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RESEARCH PAPER

Carvedilol inhibits the cardiostimulant and thermogenic effects of MDMA in humans

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BACKGROUND AND PURPOSE

The use of ±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') is associated with cardiovascular complications and hyperthermia.

EXPERIMENTAL APPROACH

We assessed the effects of the α_1- and β-adrenoceptor antagonist carvedilol on the cardiostimulant, thermogenic and subjective responses to MDMA in 16 healthy subjects. Carvedilol (50 mg) or placebo was administered 1 h before MDMA (125 mg) or placebo using a randomized, double-blind, placebo-controlled, four-period crossover design.

KEY RESULTS

Carvedilol reduced MDMA-induced elevations in blood pressure, heart rate and body temperature. Carvedilol did not affect the subjective effects of MDMA including MDMA-induced good drug effects, drug high, drug liking, stimulation or adverse effects. Carvedilol did not alter the plasma exposure to MDMA.

CONCLUSIONS AND IMPLICATIONS

α_1- and β-Adrenoceptors contribute to the cardiostimulant and thermogenic effects of MDMA in humans but not to its psychotropic effects. Carvedilol could be useful in the treatment of cardiovascular and hyperthermic complications associated with ecstasy use.

Abbreviations

AUC, area under the concentration–time curve; C_{max}, maximal plasma concentration; CYP, cytochrome P450; 5D-ASC, 5-Dimensions of Altered States of Consciousness; E_{max}, maximal effect; MDA, ±3,4-methylenedioxyamphetamine; MDMA, ±3,4-methylenedioxymethamphetamine; VAS, Visual Analogue Scale

Introduction

±3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') is widely abused for its euphoric effects. The use of ecstasy is associated with hyperthermia (Henry *et al.*, 1992; Liechti *et al.*, 2005; Halpern *et al.*, 2011). MDMA-induced hyperthermia is a life-threatening disorder that may lead to rhabdomyolysis, disseminated intravascular coagulation, acute hepatic and renal failure and death (Henry *et al.*, 1992; Liechti *et al.*, 2005). Severe hyperthermia has typically been observed when ecstasy is used in crowded clubs, at high ambient temperatures or during physical activity (Henry *et al.*, 1992; Parrott, 2012). In laboratory animals, crowding, high ambient temperature, reduced water consumption and repeated dosing similarly enhanced MDMA-induced hyperthermia (Dafters, 1995; Docherty and Green, 2010). However, MDMA also

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elevates body temperature under controlled laboratory conditions in humans in the absence of permissive factors (Liechti *et al.*, 2001; Freedman *et al.*, 2005; Dumont and Verkes, 2006; Parrott, 2012). The clinical treatment of sympathomimetic amphetamine toxicity is mainly supportive and includes volume repletion and sedation with benzodiazepines (Liechti *et al.*, 2005; Halpern *et al.*, 2011). The management of severe MDMA-related hyperpyrexia includes cooling and ventilation (Hall and Henry, 2006). Dantrolene, which acts peripherally at skeletal muscles to inhibit release of calcium from the sarcoplasmic reticulum, has also been used (Green *et al.*, 1995; Hall and Henry, 2006; Grunau *et al.*, 2010). However, dantrolene does not inhibit the thermogenic effects of MDMA (Rusyniak *et al.*, 2004) and the drug does not specifically interfere with the presumed mechanism of MDMA-induced hyperthermia. MDMA mainly releases 5-HT, NA and dopamine (Rudnick and Wall, 1992; Liechti and Vollenweider, 2001; Verrico *et al.*, 2007). Stimulation of both α_1- and β_3-adrenoceptors has been implicated in the thermogenic effects of MDMA (Sprague *et al.*, 2004a; 2005). Specifically, increasing NA levels through the inhibition of phenylethanolamine *N*-methyltransferase potentiated the hyperthermic effects of MDMA in rats (Sprague *et al.*, 2007). Combined pretreatment with the α_1-adrenoceptor antagonist prazosin plus the β_3-adrenoceptor antagonist SR59230A attenuated MDMA-induced elevations in core body temperature and creatine kinase levels in rats (Sprague *et al.*, 2004a). The α_1 and $\beta_{1,2,3}$ antagonist carvedilol similarly prevented the hyperthermic response to MDMA in rats (Sprague *et al.*, 2005). Moreover, carvedilol reversed established hyperthermia when it was administered 1 h after MDMA (Sprague *et al.*, 2005). Selective inhibition of β_3 receptors with low concentrations of SR59230A attenuated the slowly developing late hyperthermic response to MDMA, suggesting a role for β_3 receptors in this late response in mice (Bexis and Docherty, 2008). In contrast, α_1 blockade with prazosin induced an early hypothermic reaction to MDMA, consistent with a role for α_1-receptors in this early response to MDMA in mice (Bexis and Docherty, 2008). Finally, mice deficient in uncoupling protein 3, which is regulated by NA, were protected against the hyperthermic effects of MDMA (Mills *et al.*, 2003) and methamphetamine (Sprague *et al.*, 2004b). Altogether, the preclinical data suggest that MDMA-induced hyperthermia results from noradrenergic activation of mitochondrial uncoupling that involves both α_1- and β_3-adrenoceptors (Mills *et al.*, 2004; Rusyniak *et al.*, 2005). Additionally, α_1-receptors contribute to the vasoconstriction of skin blood vessels, impairing heat dissipation, which enhances hyperthermia induced by MDMA (Pedersen and Blessing, 2001).

Psychostimulants, including MDMA, also produce hypertension and tachycardia. Myocardial ischaemia and stroke are complications of the sympathomimetic action of cocaine and ecstasy (Brody *et al.*, 1990; Liechti *et al.*, 2005; Bruggisser *et al.*, 2010; Halpern *et al.*, 2011). Selective β-adrenoceptor blockers are commonly used in the treatment of myocardial infarction or acute hypertension but are not recommended if psychostimulants are involved because of the risk of unopposed α_1-receptor stimulation (Hoffman, 2008). Indeed, propranolol potentiated cocaine-induced coronary vasoconstriction (Lange *et al.*, 1990) and worsened cocaine-associated hypertension (Ramoska and Sacchetti, 1985). β blockade also did not affect the blood pressure response to MDMA (Hysek *et al.*, 2010). In contrast, α- and β-adrenoceptor blockade with labetalol (Boehrer *et al.*, 1993; Sofuoglu *et al.*, 2000b) and carvedilol (Sofuoglu *et al.*, 2000a) dose-dependently prevented the haemodynamic response to cocaine in humans. Labetalol also had no negative effect on cocaine-induced coronary vasoconstriction (Boehrer *et al.*, 1993). Combined α- and β-blockers may therefore be the treatment of choice for stimulant-associated hypertension and myocardial ischaemia.

