Psychopharmacology (2006) 184: 239–246
DOI 10.1007/s00213-005-0278-y

ORIGINAL INVESTIGATION

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Initial deficit and recovery of function after MDMA preexposure in rats

Received: 7 September 2005 / Accepted: 16 November 2005 / Published online: 16 December 2005

Abstract *Rationale:* 3,4-methylenedioxymethamphetamine (MDMA) exposure was reported to result in deficits in serotonergic neurotransmission with concomitant behavioral suppression and tolerance to MDMA. Some data have also suggested that the neurochemical deficits recover over time, raising the question as to whether behavioral suppression would show a similar recovery. *Objectives:* The possibility of recovery of behavioral deficits was examined in the present study. Rats were administered an MDMA pretreatment regimen that was shown to produce numerous serotonergic deficits and behavioral suppression 2 weeks thereafter. The full expression of MDMA-produced hyperactivity was dependent upon serotonergic integrity, therefore, the present study aimed to determine whether MDMA pretreated rats were tolerant to MDMA 2 weeks after exposure. Further, because serotonergic deficits have shown recovery over time, similar behavioral tests were conducted at a later time point to determine whether functional recovery was evident. *Methods:* MDMA-produced hyperactivity was measured at different withdrawal periods (2 and 12 weeks) to determine initial effects and the possibility of recovery of function. *Results:* In saline-pretreated control rats, +/–MDMA (0.0–10.0 mg/kg) produced a dose-dependent increase in locomotor activity. Rats that had received prior exposure to MDMA (4×10 mg/kg MDMA injections administered at 2 h intervals) demonstrated tolerance when the activity was measured 2 weeks after pretreatment. For these rats, there was a downward shift in the dose–effect curve for MDMA-produced hyperactivity. MDMA-produced hyperactivity in rats that were tested 12 weeks after pretreatment was, however, comparable to controls, suggesting recovery of function. *Conclusion:* These data are consistent with the idea that high dose MDMA exposure produces neuroadaptations that exhibit recovery with extended abstinence from the drug.

Keywords MDMA · serotonin · hyperactivity · neuroadaptation

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA or 'ecstasy') is a recreational drug with both stimulant and hallucinogenic properties. The drug produces a number of neurochemical effects (Fitzgerald and Reid 1990; Gough et al. 1991; White et al. 1996; Lyles and Cadet 2003; Colado et al. 2004; Green et al. 2004) but the effects on central serotonergic systems were the focus of most studies. Many adverse consequences of MDMA exposure were attributed to alterations in serotonin (5-HT) neurotransmission and some studies have suggested that MDMA pretreatment induces neurotoxicity in 5-HT systems (Commins et al. 1987; O'Hearn et al. 1988; Molliver et al. 1990; Schmued 2003). MDMA binds to the 5-HT transporter (SERT) with high affinity (Battaglia et al. 1988) and also induces extra- and intracellular 5-HT efflux (Gough et al. 1991; Rudnick and Wall 1992). Reverse transport of 5-HT via the SERT was also reported (Hekmatpanah and Peroutka 1990). This effect might explain the ability of SERT-selective compounds to attenuate MDMA-produced increases in synaptic levels of 5-HT (Hekmatpanah and Peroutka 1990; Berger et al. 1992; Rudnick and Wall 1992; Gudelsky and Nash 1996) and subsequent behavioral effects (Callaway et al. 1990; Callaway and Geyer 1992b).

After the initial increase in synaptic levels of 5-HT, depletions of 5-HT (Battaglia et al. 1987; Commins et al. 1987; Ricaurte et al. 1988a-c; Insel et al. 1989; Molliver et al. 1990; Scanzello et al. 1993; Aguirre et al. 1995; Colado and Green 1995; Fischer et al. 1995; McNamara et al. 1995; Sabol et al. 1996; Sexton et al. 1999; Mayerhofer et al. 2001; Boot et al. 2002; McGregor et al. 2003; Clemens et al. 2004; Sumnall et al. 2004; Wang et al. 2004) and decreased SERT binding were frequently reported in

laboratory animals (Battaglia et al. 1987; Scanzello et al. 1993; Yau et al. 1994; Aguirre et al. 1995; Colado and Green 1995; Lew et al. 1996; O'Shea et al. 1998; Scheffel et al. 1998; Colado et al. 1999; Sexton et al. 1999; Brown and Molliver 2000; Boot et al. 2002; McGregor et al. 2003; Sumnall et al. 2004). Reductions in SERT binding densities (McCann et al. 1998; Semple et al. 1999; Buchert et al. 2003; Thomasius et al. 2003) and reduced cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) levels (Bolla et al. 1998; McCann et al. 1994, 1999) were also reported in heavy MDMA users.

