Psychopharmacology (2003) 166:383–390
DOI 10.1007/s00213-002-1374-x

ORIGINAL INVESTIGATION

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Effects of MDMA exposure on the conditioned place preference produced by other drugs of abuse

Received: 21 May 2002 / Accepted: 24 November 2002 / Published online: 25 February 2003

Abstract *Rationale:* MDMA is a serotonergic neurotoxin but few pre-clinical studies have found long-term behavioural consequences. As human users of MDMA are polydrug users, it is important to investigate whether the behavioural effects of other drugs are modulated by prior exposure to MDMA. *Objectives:* This study investigated whether pretreatment with a multiple high dose regimen of MDMA altered the rewarding effects of other drugs of abuse. *Methods:* Adult male Lister Hooded rats (n=10/group) were pretreated with 10 mg/kg MDMA or 1 ml/kg saline vehicle IP every 2 h for 6 h. Fourteen days later, conditioned place preference (CPP) to *d*-amphetamine (3 mg/kg), cocaine (20 mg/kg), ethanol (2.0 g/kg), heroin (0.5 mg/kg), or MDMA (10 mg/kg) was assessed. *Results:* In general, MDMA pretreatment had no effect on drug reward or habituation to the place conditioning apparatus. However, in contrast to saline pretreated rats, those animals receiving MDMA failed to show CPP after ethanol. *Conclusion:* MDMA pretreatment reduced the rewarding properties of ethanol. This finding may represent a functional consequence of MDMA-induced neurotoxicity. By extrapolation, human users of MDMA may be exposed to an increase in risks associated with alcohol abuse.

Keywords MDMA · CPP · Behavioural neurotoxicology · -Amphetamine · Cocaine · Ethanol · Heroin

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Introduction

There is incontrovertible evidence that (±)3,4-methylenedioxymethamphetamine (MDMA) is a serotonergic neurotoxin in pre-clinical animal models. Administration of an acute high dose regimen of MDMA to experimental animals causes a long lasting, regionally specific decrease in markers of 5-HT axon viability although cell bodies are unaffected (Battaglia et al. 1991). Unlike classic 5-HT neurotoxins such as 5,7-DHT, there is no consistent evidence of neuropathology when assessed by GFAP immunoassay or silver degeneration staining (O'Callaghan and Miller 1993). The physiological viability of remaining immunoreactive neurons is also in need of description. Recovery of gross markers of 5-HT function is also evident in MDMA treated animals, suggesting that the effects may not be permanent (Scanzello et al. 1993).

Despite a large number of studies performed, there have been very few reports of baseline behavioural dysfunction in animals pretreated with neurotoxic regimens of MDMA (Slikker et al. 1995). This may be because serotonergic (5-HT) systems are able to compensate for partial loss of their axon terminals (Hall et al. 1999). However, in keeping with the 5,7-DHT and fenfluramine literature, pharmacological challenges unmask underlying neurochemical deficits in MDMA treated rats (e.g. Series et al. 1995). This has manifested in altered behavioural, circadian, and thermoregulatory responses to various 5-HT receptor agonists (e.g. Mechan et al. 2001). Furthermore, long-lasting sensitisation to hyperthermic, hyperkinetic and other behavioural effects of MDMA have been reported in some (e.g. Kalivas et al. 1998) but not all (e.g. McNamara et al. 1995) studies. Evidence also suggests that prior exposure to MDMA (20 mg/kg every 12 h for 96 h) produces an 8-fold increase in extracellular levels of dopamine (DA) in the rat nucleus accumbens after a single SC administration of 20 mg/kg cocaine, compared to a 4-fold increase in controls (Morgan et al. 1997). This neurochemical sensitisation to cocaine is reflected by the enhancement of conditioned place preference (CPP) produced by 5 and

10 mg/kg cocaine in rats (Fone et al. 2002; Horan et al. 2000), and the facilitation of acquisition of self-administration (Fletcher et al. 2001). It has been suggested by these authors that tolerance, drug sensitisation, and loss of serotonergic inhibitory controls may account for the observations of altered response to pharmacological challenge after MDMA.