Because carvedilol has been shown to prevent MDMA-induced hyperthermia and rhabdomyolysis in rats (Sprague *et al.*, 2005) and the cardiostimulant response to cocaine in humans (Sofuoglu *et al.*, 2000a), we evaluated the effects of carvedilol on the cardiovascular and hyperthermic response to MDMA in healthy subjects.

Methods

Study design

We used a double-blind, double-dummy placebo-controlled, randomized, crossover study design with four experiential conditions (placebo-placebo, carvedilol-placebo, placebo-MDMA and carvedilol-MDMA) in a balanced order. The washout periods between the sessions were at least 10 days. The study was conducted at the University Hospital of Basel in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines on Good Clinical Practice and approved by the Ethics Committee of the Canton of Basel, Switzerland, and Swiss Agency for Therapeutic Products (Swissmedic). The use of MDMA in healthy subjects was authorized by the Swiss Federal Office of Public Health. The study was registered at ClinicalTrials.gov (NCT01270672). The reduction in the MDMA-induced increase in blood pressure by carvedilol was the predefined primary outcome of this clinical trial.

Study procedures

The subjects completed a screening visit, four test sessions and an end-of-study visit. The test sessions were conducted in a quiet hospital research ward with no more than two research subjects present per session. The mean (SD) room temperature was 23.3°C (0.7°C). At the beginning of each test session, an indwelling i.v. catheter was placed in the antecubital vein for blood sampling. Carvedilol (50 mg) or placebo was administered at 8 h 00 min. MDMA (125 mg) or placebo was administered at 9 h 00 min. A standardized lunch was served at 12 h 00 min, and the subjects were sent home at 15 h 00 min.

Subjects

Sixteen healthy subjects (eight men, eight women) with a mean (SD) age of 24.2 (2.2) years and a mean body weight of 67 (13) kg were recruited from the university campus. The allocation to treatment order was performed by drawing from blocks of eight different balanced drug treatment sequences by two pharmacists not involved in the study. Each code was stored in a sealed envelope until the termination of the study. Data from all 16 subjects were available for the final analysis.

The exclusion criteria included the following: (i) age <18 or >45 years; (ii) pregnancy determined by a urine test before each test session; (iii) body mass index <18.5 $kg \cdot m^{-2}$ or >25 $kg \cdot m^{-2}$; (iv) personal or family (first-degree relative) history of psychiatric disorder [determined by the structured clinical interview for Axis I and Axis II disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (Wittchen *et al.*, 1997) supplemented by the SCL-90-R Symptom Checklist (Derogatis *et al.*, 1976; Schmitz *et al.*, 2000)]; (v) regular use of medications; (vi) chronic or acute physical illness assessed by physical examination, electrocardiogram, standard haematology and chemical blood analyses; (vii) smoking more than seven cigarettes per day; (viii) a lifetime history of using illicit drugs more than five times, with the exception of cannabis; (ix) illicit drug use within the last 2 months; and (x) illicit drug use during the study, determined by urine tests conducted before the test sessions using TRIAGE 8 (Biosite, San Diego, CA, USA). The subjects were asked to abstain from excessive alcohol consumption between test sessions and limit alcohol use to one glass on the day before each test session. All of the subjects were non-smokers. All of the subjects, with the exception of one, had previously used cannabis. Four subjects reported using illicit drugs, in which three subjects had tried amphetamine once and one had tried ecstasy once and amphetamine three times. All of the subjects were phenotyped for cytochrome P450 (CYP) 2D6 activity using dextromethorphan as the probe drug. Nine extensive, six intermediate and one poor CYP2D6 metabolizer were identified in the study. The female subjects were investigated during the follicular phase (day 2–14) of their menstrual cycle when the reactivity to amphetamines is expected to be similar to men (White *et al.*, 2002). All of the subjects provided their written informed consent before participating in the study, and they were paid for their participation.

Drugs

±MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was prepared as gelatine capsules (100 and 25 mg of the salt). Identical placebo (lactose) capsules were prepared. MDMA was administered in a single oral dose of 125 mg, corresponding to a dose of 1.93 ± 0.36 $mg \cdot kg^{-1}$ body weight. Carvedilol tablets (50 mg, Dilatrend, Roche Pharma AG, Basel, Switzerland) were encapsulated within opaque gelatine capsules, and identical placebo (lactose) capsules were prepared. An oral dose of carvedilol (50 mg) was used that has previously been shown to attenuate the smoked cocaine-induced increases in heart rate and blood pressure in humans (Sofuoglu *et al.*, 2000a). At this dose, carvedilol is expected to inhibit both α_1- and β-adrenoceptors (Tham *et al.*, 1995; Sofuoglu *et al.*, 2000a). Carvedilol or placebo was administered 1 h before MDMA or placebo administration so that the maximal plasma concentration (C_{max}) of carvedilol was reached (Morgan, 1994) shortly before the C_{max} of MDMA occurred. Oral medication administration was supervised by study personnel.

Pharmacodynamic measurements

Vital signs. Vital signs were assessed repeatedly 1 h before and 0, 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 h after MDMA or placebo administration. Heart rate, systolic blood pressure and diastolic blood pressure were measured using an OMRON M7 blood pressure monitor (Omron Healthcare Europe, Hoofddorp, The Netherlands) in the dominant arm after a resting time of 5 min. Measures were taken twice per time point with an interval of 1 min, and the average was used for analysis. Core (tympanic) temperature was assessed using a GENIUS 2 ear thermometer (Tyco Healthcare Group, Watertown, NY, USA).

Plasma catecholamines. Blood samples to determine the concentrations of NA and adrenaline were taken 1 h before and 1 and 2 h after MDMA or placebo administration. All of the blood samples were collected on ice and centrifuged within 10 min at 4°C. The plasma was then stored at –20°C until analysis. The plasma levels of free catecholamines (NA and adrenaline) were determined by HPLC with an electrochemical detector as described previously (Hysek *et al.*, 2011).