The alterations in 5-HT neurotransmission might explain behavioral changes observed after exposure to MDMA. MDMA exposure can result in either behavioral sensitization or tolerance, depending on the pretreatment regimen. Sensitization was reported after repeated, intermittent exposure to low doses (Spanos and Yamamoto 1989; Dafters 1995; Kalivas et al. 1998; McCreary et al. 1999; Ramos et al. 2004, 2005) but tolerance was reported after chronic high dose exposure (Callaway and Geyer 1992a). Tolerance might be attributable to serotonergic depletions because of *para*-chlorophenylalanine (Callaway et al. 1990) or 5,7-DHT lesions (Kehne et al. 1996) also attenuated the ability of MDMA to produce hyperactivity. MDMA pretreated rats were also tolerant to the ability of MDMA to produce hyperthermia and the 5-HT-syndrome, and in vivo microdialysis revealed that the ability of MDMA to increase striatal 5-HT overflow was compromised in MDMA pretreated rats (Shankaran and Gudelsky 1999). Tolerance to the subjective effects of MDMA was also reported among users (Verheyden et al. 2003; Scholey et al. 2004; Parrott 2005) and more experienced users are probably at greater risk of serotonergic deficits because they tend to consume MDMA in 'binges' (Verheyden et al. 2003; Scholey et al. 2004; Parrott 2005).

5-HT depletion and reduced SERT binding are often considered indices of serotonergic neurotoxicity. Indeed, after high doses of MDMA, there were reports of structural damage to serotonergic neurons and reduced SERT binding, a consequence of axon terminal destruction (Battaglia et al. 1987; Mokler et al. 1987; Brodkin et al. 1993; Colado and Green 1995). Recent investigations have suggested, however, that 5-HT depletions might reflect other consequences of MDMA exposure because decreased levels were obtained in the absence of structural damage to 5-HT neurons (Wang et al. 2004). Neurotoxic damage produced by 5,7-DHT, increased glial fibrillary protein mRNA and depleted 5-HT, but MDMA produced only 5-HT depletion (Wang et al. 2004). Pretreatment decreased SERT binding densities but did not alter SERT mRNA expression or SERT levels in endosomes or plasma membranes (Wang et al. 2005). Serotonergic deficits were also reported to recover over time (Scanzello et al. 1993; Fischer et al. 1995; Lew et al. 1996; Sabol et al. 1996). These findings raise the possibility that MDMA produces neuroadaptations subject to recovery, rather than neurotoxicity that would be less likely to exhibit recovery.

The present study aimed to measure initial behavioral effects of a high dose regimen of MDMA and to investigate whether there was recovery of function. A pretreatment regimen was selected that produced widespread 5-HT depletion and reduced SERT binding (Scanzello et al. 1993; Fischer et al. 1995; Sumnall et al. 2004). Because neurochemical studies have shown some recovery of 5-HT levels by 12 weeks after pretreatment (Scanzello et al. 1993; Fischer et al. 1995), MDMA-produced hyperactivity was compared 2 and 12 weeks after MDMA pretreatment.

Materials and methods

Subjects

The subjects were male Sprague–Dawley rats, weighing between 200 and 250 g. The animals were bred at Victoria University in Wellington, New Zealand and were housed individually in a temperature- (21°C) and humidity- (79%) controlled room. There was a controlled 12-hr light/dark cycle with lights on at 0700 h. Food and water were available ad libitum except during testing periods. All experimental protocols were consistent with the Office of Laboratory Animal Welfare regulations and were approved by the Animal Ethics Committee of Victoria University.