Human users of ecstasy engage in a specific type of polydrug use termed "dance drug" use, whereby specific drug combinations are used to aid all night dancing (Forsyth 1996). Initiates tend to use ecstasy in isolation (with the exception of alcohol), but as they become more experienced they exhibit a pattern of use that includes the consumption of greater amounts of ecstasy and an increasing combination of other drugs (Hansen et al. 2001). Young people attending dance music events report use of a wide range of compounds and have considerably greater drug experience than the general population of corresponding age. Characteristically, dance music event attendees ingest a mixture of stimulants and hallucinogens with the overwhelming majority being polydrug users. The variable nature of ecstasy tablet content partly contributes to this polydrug use (Cole et al. 2003).

The present study extended earlier work with cocaine, investigating the effects of pretreatment with a neurotoxic regimen of MDMA upon the CPP produced by five popular drugs of abuse. The dose regimen (see Materials and methods) was chosen because of its reported ability to produce 5-HT neurotoxicity at a relatively low total dose. For at least 2 weeks post-treatment, 5-HT concentrations and SERT density are decreased by 40–80% of control levels in regions such as the cortex and hippocampus. Furthermore, pilot experiments showed that unlike other popular protocols (e.g. 20 mg/kg every 12 h for 96 h (Battaglia et al. 1987) this treatment did not have lethal consequences in Lister hooded rats. Investigation of the rewarding effects of *d*-amphetamine, cocaine, ethanol, heroin, and MDMA, was based upon reports of their abuse in human ecstasy users (Gervin et al. 2001; Winstock et al. 2001). A "fixed assignment" method was used to quantify the magnitude of CPP in all experiments (Tzschentke 1998).

Materials and methods

Animals

Male Lister hooded rats (Charles River UK Limited, Kent, UK), weighing 180–210 g on arrival, were used for all experiments. Rats were individually housed in standard acrylic cages under a 12-h reversed lighting schedule (dark phase 1400–0200 hours) at a constant room temperature of 21±1°C. Food and water were available ad lib. (Special Diet Services, Witham, UK). Testing took place in the dark cycle and all animals were experimentally naïve. Animals were allowed 7 days to acclimatise to the laboratory environment before testing began.

Rats (total n=400) were randomly assigned to treatment groups (n=10 per group; 4×groups for each dose-response study, Vehicle/Vehicle, MDMA/Vehicle, Vehicle/Drug of interest, MDMA/Drug of interest). On day 0 MDMA pretreated animals received four injections of MDMA (10 mg/kg IP) at 2-h intervals. Control animals received an equivalent volume of saline vehicle. The place conditioning procedure began on day 14 as detailed below. All experiments were carried out under procedures prescribed by Home Office Project licence 40/1905 according to guidelines described in the UK Animals (Scientific Procedures) Act (1986).

Place conditioning

Three compartmental conditioning chambers (MED Associates ENV-013; Med Associates, Vt., USA) measuring 21×21×68 cm were used. Each consisted of three distinct chambers separated by temporary cardboard doors (9×10 cm) when sections of the apparatus were isolated during conditioning. The choice compartments were 28 cm long, one having black walls with a stainless steel rod floor consisting of 4.8 mm rods, the other having white walls with a 1.25×1.25 cm stainless steel mesh floor. The central compartment was 12 cm long, finished in neutral grey with a smooth PVC removable floor. All three compartments had hinged clear polycarbonate lids for loading the test animal. During conditioning phases, the movement of the rats was restricted by closing the doors between adjacent compartments.

Automated data collection was accomplished through a computerised tracking system. Six photobeams were placed across the white and black zones 1.25 cm from the end wall and 5 cm between beams. Three photobeams were placed across the central grey zone spaced 4.75 cm apart. Photobeam signals from the chambers were relayed to a desktop PC running MED-PC® for Windows (Med Associates).