Psychometric scales. Subjective measures were repeatedly assessed using Visual Analogue Scales (VASs; (Hysek *et al.*, 2011) 1 h before and 0, 0.33, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 6 h after MDMA or placebo administration. The VASs included 'any drug effect', 'good drug effect', 'bad drug effect', 'drug liking', 'drug high' and 'stimulated' (Farre *et al.*, 2007; Kolbrich *et al.*, 2008; Hysek *et al.*, 2011). The VASs were presented as 100-mm horizontal lines marked 'not at all' on the left and 'extremely' on the right. Additionally, the 5-Dimensions of Altered States of Consciousness Scale [5D-ASC; (Dittrich, 1998; Studerus *et al.*, 2010)] was applied 4 h after MDMA or placebo administration. The 5D-ASC rating scale measures alterations in mood, perception and experience of self in relation to the environment and thought disorder (Studerus *et al.*, 2010). The 5D-ASC dimension 'oceanic boundlessness' (27 items) measures derealization and depersonalization associated with positive mood. The dimension 'anxious ego dissolution' (21 items) summarizes ego disintegration and loss of self-control, phenomena associated with anxiety. The dimension 'visionary restructuralization' (18 items) describes perceptual alterations. Two other dimensions of the scale were not used in our study. The total ASC score was determined by adding the scores of the three dimensions.

Adverse effects. Adverse effects were assessed 1 h before and 3 and 24 h after MDMA or placebo administration using the List of Complaints (Zerssen, 1976; Hysek *et al.*, 2011). The scale consists of 66 items that yield a total adverse effects score, reliably measuring physical and general discomfort.

Pharmacokinetic measurements

Samples of plasma for the determination of MDMA and ±3,4-methylenedioxyamphetamine (MDA), the active metabolite of MDMA, were collected 1 h before and 0 (just before), 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4 and 6 h after MDMA or placebo administration. The plasma concentrations of MDMA and MDA were determined using HPLC coupled to tandem MS as described previously (Hysek *et al.*, 2012).

Data analysis

Pharmacokinetic analysis. The data for the plasma concentrations of MDMA and MDA were analysed using non-

compartmental methods. C_{max} and time to C_{max} were obtained directly from the concentration–time curves of the observed values. The area under the plasma concentration–time curve $(AUC)_{0-6\,h}$ was calculated using the linear trapezoidal rule. Plasma concentrations were only determined up to 6 h after MDMA administration because the aim of the study was to assess potential changes in plasma levels of MDMA during the time of the pharmacodynamic effects of MDMA.

Statistical analysis. Values were transformed to differences from baseline. The maximal effect (E_{max}) values were determined for repeated measures and analysed by two-way General Linear Models repeated-measures ANOVA with the two drug factors MDMA (MDMA vs. placebo) and carvedilol (carvedilol vs. placebo) using STATISTICA 6.0 software (StatSoft, Tulsa, OK, USA). Tukey's *post hoc* comparisons were performed based on significant main effects or interactions. Additional ANOVAs were performed, with drug order as an additional factor, to exclude carry-over effects. The criterion for significance was $P < 0.05$. A sample-size estimation based on previous data (Hysek *et al.*, 2011; 2012) showed that eight subjects would be needed to detect a relevant change in the primary study outcome with 80% power using a within-subjects study design.

Results

Vital signs and circulating catecholamines

MDMA significantly increased blood pressure, heart rate and body temperature compared with placebo (Table 1 and Figure 1). Carvedilol significantly inhibited the MDMA-induced increases in blood pressure, heart rate and body temperature (Table 1 and Figure 1). Carvedilol alone also moderately lowered blood pressure and heart rate compared with placebo. The effect of carvedilol on the pressure and hyperthermic response to MDMA was more pronounced than the effect of carvedilol alone compared with placebo, corroborated by the significant carvedilol × MDMA interaction in the two-way ANOVA. Carvedilol alone increased the plasma concentration of NA compared with placebo. MDMA also tended to increase circulating NA compared with placebo, but the effect was not significant. The co-administration of carvedilol and MDMA significantly increased both circulating adrenaline and NA (Table 1 and Figure 2).

Subjective effects

Carvedilol did not affect the psychotropic response to MDMA. It did not alter the pronounced MDMA-induced increases in the VAS (Table 1 and Figure 3) or 5D-ASC ratings of subjective drug effects (Table 1). Carvedilol alone had no subjective effects.

Adverse effects

MDMA increased the total adverse effect score on the List of Complaints, both 3 and 24 h after drug administration compared with placebo (Table 1). Carvedilol had no effect on the MDMA-induced increase in the total score. However, fewer subjects reported palpitations and hot flushes after carvedilol and MDMA co-treatment (n = 2 and n = 2, respectively) compared with MDMA treatment alone (n = 6 and n = 5, respectively). Frequent adverse effects of MDMA and carvedilol-MDMA were thirst (n = 10 and n = 11, respectively), lack of appetite (n = 9 and n = 7, respectively), sweating (n = 8 and n = 7, respectively), restlessness (n = 7 and n = 5, respectively) and bruxism (n = 7 and n = 7, respectively). No severe adverse effects were reported.

Pharmacokinetics and pharmacokinetic–pharmacodynamic relationship

The decrease in the cardiovascular and thermogenic response to MDMA after carvedilol pretreatment was not attributable to a pharmacokinetic interaction between carvedilol and MDMA. Carvedilol did not affect the C_{max} or $AUC_{0-6\,h}$ of MDMA or MDA (Table 2 and Figure 4A). The effect of MDMA on blood pressure in relation to the plasma concentration of MDMA is illustrated by the hysteresis curves in Figure 4B. Carvedilol produced a pronounced downward shift in the E_{max} of the systolic pressure response to MDMA and a rightward shift in the C_{max} of MDMA in the concentration-effect curve (Figure 4B). The pharmacokinetic parameters of MDMA did not depend on CYP2D6 phenotype or the dextromethorphan : dextrorphan ratio in our small study sample.