Apparatus

Locomotor activity was assessed using the Activity Monitor Version 5 program (Med Associates Inc, US) consisting of eight sound attenuated containment chambers. The subject location was tracked using 16 evenly spaced infrared sources and sensors positioned around the periphery of a four-sided chamber. A white noise generator masked extraneous noise during testing. Prior to and after each locomotor activity test, the chamber interiors were cleaned and wiped with Virkon 'S' disinfectant (Southern Veterinary Supplies, NZ).

Procedures

MDMA pretreatment regimen

Rats were placed in individual cages for the day of treatment whereupon they received an injection regimen comprising four injections of either MDMA [10 mg/kg per injection, intraperitoneally (I.P.)] or the saline vehicle administered at 2 h intervals (total MDMA exposure=40.0 mg/kg) in the home cage. This regimen was selected because it was demonstrated in other studies to produce significant effects on 5-HT neurotransmission 2 weeks after treatment (Scanzello et al. 1993; Fischer et al. 1995; Shankaran and Gudelsky 1999; Sumnall et al. 2004) and was relatively well tolerated in these groups with an approximately 10% mortality rate (six of the 59 rats died after pretreatment). The rats were housed in pairs of vehicle and MDMA-pretreated individuals during a withdrawal period of either 2 or 12 weeks before commencement of

behavioral tests. Rats were isolated and placed in separate cages the day before the behavioral testing. All behavioral tests were conducted during the light phase of the light cycle.

Dose effect curves for MDMA-produced hyperactivity

Two or 12 weeks after pretreatment, MDMA pretreated animals (2 weeks: n=27, 12 weeks: n=32) and the controls (2 weeks: n=32, 12 weeks: n=36) were first habituated to the activity chambers for 30 min. After this habituation period, they were injected with MDMA (0.0, 2.5, 5.0, or 10.0 mg/kg, I.P.) and the activity was recorded at 5-min intervals for an additional 60 min.

Drugs

+/–MDMA hydrochloride (MDMA, ESR, NZ) was dissolved in 0.9% saline. Injections were intraperitoneal and MDMA was administered in a volume of 1 ml/kg. MDMA was prepared fresh daily and drug weights refer to the salt.

Statistical analyses

Time course data for the activity tests were analyzed using 3-way ANOVAs (time X pretreatment X MDMA dose) where time was the repeated measure. Univariate analyses followed by Tukey post hoc tests determined whether there were significant differences as a result of pretreatment in the event of main effects or interactions.

