing schedules) and the selectivity of these metabolites for monoamine nerve endings, or the endogenous free radical trapping ability of specific nerve endings, or both.

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