Discussion

The α_1- and $\beta_{1,2,3}$-adrenoceptor antagonist carvedilol reduced the cardiostimulant and hyperthermic response to MDMA in healthy subjects. Carvedilol similarly reduced MDMA-induced hyperthermia in rats (Sprague *et al.*, 2004a; 2005). Additional studies in rats and mice showed that the transient and early hypothermic effect of MDMA are enhanced by blocking α_1-receptors (Bexis and Docherty, 2008), whereas the late hyperthermic response to MDMA is blunted by blocking β_3-receptors (Sprague *et al.*, 2004a; Bexis and Docherty, 2008). Moreover, α_1-receptors mediate peripheral vasoconstriction and heat dissipation, which are impaired by MDMA (Pedersen and Blessing, 2001). Administration of $\beta_{1,2}$-receptor antagonists had no effect on the thermogenic response to MDMA in rats (Sprague *et al.*, 2005) or humans (Hysek *et al.*, 2010). These data suggest a role for both α_1- and β_3-receptors in MDMA-induced hyperthermia. Carvedilol should be considered for the treatment of hyperthermia associated with ecstasy use because it effectively reduced MDMA-induced hyperthermia in both animals and humans and reversed established hyperthermia in rats (Sprague *et al.*, 2005).

In addition to adrenoceptors, other sites have been implicated in stimulant-induced hyperthermia. MDMA primarily induces the release of 5-HT, NA and dopamine through their respective presynaptic monoamine transporters (Rudnick and Wall, 1992; Rothman *et al.*, 2001; Verrico *et al.*, 2007). MDMA binds to α_2-adrenoceptors, 5-HT_{2A}-receptors, H_1-histamine and trace amine-1 receptors (Battaglia *et al.*, 1988; Bunzow *et al.*, 2001). The 5-HT_{2A}-receptor antagonist ketanserin inhibited the thermogenic effects of MDMA in rats (Shioda *et al.*, 2008), mice (Di Cara *et al.*, 2011) and humans (Liechti *et al.*, 2000). In both mice and humans, ketanserin administered alone lowered body temperature compared with vehicle and placebo, respectively (Liechti *et al.*, 2000; Di Cara *et al.*, 2011).

Table 1

Values and statistics of pharmacodynamic changes

	Placebo-placebo Mean (SEM)	Carvedilol-placebo	Placebo-MDMA	Carvedilol-MDMA	MDMA		Carvedilol		Carvedilol × MDMA	
					$F_{1,15}$	P	$F_{1,15}$	P	$F_{1,15}$	P
Physiological effects										
Systolic blood pressure (mmHg)	4.7 (1.8)	−8.1 (2.0)***$^{\#\#\#}$	28.1 (3.2)***	6.5 (2.2)$^{\#\#\#}$	59.30	<0.001	72.33	<0.001	5.02	<0.05
Diastolic blood pressure (mmHg)	−1.0 (1.4)	−8.1 (1.6)*$^{\#\#\#}$	15.3 (1.6)***	9.3 (1.9)***$^{\#}$	151.10	<0.001	16.40	<0.001	1.70	NS
Heart rate (beats min^{-1})	5.8 (3.0)	−5.0 (2.5)*$^{\#\#\#}$	26.2 (3.9)***	5.5 (3.0)$^{\#\#\#}$	15.44	<0.001	38.84	<0.001	18.64	<0.001
Body temperature (°C)	0.24 (0.06)	0.32 (0.06)$^{\#\#}$	0.69 (0.10)***	0.40 (0.06)$^{\#}$	13.78	<0.01	3.29	NS	7.65	<0.05
Circulating catecholamines										
Adrenaline (nM)	−0.03 (0.03)	0.08 (0.05)	0.23 (0.06)	0.70 (0.15)***$^{\#\#\#}$	19.63	<0.001	14.04	<0.01	14.20	<0.01
Noradrenaline (nM)	−0.34 (0.14)	1.85 (0.36)***$^{\#\#\#}$	0.29 (0.14)	2.58 (0.40)***$^{\#\#\#}$	4.33	0.055	59.86	<0.001	0.04	NS
Visual Analogue Scale (%max)										
Any drug effect	2.4 (1.4)	7.1 (3.4)$^{\#\#\#}$	64.8 (7.5)***	69.6 (7.6)***	94.67	<0.001	1.50	NS	0.00	NS
Good drug effect	1.4 (1.4)	0.0 (0.0)$^{\#\#\#}$	71.1 (7.6)***	76.8 (7.2)***	112.69	<0.001	0.40	NS	1.01	NS
Bad drug effect	0.3 (0.3)	2.5 (1.1)	13.6 (5.1)	25.3 (9.1)**	13.70	<0.01	1.51	NS	0.92	NS
Drug liking	1.6 (1.4)	0.0 (0.0)$^{\#\#\#}$	74.8 (7.1)***	75.9 (7.9)***	106.20	<0.001	0.01	NS	0.20	NS
Drug high	1.7 (1.7)	0.0 (0.0)$^{\#\#\#}$	59.4 (9.0)***	66.3 (8.7)***	56.46	<0.001	0.49	NS	1.15	NS
Stimulated	2.0 (2.0)	0.4 (0.4)$^{\#\#\#}$	57.8 (9.2)***	61.7 (8.9)***	47.78	<0.001	0.10	NS	0.38	NS
5D-ASC Scale										
Total ASC score	8.7 (8.7)	0.0 (0.0)$^{\#\#}$	747 (177)**	894 (227)***	20.06	<0.001	0.55	NS	0.68	NS
Oceanic boundlessness	7.6 (7.6)	0.0 (0.0)$^{\#\#\#}$	436 (119)**	531 (152)***	13.91	<0.01	0.86	NS	1.12	NS
Anxious ego dissolution	0.7 (0.7)	0.0 (0.0)$^{\#}$	192 (75)*	161 (55)	13.53	<0.01	0.12	NS	0.11	NS
Visionary restructuralization	0.4 (0.4)	0.0 (0.0)$^{\#}$	119 (33)*	202 (54)***	16.39	<0.001	3.88	NS	3.94	0.07
List of complaints (total score)										
Acute adverse effects (at 3 h)	−0.2 (0.3)	0.9 (0.4)$^{\#\#\#}$	8.4 (1.5)***	9.9 (2.0)***	46.96	<0.001	0.37	NS	0.08	NS
Subacute adverse effects (at 24 h)	0.1 (0.3)	1.1 (0.8)	5.3 (1.6)*	4.9 (1.5)*	25.96	<0.001	0.08	NS	0.47	NS

Values are expressed as mean (SEM) changes from baseline of 16 subjects. ASC, Altered States of Consciousness; NS, not significant.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared with placebo-placebo. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, compared with placebo-MDMA.