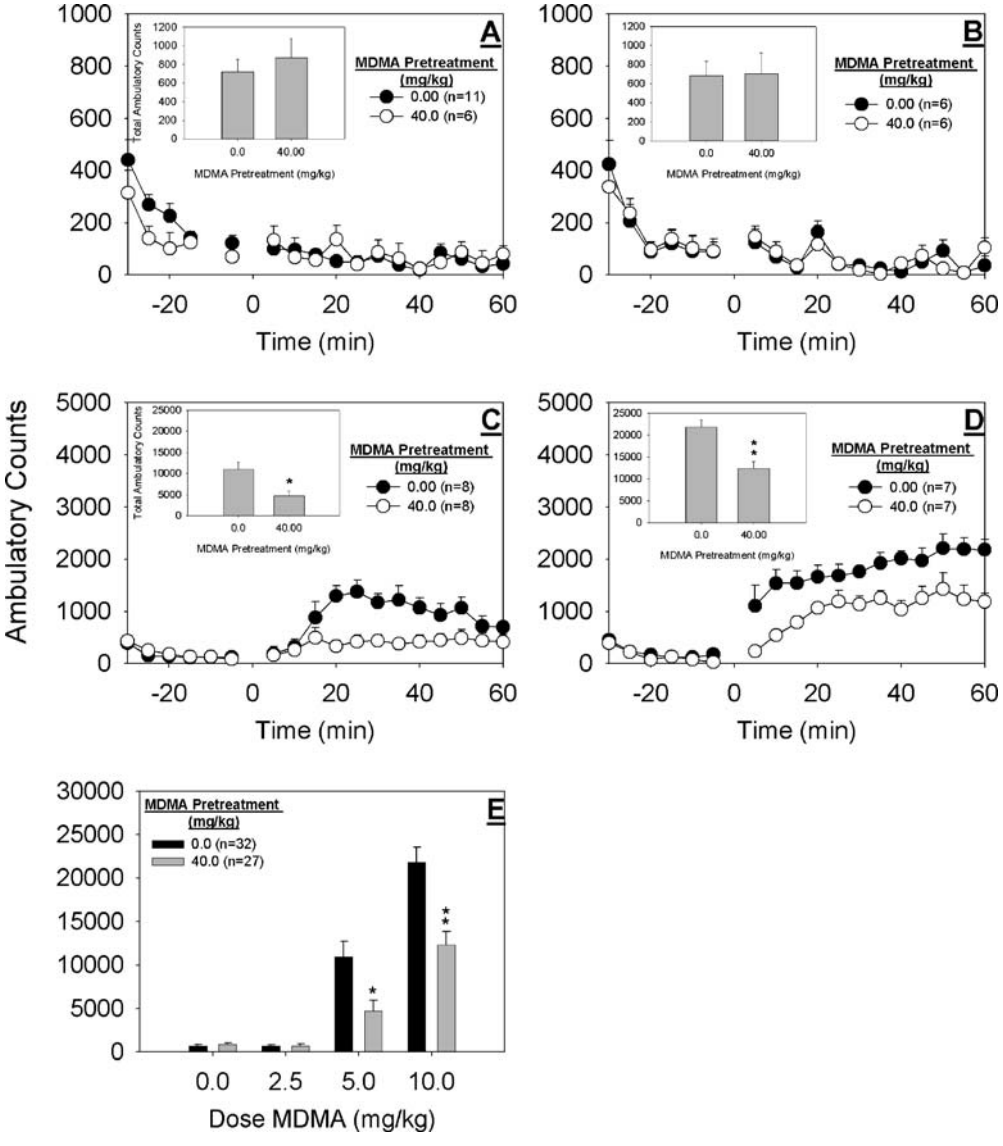

Fig. 1 Ambulatory counts produced after acute MDMA (0.0, 2.5, 5.0, or 10.0 mg/kg) administration in rats 2 weeks after saline or MDMA pretreatment. The time course of the mean ambulatory counts produced after **a** 0.0, **b** 2.5, **c** 5.0, or **d** 10.0 mg/kg MDMA are shown (+SEM). *Insets* show total ambulatory counts during the 60-min period post-MDMA injection for the two pretreatment groups (+SEM); **e** shows total ambulatory counts produced by all MDMA doses for the 60-min period post-MDMA injection for the two pretreatment groups (+SEM). Significant difference relative to saline pretreated group * p<0.05, ** p<0.01

Results

MDMA dose effect: 2 weeks posttreatment

Figure 1a–d show the time course and dose-dependency of MDMA-produced hyperactivity for saline and MDMA-pretreated rats 2 weeks after preexposure. The inset figures illustrate total ambulatory counts (+SEM) for the 60-min post-MDMA injection period. The mean total ambulatory counts are shown (Fig. 1e) as a function of MDMA dose for the 60-min post-MDMA injection time period in saline and MDMA pretreated rats (+SEM). A 3-way ANOVA with time as a repeated measure showed significant interaction between these factors ($F(13.227)=1.96$, $p<0.05$). ANOVAs on total ambulatory counts for each dosage group revealed no significant differences as a result of pretreatment for rats that received either the 0.0 (Fig. 1a) ($F(1.15)=0.380$, $p>0.05$) or 2.5 mg/kg (Fig. 1b) ($F(1.10)=0.007$, $p>0.05$) doses. MDMA-produced hyperactivity was greater for the saline pretreated rats that received 5.0 (Fig. 1c) ($F(1.14)=8.07$, $p<0.05$) and 10.0 mg/kg (Fig. 1d) ($F(1.12)=16.42$, $p<0.01$) doses. A 2-way ANOVA (pretreatment X MDMA dose) revealed significant main effects of MDMA dose ($F(3.51)=84.33$, $p<0.001$) and pretreatment ($F(1.51)=21.64$, $p<0.001$), and a significant interaction between pretreatment and MDMA dose ($F(3.51)=8.07$, $p<0.001$). Post hoc analyses revealed that the MDMA pretreated group was less responsive to the 5.0 and 10.0 mg/kg doses.