On experimental days 10–13, animals were habituated to the general procedures. Animals were transported to the experimental room, weighed, briefly handled and then returned to the holding room. Preconditioning took place on days 14–16; rats were placed in the central grey compartment and allowed 15 min of free exploration of all three test compartments. On day 16, the time spent by the rat in each compartment was recorded and their place preference established (pre-conditioning test). The compartment in which the rat spent the most time was designated the "preferred side", the other the "non-preferred side". Drug conditioning (see below for details) spanned 4 days (days 17–20). During drug conditioning, rats received drug injections before being restricted to the non-preferred side. On the following day, animals were administered vehicle and restricted to the preferred side. Conditioning sessions lasted for 15 min. On day 21, 24 h after the last of the four pairings (two each of drug and vehicle) had been completed, each rat was allowed to freely explore the apparatus for 15 min with the dividing doors removed. The time spent in the paired and non-paired side was recorded (post-conditioning test). The time spent in the designated compartments (i.e. drug paired and non-paired) formed the basis of the analysis. Data were reduced by subtracting the time spent in the drug-paired side during the pre-conditioning test from time recorded in the post-conditioning test. This gave the change in time spent in the drug-paired compartment. In the CPP model, a significant increase in time spent in the drug-paired compartment relative to vehicle indicates drug reward.

Active doses of investigated drugs were initially identified in a series of pilot dose-response experiments (see Results). Doses (3.0 mg/kg *d*-amphetamine; 20.0 mg/kg cocaine; 2.0 g/kg ethanol; 0.5 mg/kg heroin; 10.0 mg/kg MDMA) investigated after MDMA pretreatment were chosen on the basis of place conditioning compared to the vehicle control.

Drugs

(±)MDMA hydrochloride was custom manufactured by Ultrafine chemicals (Manchester, UK). Ethanol was received from the Department of Chemistry, University of Liverpool. *d*-Amphetamine sulphate was obtained from Sigma Aldrich (Dorset, UK). Heroin hydrochloride and cocaine hydrochloride were purchased from MacFarlen Smith Ltd (Edinburgh, UK). Drug solutions were freshly prepared on each experimental day, dissolved in 0.9% w/v

physiological saline, administered IP in a volume of 1 ml/kg and tested at 20 min post-injection. Ethanol was prepared as a 20% v/v stock solution with 0.9% physiological saline, and administered in a volume appropriate for the weight of the animal immediately prior to conditioning (Patkina and Zvartau 1998). Administered doses were calculated as the free-base weight.

Statistics

Animals were removed from analysis if time spent in a particular chamber was >2 SD from the respective group mean. These data represented legitimate values recorded from sessions where experimental animals remained largely immobile and spent the majority of the test confined to one compartment. Data were statistically analysed using the software package SPSS for Windows (v10.07; SPSS Inc., USA). Dose-response data (change in time spent in drug paired compartment) were analysed by one-way ANOVA with Dunnett's post hoc test to identify significant differences between drug doses and the vehicle control. For MDMA pretreatment studies, a two-way ANOVA was performed with levels of pre- (MDMA versus Vehicle) and conditioning (Vehicle versus Drug of interest) treatments as between-subjects factors. Significance was set at $P<0.05$.

Results

Dose-response studies

The results of the dose-response studies are shown in Fig. 1.

d-Amphetamine

One-way ANOVA showed a significant effect of drug conditioning upon the change in time spent in the drug paired compartment [$F(3,35)=5.08$, $P<0.01$]. Post hoc analysis showed a significant difference between the 0 and 3 mg/kg dose levels.

Cocaine

Statistical analysis showed a significant difference between groups in time spent in the drug paired compartment [$F(3,34)=2.99$, $P<0.05$]. This was only evident between the 0 and 20 mg/kg groups.

Ethanol

Overall, there was a significant effect of drug conditioning upon the change in time spent in the paired chamber [$F(3,34)= 3.34$, $P<0.05$]. Animals conditioned with 2.0 g/kg showed preference for the drug-paired compartment compared to controls.

Heroin

There were no differences between groups and so no dose dependent effects could be established [$F(3,34)=1.52$, NS]. However, 1.0 mg/kg, the largest dose of heroin administered, produced a robust increase in preference for the drug paired compartment (106.3±35.6 s) and so was chosen for the main experiment.

MDMA

There was no significant effect of drug conditioning compared to the vehicle group [$F(3,33)=1.85$, NS]. As with heroin, the largest dose of MDMA used, 10 mg/kg, produced a large increase in preference for the drug paired compartment (126.4±46.2) and so was chosen for the main experiment.