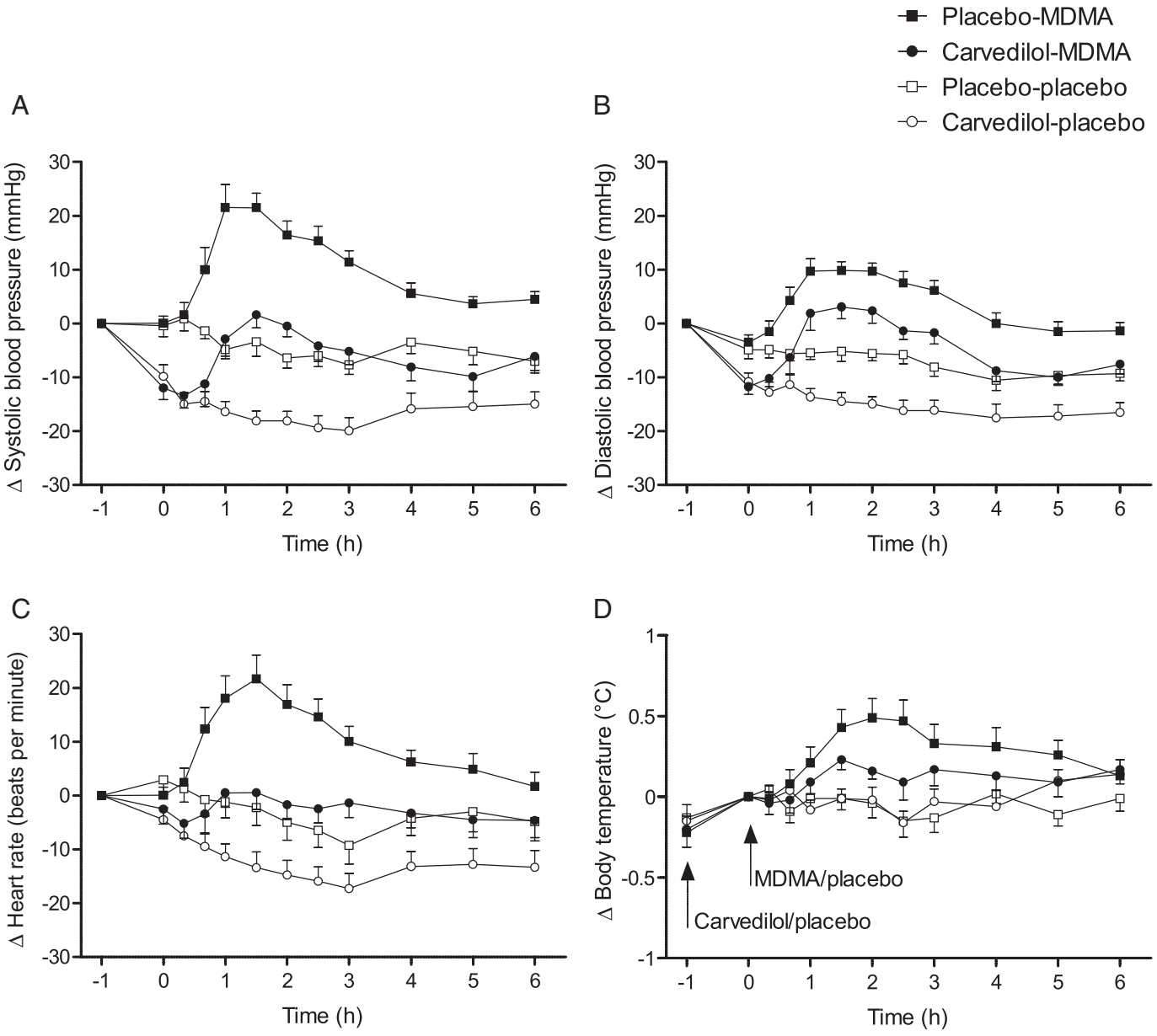

Figure 1

Physiological effects of carvedilol and MDMA. Carvedilol reduced MDMA-induced elevations in systolic (A) and diastolic (B) blood pressure, heart rate (C) and body temperature (D). Carvedilol was administered at t = –1 h. MDMA was administered at t = 0 h. The values are expressed as mean ± SEM changes from baseline in 16 subjects.

Thus, no interactive effect of ketanserin and MDMA on body temperature was observed, in contrast to carvedilol and MDMA in the present study. Furthermore, ketanserin has α_1-adrenoceptor-blocking properties (Brogden and Sorkin, 1990), and its ability to reduce MDMA-associated hyperthermia may be explained, at least partially, by α_1-receptor antagonism. A recent study showed that mice that lack trace amine-1 receptors did not exhibit the early hypothermic response to MDMA, indicating a role for this receptor in the early hypothermic effects of MDMA (Di Cara *et al.*, 2011). D_1- and D_2-dopamine receptors, α_2-adrenoceptors and 5-HT_1-receptors do not appear to be involved in the effects of MDMA on body temperature, demonstrated by preclinical (Docherty and Green, 2010; Di Cara *et al.*, 2011) and clinical (Liechti and Vollenweider, 2000; Hysek *et al.*, 2010; 2012) studies.

Recreational users of ecstasy report subjective increases in body temperature, sweating and hot flushes (Parrott *et al.*, 2008). Hot flushes and sweating were also reported after administration of MDMA in the present and in previous studies (Liechti *et al.*, 2001; Freedman *et al.*, 2005). Carvedilol did not reduce the number of subjects who reported MDMA-induced subjective sweating but reduced the number of subjects reporting flushes. Interestingly, in another laboratory