MDMA dose effect curve: 12 weeks posttreatment

Figure 2a–d show the time course and dose-dependency of MDMA-produced hyperactivity for saline and MDMA-pretreated rats 12 weeks after preexposure. The mean total ambulatory counts are shown (Fig. 2e) as a function of MDMA dose for the 60-min post-MDMA injection time period in saline and MDMA pretreated rats (+SEM). The 3-way ANOVA with time as a repeated measure failed to reveal a significant interaction between these factors (F

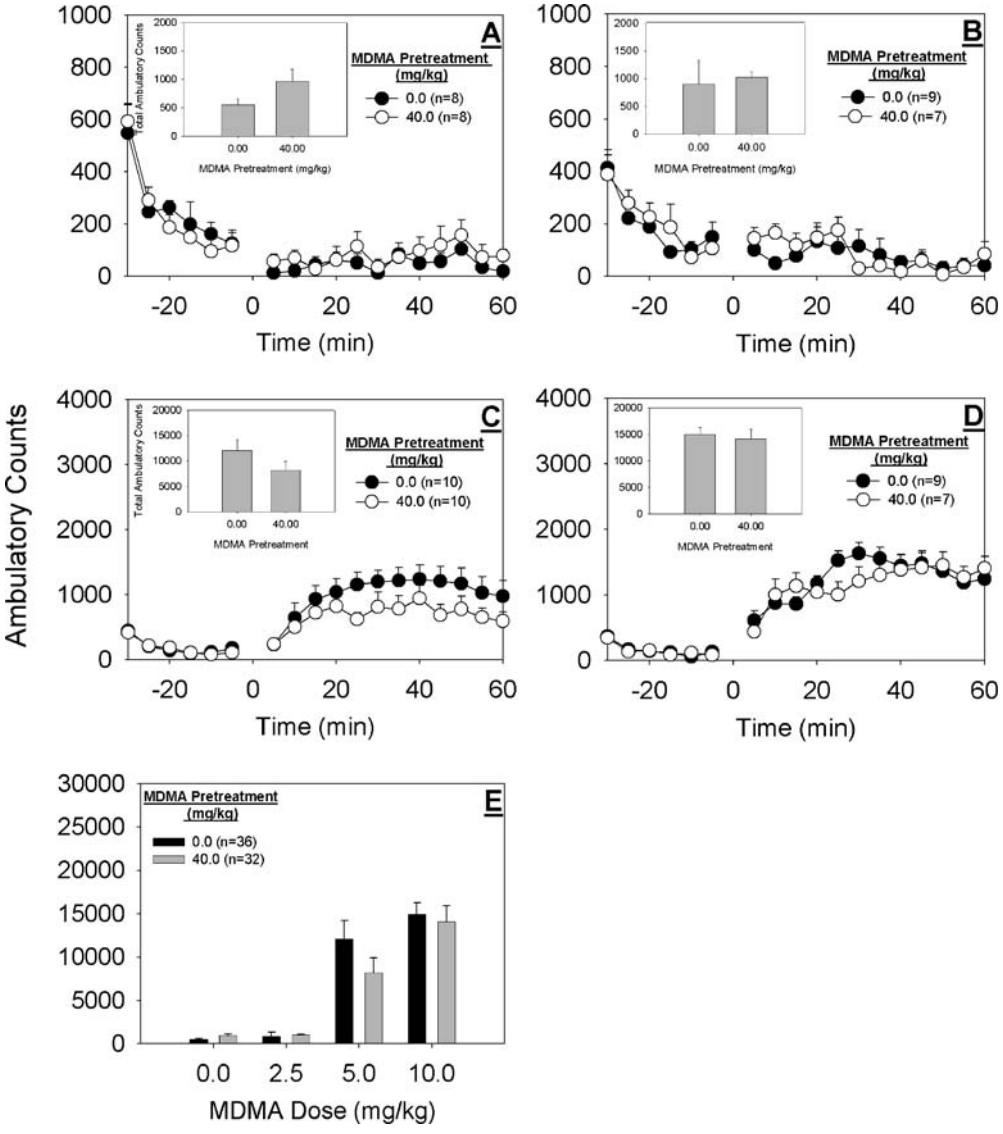

Fig. 2 Ambulatory counts produced after acute MDMA (0.0, 2.5, 5.0, or 10.0 mg/kg) administration in rats 12 weeks after saline or MDMA pretreatment. The time course of the mean ambulatory counts produced after **a** 0.0, **b** 2.5, **c** 5.0, or **d** 10.0 mg/kg MDMA (+SEM) are shown. *Insets* show total ambulatory counts at each MDMA dose for the 60-min period post-MDMA injection for the two pretreatment groups (+SEM); **e** shows total ambulatory counts produced during the 60-min period post-MDMA injection for the two pretreatment groups (+SEM)