MDMA pretreatment studies

Compared to vehicle, *d*-amphetamine caused a significantly greater increase in time spent in the paired compartment [$F(1,34)=8.18$, $P<0.01$] (Fig. 2). However, there was no significant main effect of MDMA pretreatment on the change in time spent in the drug paired compartment, and no significant interaction between MDMA pretreatment and *d*-amphetamine. Similarly, cocaine [$F(1,34)=14.21$, $P<0.001$], heroin [$F(1,36)=5.78$, $P<0.05$], and MDMA [$F(1,35)=4.27$, $P<0.05$] caused a significantly greater increase in the time spent in the paired compartment compared to vehicle but there was no effect of MDMA pretreatment and no significant interaction between MDMA pretreatment and the conditioning drug treatment. However, in the case of ethanol, whilst there were no main effects of MDMA pretreatment or ethanol conditioning upon preference [$F(1,34)=2.77$, $F(1,34)=0.33$, respectively], there was an interaction between MDMA pretreatment and ethanol [$F(1,34)=3.52$, $P<0.05$]. Inspecting groups, ethanol produced a CPP in saline-, but not MDMA-pretreated animals.

Discussion

Results from the present study suggest that prior exposure to a high dose, multiple injection regimen of MDMA attenuates the rewarding effects of 2.0 g/kg ethanol. In keeping with the literature, *d*-amphetamine, cocaine, heroin, and MDMA produced a significant increase in time spent in the drug-paired compartment, highlighting the sensitivity of the CPP paradigm and the conditioning protocol used to the rewarding effects of these drugs (Bilsky et al. 1990; Bardo et al. 1995). In contrast to ethanol, the CPP produced by these compounds were unaffected by the MDMA dosing regimen, indicating specificity of effect.