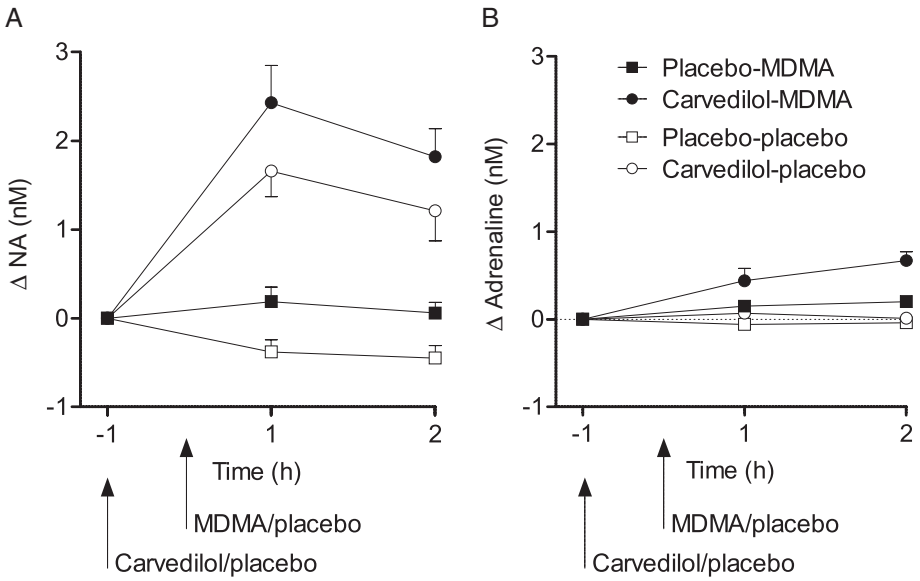

Figure 2

Effects of carvedilol and MDMA on circulating catecholamines. Carvedilol alone increased the plasma levels of noradrenaline (A) compared with placebo. MDMA alone produced a similar non-significant increase in noradrenaline. Co-administration of carvedilol and MDMA increased the concentrations of circulating noradrenaline (A) and adrenaline (B) compared with placebo. The values are expressed as mean ± SEM changes from baseline in 16 subjects.

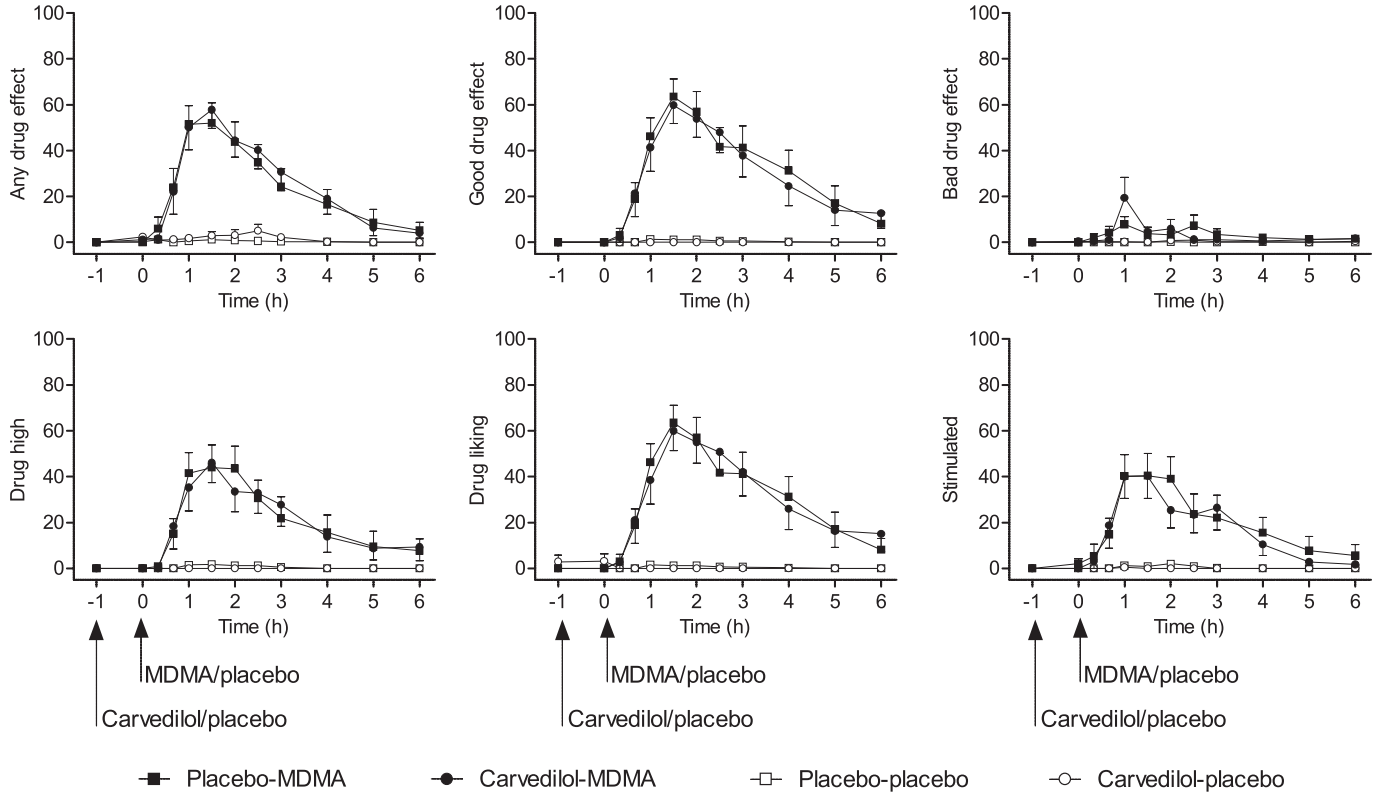

Figure 3

Time course of subjective drug effects on Visual Analogue Scale ratings. MDMA increased scores on all scales. Carvedilol did not affect any of the MDMA-induced increases in Visual Analogue Scale ratings. Carvedilol was administered at t = –1 h. MDMA was administered at t = 0 h. The values are expressed as mean ± SEM percentage of maximal values in 16 subjects.