(11.214)=1.04, $p>0.05$). ANOVAs failed to reveal significant differences as a result of pretreatment for any of the doses tested [0.0 mg/kg: ($F(1.14)=3.11$, $p>0.05$); 2.5 mg/kg: ($F(1.14)=0.071$, $p>0.05$); 5.0 mg/kg: ($F(1.18)=2.00$, $p>0.05$); and 10.0 mg/kg: ($F(1.14)=0.162$, $p>0.05$)]. A 2-way ANOVA revealed a significant main effect of MDMA dose ($F(3.60)=47.89$, $p<0.001$) but the effect of pretreatment ($F(1.60)=1.16$, $p>0.05$) or the interaction between pretreatment and MDMA ($F(3.60)=1.13$, $p>0.05$) were not significant.

Discussion

Consistent with previous reports, MDMA-produced hyperactivity was dose-dependent (Spanos and Yamamoto 1989; Callaway et al. 1990; Kehne et al. 1996). MDMA pretreated rats exhibited significant tolerance to MDMA-produced hyperactivity after a 2-week recovery period (Fig. 1e) but there was recovery of this behavioral effect of MDMA when rats were tested 12 weeks after treatment (Fig. 2e). These data concur with past studies reporting transient tolerance to MDMA after pretreatment (Callaway and Geyer 1992a) and extend these findings to show recovery of behavioral function after a longer withdrawal period.

MDMA-produced hyperactivity is dependent on the activation of specific 5-HT receptor subtypes such as the 5-HT1b and 2a receptors (Kehne et al. 1996; McCreary et al. 1999; Fletcher et al. 2002; Herin et al. 2005). Because MDMA-produced hyperactivity was attenuated by 5-HT uptake inhibitors (Callaway et al. 1990; Callaway and Geyer 1992b) and SERT knockout mice did not exhibit MDMA-produced hyperactivity (Bengel et al. 1998), the ability to block 5-HT uptake must be a critical mechanism for MDMA-produced hyperactivity. As a result of uptake inhibition, there is an increase in synaptic 5-HT levels (Hekmatpanah and Peroutka 1990; Berger et al. 1992; Rudnick and Wall 1992; Gudelsky and Nash 1996) and a subsequent activation of postsynaptic receptors that mediate the hyperactive response. After MDMA pretreatment, a reduced ability of MDMA to elevate synaptic 5-HT levels was demonstrated and this effect was associated with behavioral suppression (Shankaran and Gudelsky 1999). These effects were likely due to reduced 5-HT receptor activation resulting from decreased synaptic levels (Kehne et al. 1996; McCreary et al. 1999; Fletcher et al. 2002; Herin et al. 2005). In addition, 5-HT2a receptor densities were significantly reduced after MDMA exposure, which might also contribute to reduced responsiveness to MDMA. The tolerance to the ability of MDMA to produce hyperactivity observed 2 weeks after pretreatment might, therefore, reflect decreases in 5-HT neurotransmission (Scanzello et al. 1993; Fischer et al. 1995; Sumnall et al. 2004).