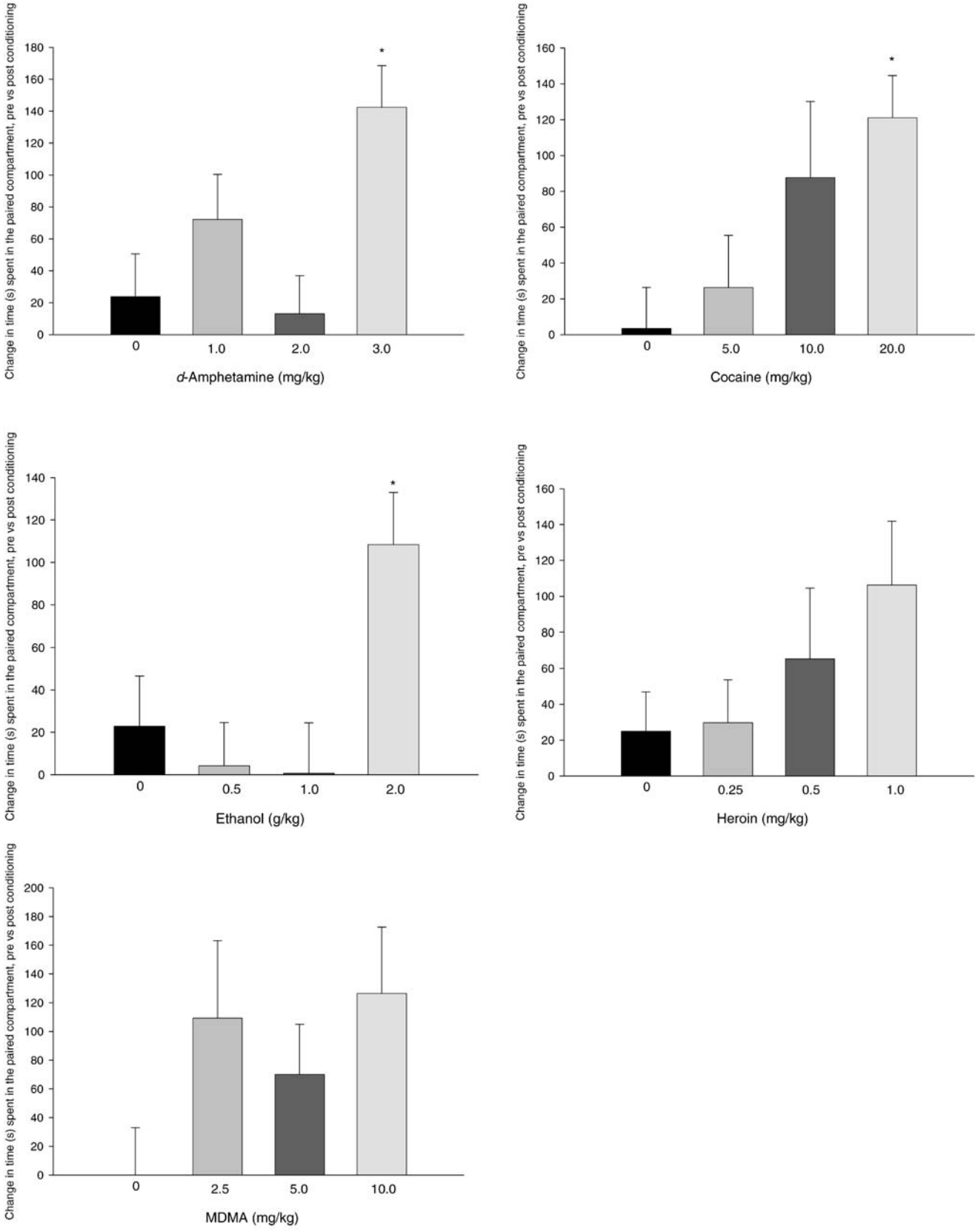
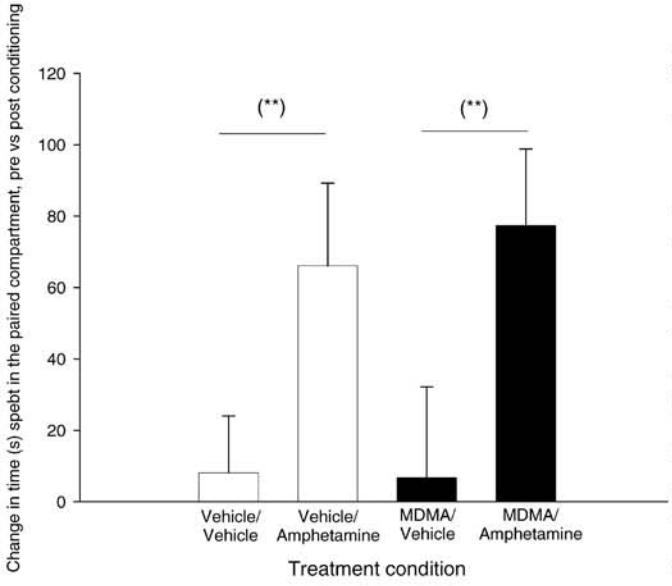
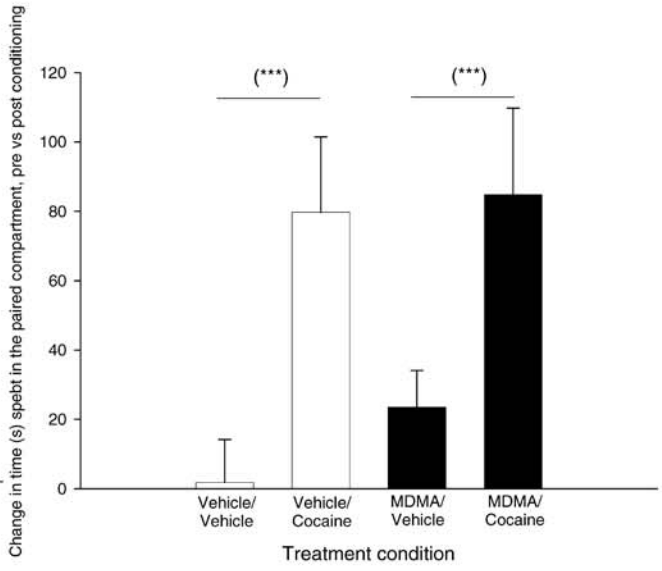
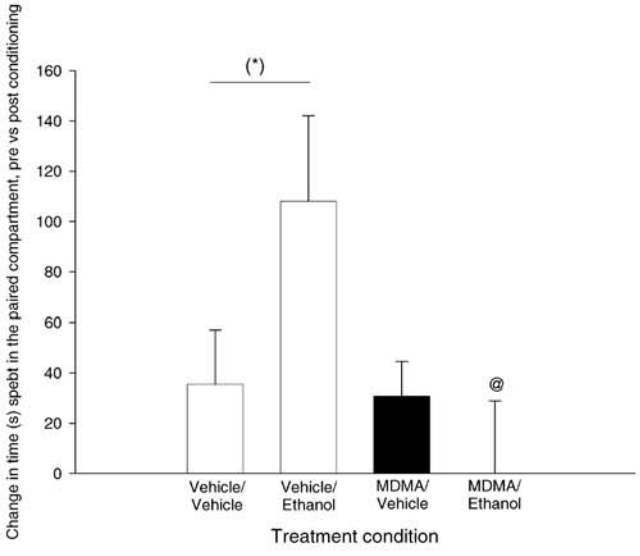
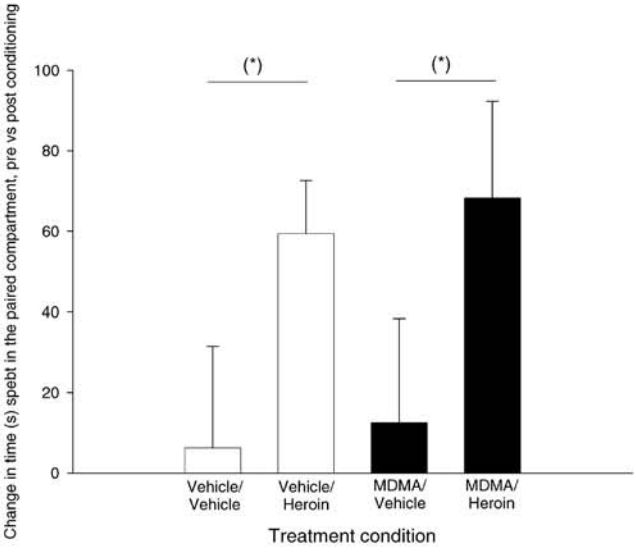