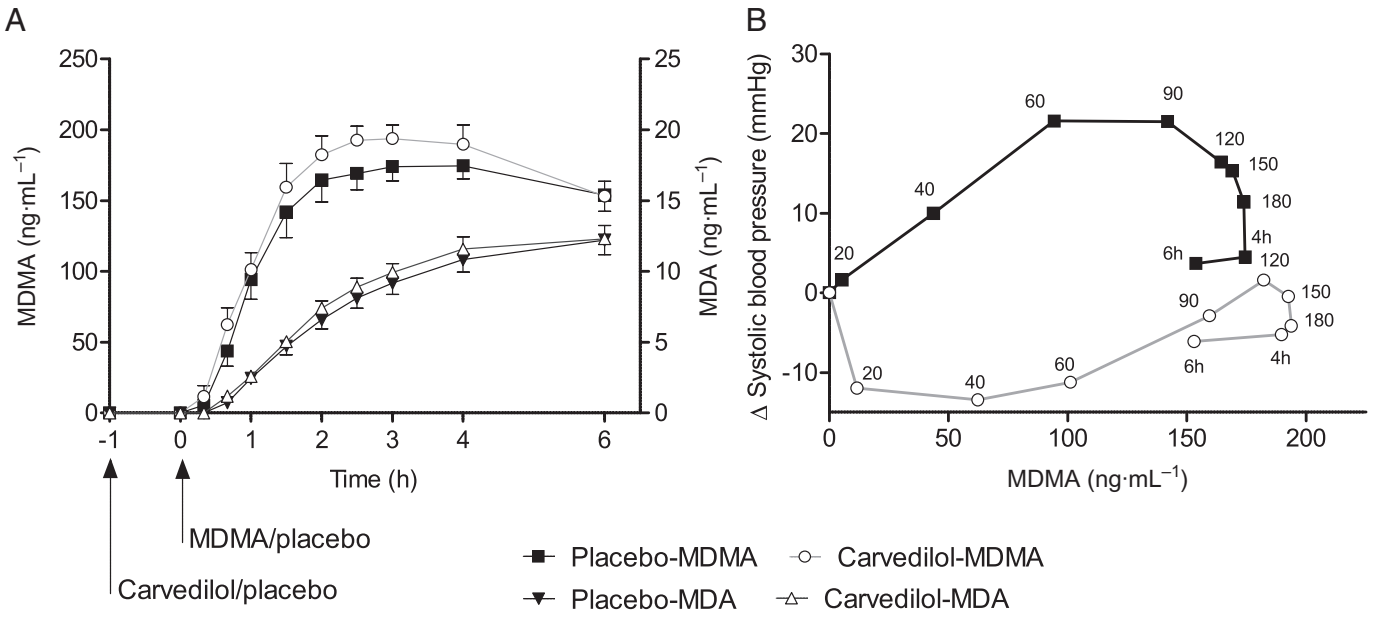

Figure 4

Pharmacokinetics (A) and pharmacokinetic–pharmacodynamic relationship (B). Carvedilol non-significantly increased the exposure to MDMA and MDA (A). The values are expressed as mean ± SEM in 16 subjects. Carvedilol was administered at t = –1 h. MDMA was administered at t = 0 h. MDMA effects on systolic blood pressure plotted against MDMA plasma concentration (B). The values are expressed as means of the changes from baseline in 16 subjects. The time of sampling is noted next to each point in min or h after MDMA administration. Carvedilol produced a downward and rightward shift of the concentration-blood pressure response curve of MDMA (B).

Table 2

Pharmacokinetic parameters of MDMA and MDA

	C_{max} (ng·mL^{-1})	T_{max} (h)	$AUC_{0-6\,h}$ (h·ng·mL^{-1})
MDMA			
Placebo-MDMA	214 (12)	2.9 (0.3)	866 (47)
Carvedilol-MDMA	224 (12)	2.8 (0.2)	921 (45)
MDA			
Placebo-MDMA	12.3 (1.0)	5.5 (0.2)	46.3 (3.5)
Carvedilol-MDMA	12.5 (0.9)	5.0 (0.4)	49.3 (2.8)

Values are mean (SEM) of 16 healthy subjects. AUC, area under concentration–time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration.

study, MDMA did not influence the perceptions of warmth and cold but delayed the onset of sweating at a warm ambient temperature along with an MDMA-induced increase in body temperature (Freedman *et al.*, 2005).

Carvedilol also reduced the cardiostimulant response to MDMA, including blood pressure and heart rate. The α- and β-blockers carvedilol and labetalol have similarly been shown to inhibit the blood pressure response to cocaine in humans (Boehrer *et al.*, 1993; Sofuoglu *et al.*, 2000a,b). Blockade of β-receptors alone did not reduce the pressure response to cocaine (Ramoska and Sacchetti, 1985) or MDMA (Hysek *et al.*, 2010) in humans and enhanced cocaine-induced coronary vasoconstriction (Lange *et al.*, 1990). In rats, the blockade of α_1-receptors inhibited both the pressure response and vasoconstriction in isolated vessels in response to cocaine (Mo *et al.*, 1999). The data indicate that dual α,β-blockers, but not selective β-blockers, should be used in the treatment of psychostimulant-associated hypertension and myocardial ischaemia. The data indicate that carvedilol could be useful in the treatment of both psychostimulant-induced hypertension and hyperthermia.

Circulating catecholamine levels were increased by both MDMA and carvedilol. Plasma adrenaline is mainly derived from the adrenals, whereas plasma NA stems largely from transmitters released by sympathetic nerves and the escape of NA into the circulation (Esler *et al.*, 1990; Eisenhofer *et al.*, 1995). Circulating NA is therefore considered an indicator of sympathetic system activation. We observed a marked increase in plasma NA concentrations after carvedilol administration. This compensatory sympathoadrenal response with enhanced levels of catecholamines has previously been documented after α_1- or α- and β-adrenoceptor blockade (Omvik *et al.*, 1992; Mazzeo *et al.*, 2001). The MDMA-induced increase in circulating NA in the present study did not reach statistical significance compared with previous work (Dumont *et al.*, 2009; Hysek *et al.*, 2011; 2012). It is possible that the peak effect was missed because we took only two samples. The catecholamine response was enhanced when MDMA was administered following carvedilol. A similar potentiation of the exercise-induced increases in plasma catecholamines has been shown following blockade of α_1-adrenoceptors or α- and β-adrenoceptors (Berlin *et al.*, 1993).