Tolerance to MDMA-produced hyperactivity was apparent 2 weeks but not 12 weeks after treatment. These findings concur with a study showing tolerance to the activating effects of MDMA 3 days after pretreatment and partial recovery 3 weeks after treatment (Callaway and Geyer 1992a). The present study replicated and extended these findings by using several MDMA doses, a longer withdrawal period, and a pretreatment regimen that was shown to produce initial neurochemical deficits and subsequent recovery (Scanzello et al. 1993; Fischer et al. 1995). Initial MDMA exposure produced decreased 5-HT and 5-HIAA levels (Battaglia et al. 1987; Commins et al. 1987; Ricaurte et al. 1988a-c; Insel et al. 1989; Molliver et al. 1990; Scanzello et al. 1993; Aguirre et al. 1995; Colado and Green 1995; Fischer et al. 1995; McNamara et al. 1995; Sabol et al. 1996; Sexton et al. 1999; Mayerhofer et al. 2001; Boot et al. 2002; McGregor et al. 2003; Clemens et al. 2004; Sumnall et al. 2004; Wang et al. 2004), reduced SERT binding (Battaglia et al. 1987; Scanzello et al. 1993; Yau et al. 1994; Aguirre et al. 1995; Colado and Green 1995; Lew et al. 1996; O'Shea et al. 1998; Scheffel et al. 1998; Colado et al. 1999; Sexton et al. 1999; Brown and Molliver 2000; Boot et al. 2002; McGregor et al. 2003; Sumnall et al. 2004), decreased 5-HT2a receptor densities (Reneman et al. 2002), and produced tryptophan hydroxylase (TPH) deactivation (Stone et al. 1987; Schmidt and Taylor 1987; Stone et al. 1989a,b; Garcia-Osta et al. 2004). After the initial deficits, the recovery of 5-HT neurotransmission was observed. For example, after longer withdrawal periods, TPH levels increased as did TPH mRNA expression in cortical regions (Garcia-Osta et al. 2004). The 5-HT levels, SERT binding (Scanzello et al. 1993; Fischer et al. 1995), and 5-HT2a receptor binding densities (Reneman et al. 2002) have all demonstrated recovery over time. These neurochemical findings are consistent with the notion that MDMA produces neuroadaptations that recover over time rather than neurotoxicity (Wang et al. 2004; Wang et al. 2005), which would be less likely to demonstrate significant recovery.

The pretreatment regimen used in the present study produced comparable results to those observed in MDMA users. The most frequently reported consequence of MDMA use in humans was tolerance to the subjective effects of the drug (Verheyden et al. 2003; Scholey et al. 2004; Parrott 2005). Also, in corroboration with animal studies, recent MDMA use was associated with significant reductions in SERT binding (McCann et al. 1998; Semple et al. 1999; Buchert et al. 2003; Thomasius et al. 2003), 5-HT2a receptor densities (Reneman et al. 2002), and central 5-HT levels (McCann et al. 1994, 1999; Bolla et al. 1998; McCann et al. 1994, 1999). Reduced SERT availability likely contributes to tolerance to MDMA, as SERT blockade with citalopram decreased the subjective effects of MDMA (Liechti et al. 2000b, 2001; Liechti and Vollenweider 2001). In addition, because the 5-HT2a receptor activation was associated with hallucinogenic drug effects (Jakab and Goldman-Rakic 1998; Aghajanian and Marek 1999; Nelson et al. 1999), it is possible that decreased receptor densities contribute to subjective tolerance. Indeed, pretreatment with a 5-HT2a/2c receptor antagonist attenuated MDMA-produced perceptual changes and emotional excitation in human subjects (Liechti et al. 2000a, 2001; Liechti and Vollenweider 2001).

Abstinence from MDMA use was positively correlated with recovery of SERT binding (Semple et al. 1999; Buchert et al. 2003; Thomasius et al. 2003) and 5-HT2a receptor densities (Reneman et al. 2002) in users, although tolerance was not concomitantly assessed. Because the effects in humans are comparable to the effects that were reported in laboratory studies in animals, the present data suggest that tolerance to the effects of MDMA might also diminish in humans who abstain from drug use for a significant period of time. Further, experienced users tend to 'binge' on MDMA, purportedly because they are tolerant to the effects of the drug (Verheyden et al. 2003; Scholey et al. 2004; Parrott 2005) and these high dose exposures might perpetuate serotonergic deficits. The present study suggests that abstinence might be required for a reduction of tolerance and recovery of neurochemical deficits.

Acknowledgements Funding was provided by the Lottery Health Foundation, Neurological Foundation of New Zealand, and the School of Psychology at Victoria University in Wellington, NZ. The authors greatly acknowledge the technical assistance of Richard Moore, Evangeline Daniela, and David Gittings.

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