Fig. 1 CPP dose-response studies for *d*-amphetamine (*top left*), cocaine (*top right*), ethanol (*above left*), heroin (*above right*), and MDMA (*bottom left*). Shown is the change in preference (seconds) for the drug-paired compartment for each dose. *Bars* represent mean±SD









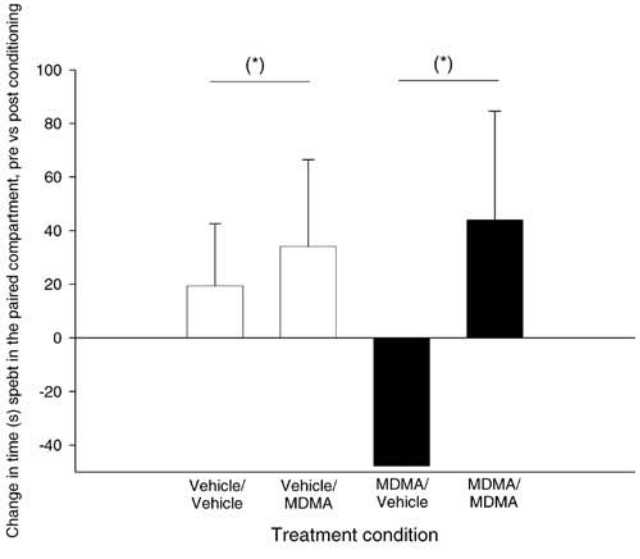


Fig. 2 Legend see page 388

Acquisition of contextual stimuli in the CPP paradigm is dependent upon successful learning of the association between the pairing of the conditioned and unconditioned stimuli (Bardo and Bevins 2000). The present results show that MDMA pretreatment had no effect on undrugged contextual association. This is supported by earlier work showing no alterations in saline preference produced by MDMA in the CPP model (Schechter 1991; Horan et al. 2000). Parallels may be drawn with other investigations of MDMA that have generally shown no changes in learning or memory (e.g. Ricaurte et al. 1993; Robinson et al. 1993). In the current study, an increase in time spent in the initially non-preferred chamber across conditioning trials was exhibited by all groups of MDMA/Vehicle treated animals, indicating that MDMA pretreatment had no effect upon subsequent learning of contextual cues and/or environmental familiarisation.