Preclinical and clinical studies suggest that NA contributes to the mediation of the subjective effects of MDMA and other psychostimulants (Sofuoglu and Sewell, 2009; Hysek *et al.*, 2011; Newton, 2011). For example, MDMA is more potent in releasing NA than 5-HT or dopamine from monoamine-preloaded human embryonic kidney cells transfected with the corresponding human monoamine transporters (Verrico *et al.*, 2007). Additionally, doses of stimulants that produce amphetamine-type subjective effects in humans correlated with their potency to release NA (Rothman *et al.*, 2001). Furthermore, the NA transporter inhibitor reboxetine attenuated the cardiovascular and subjective response to MDMA in humans, indicating a role for MDMA-induced transporter-mediated NA release in the psychostimulant effects of MDMA (Hysek *et al.*, 2011). Similarly, atomoxetine attenuated the effects of amphetamine in humans (Sofuoglu *et al.*, 2009). Clonidine, which blocks the vesicular release of NA, did not affect the psychological effects of MDMA in humans (Hysek *et al.*, 2012). Although these data suggest a role for transporter-mediated NA release in the psychotropic effects of psychostimulants, how and which postsynaptic adrenoceptors are involved are still unclear. Carvedilol did not alter the subjective effects of MDMA in the present study. Similar to our results, carvedilol and labetalol did not affect the subjective responses to cocaine in humans at doses of cocaine that effectively inhibited the cardiostimulant effects of the drug (Sofuoglu *et al.*, 2000a,b). The available clinical data do not support a critical role for α_1- and $\beta_{1,2,3}$-receptors in the subjective effects of psychostimulants. Alternatively, the carvedilol concentrations in humans may not have been high enough to produce sufficient adrenoceptor occupancy in the brain. Carvedilol is lipophilic and enters the brain (Elsinga *et al.*, 2005). However, carvedilol is a substrate of the efflux transporter P-glycoprotein in the blood-brain barrier (Elsinga *et al.*, 2005; Bachmakov *et al.*, 2006), and P-glycoprotein activity is known to limit brain exposure to carvedilol (Elsinga *et al.*, 2005).

Preclinical studies indicate that α_1-receptors are involved in the mechanism of action of psychostimulants, including MDMA. For example, pretreatment with the α_1-receptor antagonist prazosin inhibited locomotor stimulation induced by cocaine (Wellman *et al.*, 2002), amphetamine (Vanderschuren *et al.*, 2003) and MDMA (Fantegrossi *et al.*, 2004; Selken and Nichols, 2007) in rats and mice. Additionally, α_1-receptor activation in the ventral tegmental area contributed to the amphetamine-induced release of dopamine in the nucleus accumbens (Pan *et al.*, 1996). Injection of prazosin directly into the ventral tegmental area also blocked the locomotor response to MDMA in rats (Selken and Nichols, 2007). Furthermore, administration of prazosin in the rat prefrontal cortex also blocked amphetamine-induced dopamine release in the nucleus accumbens and hyperactivity (Forget *et al.*, 2011). Finally, α_1-adrenoceptor knockout mice do not show increased amphetamine-induced dopamine release in the nucleus accumbens (Auclair *et al.*, 2002) or behavioural sensitization to amphetamine or cocaine (Drouin *et al.*, 2002). In contrast to α_1-antagonism, the β-blocker propranolol enhanced both cocaine-induced locomotion and the cocaine-induced increase in dopamine in the nucleus accumbens (Harris *et al.*, 1996). Altogether, the preclinical studies indicate that α_1-adrenoceptors, but not β-receptors, play a role in the hyperlocomotion and dopaminergic neurochemical response to psychostimulants. However, the role of adrenoceptors in the reinforcing effects of psychostimulants is unclear. For example, prazosin reduced the self-administration of cocaine (Wee *et al.*, 2008) and nicotine (Forget *et al.*, 2011) in rats. In contrast, prazosin had no effect on cocaine self-administration in rhesus monkeys (Woolverton, 1987). The β-blocker propranolol also inhibited cocaine self-administration in rats (Harris *et al.*, 1996). Carvedilol lowered the number of cocaine self-administrations in humans at a low but not high dose (Sofuoglu *et al.*, 2000a). At low doses, carvedilol preferentially blocks β-receptors (Tham *et al.*, 1995; Sofuoglu *et al.*, 2000a) and active metabolites of carvedilol may contribute to the β- but not the α-adrenoceptor blocking effects of the drug (Spahn-Langguth and Schloos, 1996). The antagonism of α_1-adrenoceptors by carvedilol may not have been sufficient in the brain to attenuate the subjective effects of MDMA and we cannot exclude a role for these receptors. The efficacy of carvedilol to reduce cocaine use or abstinence in addicted patients is currently being investigated in ongoing clinical trials [(Sofuoglu and Sewell, 2009) clinicaltrials.gov identifier: NCT00566969 and NCT01171183]. Further trials have investigated the effects of selective α_1-blockers on the acute response to MDMA (NCT01386177) and cocaine (NCT01062945) and abstinence from cocaine use (NCT00880997).

Pharmacokinetic interactions between carvedilol and MDMA need to be considered in the interpretation of the present findings, because both drugs are metabolized by CYP2D6 (Graff *et al.*, 2001; O'Mathuna *et al.*, 2008). We therefore assessed the potential effects of carvedilol on the pharmacokinetics of MDMA. We found that carvedilol non-significantly increased the plasma exposure to MDMA or MDA. Thus, the reduced haemodynamic and thermogenic effects of MDMA after carvedilol pretreatment did not result from lower plasma levels of MDMA or MDA. We did not assess the plasma concentrations of carvedilol. MDMA inhibits CYP2D6 (O'Mathuna *et al.*, 2008). CYP2D6 inhibition has been shown to increase the exposure to carvedilol but not its pharmacodynamic or adverse effects in humans (Graff *et al.*, 2001).

Our laboratory study has a few limitations. The study design is limited by the use of single doses. We did not use a dose–response study because we did not want to expose the subjects to more than two doses of MDMA in a within-subject design. However, moderate to highly effective doses of both drugs were selected. The primary goal of the study was to investigate the role of adrenoceptors in the mechanism of action of MDMA in humans. Therefore, the study provides only indirect support for the use of carvedilol in the treatment of stimulant toxicity, in which carvedilol would be administered following the ingestion of ecstasy or other stimulants. Furthermore, the MDMA-induced increase in body temperature in our study was moderate, and we do not know whether carvedilol would also be effective in cases of severe hyperthermia following ecstasy use. Finally, thyroid function may modulate the thermogenic effects of MDMA (Martin *et al.*, 2007; Sprague *et al.*, 2007) and thyroid function parameters were not assessed in this study.

In conclusion, carvedilol inhibited the MDMA-induced increase in blood pressure and body temperature under con-

trolled laboratory conditions. The results demonstrate that α_1- and/or $\beta_{1,2,3}$-adrenoceptors contribute to the cardiostimulant and thermogenic effects of MDMA in humans. The absence of an effect of carvedilol on the psychotropic response to MDMA does not support a role for α- and β-adrenoceptors in the mediation of the subjective effects of MDMA in humans. Combined α- and β-blockers could be useful in the treatment of intoxications with MDMA or other psychostimulants including other amphetamine derivatives or cocaine.

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Conflict of interest

None.

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