Despite powerful rewarding effects in humans, studies of ethanol-induced CPP in rodents have produced contradictory data (Tzschentke 1998). In drug naive rats ethanol has generally produced either a conditioned place aversion (CPA) or had no effect (e.g. Asin et al. 1985; Bormann and Cunningham 1998). Nevertheless, in rats exposed to (i) ethanol prior to the conditioning sessions, (ii) extended conditioning training, or (iii) confinement to the conditioning chamber immediately after injection, ethanol has produced a CPP (Reid et al. 1985; Bozarth 1990; Holloway et al. 1992). The rewarding effects of 1.2 g/kg via the intragastric route have been shown in male Wistar rats using CPP (Zvartau et al. 1995). Rats previously classed as "anxious" on the basis of prior plus-maze behaviour have also shown a dose-independent, but statistically significant, ethanol CPP (1.0–4.0 g/kg IP) after two conditioning sessions (Risinger 1997). These findings support the notion that under some protocols, ethanol is capable of producing a CPP.

Examining individual treatment groups in the current study, there was statistical evidence that 2.0 g/kg ethanol produced rewarding effects. This was supported by the findings of the dose-response study. The increase in time spent in the drug paired compartment was almost identical in saline-pretreated rats in the MDMA pretreatment experiment to 2.0 g/kg ethanol conditioned rats in the dose-response study indicating that ethanol CPP at this dose was a robust response in this laboratory. Importantly, ethanol reward was observed in those animals that had previously been treated with saline vehicle but not their MDMA counterparts. This finding represents a functional consequence of MDMA exposure and may reflect (i) attenuation of the expression of ethanol-induced reward, (ii) failure to acquire an association between the conditioned and unconditioned stimuli (see above), or (iii) failure to habituate to the aversive nature of the drug conditioning chamber (see below).

It is tempting to speculate, considering the neurotoxic actions of MDMA, that this finding indicates 5-HT dysfunction. Although neurochemical analysis was not performed in this set of animals, parallel experiments showed that the MDMA pretreatment regime employed produced approximately 20–25% reduction in hippocampal 5-HT and 5-HIAA concentrations, and a similar decrease in binding to cerebrocortical 5-HT transporters (unpublished data). These changes lasted at least 80 days post-treatment. This suggests that animals in this experiment may have been subject to disruptions in serotonergic transmission. Whilst there is good evidence to suggest a role for 5-HT in ethanol-induced reward/reinforcement, 5,7-DHT-induced lesions of the hippocampal formation and forebrain limbic complex (80–85% depletion of tissue 5-HT), areas also sensitive to the long-term actions of MDMA, failed to affect the expression of ethanol CPP in Wistar rats (Bienkowski et al. 1997). Specific lesions of the dorsal raphé nucleus (DRN), median raphé nucleus (MRN), or both, failed to alter ethanol intake in the Sprague-Dawley or low alcohol preferring rat (Adell and Myers 1996). However, the limited number of studies performed so far have focused upon moderate-to-severe generalised lesions of the 5-HT system, which do not reflect the regionally specific, and often mild, neurotoxic actions of MDMA (Battaglia et al. 1991). MDMA, for instance, exhibits preferential toxic actions upon fine fibres arising from the DRN and has no neurotoxic effect upon raphé cell bodies. Until further work has investigated the effects of localised 5,7-DHT lesions (e.g. DRN versus MRN) in paradigms that have been shown to produce ethanol CPP, it would be premature to dismiss a potential role for 5-HT in this process. Through indirect effects upon GABA transmission, 5-HT depletion may also augment the aversive effects of ethanol (Chester and Cunningham 1999). This may have contributed to attenuation of the expression of ethanol CPP observed in MDMA treated rats.

It is conceivable that a "false positive" result was obtained. One criticism aimed at the fixed assignment CPP design is that drugs that possess strong anxiolytic activity may overcome initial aversion towards the non-preferred chamber, independently of reward (Tzschentke 1998). This would result in an increase in time spent in the initially non-preferred compartment during the post-conditioning test. Ethanol produces strong, fluoxetine-sensitive anxiolytic-like effects (Durcan et al. 1988). MDMA-induced alterations in 5-HT function, particularly those associated with 5-HT transporter activity (Rudnick and Wall 1992), may abolish the anxiolytic effects of ethanol, thus maintaining pre-conditioning compartmental preference. However, in parallel experiments MDMA pretreatment had no effect on the effects of ethanol in the

◀ **Fig. 2** Effects of pretreatment with MDMA (4×10 mg/kg IP) on the expression of *d*-amphetamine (3 mg/kg; *top left*), cocaine (20 mg/kg; *top right*), ethanol (2 mg/kg; *above left*), heroin (0.5 mg/kg; *above right*) and MDMA (10 mg/kg; *bottom left*) CPP 21 days later (two IP parings in a fixed assignment design). Shown are changes in preference (seconds) for the drug paired compartment for each treatment condition. *Bars* represent mean±SEM of groups of nine to ten rats. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, significant effect of drug conditioning. $^{@}P<0.05$, significant interaction between pretreatment and drug conditioning

elevated plus-maze suggesting that the effects observed in this study were independent of ethanol-induced anxiolysis and are probably associated with ethanol-induced reward (unpublished data).

There is a large body of evidence to suggest that decreased 5-HT function or pretreatment with repeated drug regimens is associated with an increase in drug reward (e.g. Horger et al. 1990; Broderick and Phelix 1997). However, the present study found no effect of multiple dose MDMA administration on CPP to commonly abused drugs. In agreement with the current findings, prior exposure to MDMA (20 mg/kg SC every 12 h for 96 h) was found to have no effect upon the CPP produced by 1.5 mg/kg MDMA (Schechter 1991). Yet in contrast to the data reported here, multiple dose MDMA regimens have been shown to increase cocaine-induced CPP (Horan et al. 2000; Fone et al. 2002). Essentially, the use of an alternative MDMA regimen or CPP protocol may have yielded results that were more in keeping with the literature. Fone and colleagues (2002) examined adolescent rats, which are generally resistant to MDMA-induced neurotoxicity (Aguirre et al. 1998). In the study of Horan and colleagues (2001), groups of Sprague-Dawley rats were pretreated with 20.0 mg/kg SC MDMA twice daily for 4 days and received four (versus two in the present study) cocaine conditioning injections over a range of doses (5.0, 10.0, or 20.0 mg/kg) using a random assignment procedure. This group found an augmentation of cocaine CPP after 5.0 and 10.0 mg/kg cocaine, but not 20.0 mg/kg, suggesting a ceiling effect had been reached at 10.0 mg/kg, whereby MDMA pretreatment had no additional effects. This may have also been true for all the drugs used in the present study; peak-rewarding effects may have been reached at the doses used for conditioning, which were resistant to 5-HT manipulations.

Over 90% of the UK adults drink alcohol and nearly half of the male population, and one in seven of the female population, will have been intoxicated by the drug within the previous 3 months (Lader and Meltzer 2001). Consumption of ethanol within the dance music culture mirrors its use in the general population. The mixing of alcohol with "dance drugs" and/or as part of the "come-down" is commonplace (Hansen et al. 2001). Extrapolating the data reported in this study to humans, it is conceivable that prior exposure to MDMA might increase vulnerability to alcohol abuse. If MDMA users require larger quantities of ethanol to gain the desired rewarding effects, the attendant risks of alcohol abuse will also be increased (Gill 1994). Alternatively, if the alcohol cue is extinguished, MDMA using individuals may reduce their consumption. However, it is apparent that young people "drink to get drunk" and so may be unlikely to reduce their intake (Wechsler et al. 2002). As alcohol initiation generally precedes MDMA use in community samples (Pedersen and Skrondal 1999), this may have the effect of altering existing drinking patterns rather than the initiation of use.

In conclusion, MDMA pretreatment did not alter the rewarding effects of d-amphetamine, cocaine, heroin, or MDMA. The rewarding effects of ethanol were attenuated. Extrapolating these data study to humans, it is conceivable that MDMA use might increase vulnerability to alcohol abuse. If MDMA users require larger quantities of ethanol to gain the desired rewarding effects, the attendant risks of alcohol abuse will also be increased.

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