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Interactions between Bupropion and 3,4-Methylenedioxymethamphetamine in Healthy Subjects

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ABSTRACT

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a popular recreational drug. The aim of the present study was to explore the role of dopamine in the psychotropic effects of MDMA using bupropion to inhibit the dopamine and norepinephrine transporters through which MDMA releases dopamine and norepinephrine. The pharmacodynamic and pharmacokinetic interactions between bupropion and MDMA in 16 healthy subjects were investigated using a double-blind, placebo-controlled, crossover design. Bupropion reduced the MDMA-induced elevations in plasma norepinephrine concentrations and the heart rate response to MDMA. In contrast, bupropion increased plasma MDMA concentrations and prolonged its subjective effects. Conversely, MDMA increased plasma bupropion concentrations. These results indicate a role for the transporter-mediated release of norepinephrine in the cardiostimulant effects of MDMA but do not support a modulatory role for dopamine in the mood effects of MDMA. These results also indicate that the use of MDMA during therapy with bupropion may result in higher plasma concentrations of both MDMA and bupropion and enhanced mood effects but also result in lower cardiac stimulation.

Introduction

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a popular recreational drug that acts by releasing dopamine (DA), norepinephrine (NE), and serotonin (5-HT) through their corresponding transporters (Verrico et al., 2007; Hysek et al., 2012d). The present study (ClinialTrials.gov #NCT01771874; http://www.clinicaltrials.gov/ct2/show/NCT01771874) was designed to contribute to elucidation of the mechanism of action of MDMA in humans. Specifically, we explored the modulatory role of DA in the psychotropic effects of MDMA by using bupropion pretreatment to block MDMA-induced DA release. Dopamine transporter inhibition prevents the release of DA through the DA transporter induced by MDMA or other amphetamines (Verrico et al., 2008; Simmler et al., 2013b). Dopamine mediates the reinforcing addictive effects of psychostimulants, but its role in the drug-induced subjective effects of different psychostimulants, such as euphoria, is less clear (Wise, 2008). Bupropion inhibits the DA transporter, less potently the NE transporter, but not the 5-HT transporter (Richelson and Pfenning, 1984; Andersen, 1989; Stahl et al., 2004). Using previously published methods (Simmler et al., 2013b), we also confirmed that bupropion inhibited the human DA, NE, and 5-HT transporter with IC_{50} values of 1.6, 18, and >100 μM, respectively. Bupropion has been shown to inhibit the amphetamine- and methamphetamine-induced release of DA in vitro (Gruner et al., 2009; Simmler et al., 2013b) and decrease methamphetamine self-administration in rats (Reichel et al., 2009) and monkeys (Schindler et al., 2011). Bupropion also reduced methamphetamine-induced subjective and cardiostimulant effects in humans (Newton et al., 2005, 2006) and may reduce drug use in subsets of methamphetamine users (Elkashef et al., 2008; Heinzerling et al., 2014). These findings suggest a role for DA in both the rewarding and subjective effects of methamphetamine. In contrast, the role of DA in the acute mechanism of action of MDMA is less clear. In preclinical studies, DA receptor gene deletion in mice had minimal effects on MDMA-induced behavioral changes (Risbrough et al., 2006), and DA transporter inhibition did not alter the acute response to MDMA in rhesus monkeys (Verrico et al., 2008). In contrast, 5-HT and NE have been well documented to mediate most of the acute psychotropic and physiologic effects of MDMA in humans (Liechti et al., 2000; Liechti and Vollenweider, 2000; Farre et al., 2007; Hysek et al., 2011, 2012d). In particular, inhibition of both the 5-HT and NE transporters with duloxetine, which prevents the MDMA-induced release of 5-HT and NE through their respective transporters, almost

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ABBREVIATIONS: AUC, area under the plasma concentration-time curve; AUEC, area under the effect-time curve; [^{11}C]β-CIT-FE, *N*-(2-fluoroethyl)-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane; DA, dopamine; HMMA, 4-hydroxy-3-methoxymethamphetamine; 5-HT, 5-hydroxytryptamine (serotonin); LLOQ, lower limit of quantification; MDA, 3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; NE, norepinephrine; VAS, Visual Analog Scale.

completely abolished the subjective and cardiostimulant response to MDMA in humans (Hysek et al., 2012d).

We previously showed that the DA and NE transporter inhibitor methylphenidate did not alter the subjective response to MDMA in healthy subjects, which is consistent with DA having no relevant contribution to the psychotropic effects of MDMA in humans (Hysek et al., 2014). Because methylphenidate produced substantial subjective effects on its own (Hysek et al., 2014), however, this prior study was inconclusive. In contrast to methylphenidate, bupropion is a more potent DA transporter inhibitor than NE transporter inhibitor (Stahl et al., 2004) and is more selective for DA compared with methylphenidate, which blocks the DA and NE transporters with equal potency (Simmler et al., 2014). Additionally, bupropion has been proposed to bind to the substrate recognition site on the DA transporter similarly to MDMA, whereas psychoactive DA transporter ligands, such as methylphenidate and cocaine, may interact with a different binding site on the DA transporter (Heal et al., 2014). Bupropion reaches a high brain-to-plasma ratio and brain concentrations above its IC_{50} value for DA transporter inhibition (Stahl et al., 2004). Thus, we investigated the effects of pretreatment with bupropion or placebo on the pharmacodynamics and pharmacokinetics of MDMA in healthy subjects. We hypothesized that bupropion pretreatment would prevent the MDMA response to the extent that the effects of MDMA in humans depend on an interaction with the DA and NE transporters. Specifically, we expected bupropion to reduce the mood and cardiostimulant effects of MDMA through DA and NE transporter inhibition, respectively.

Bupropion inhibits CYP2D6 (Kotlyar et al., 2005), which inactivates MDMA to 4-hydroxy-3-methoxymethamphetamine (HMMA; de la Torre et al., 2012). Therefore, bupropion can be expected to increase plasma concentrations of MDMA. Furthermore, CYP2B6, which metabolizes bupropion to hydroxybupropion (Jefferson et al., 2005), is also involved in the minor metabolic pathway of MDMA to form the psychoactive metabolite 3,4-methylenedioxyamphetamine (MDA) by *N*-demethylation, in addition to the involvement of CYP1A2 and CYP3A4 (Kreth et al., 2000). Thus, the competitive inhibition of CYP2B6 by bupropion might alter the conversion of MDMA to MDA, and MDMA may inhibit the metabolism of bupropion. Thus, in addition to pharmacodynamic interactions at the DA and NE transporters, complex pharmacokinetic interactions between bupropion and MDMA are also likely and were examined in the present study.

Materials and Methods

Study Design

This study used a double-blind, placebo-controlled, crossover design with four experimental test sessions (placebo–placebo, bupropion–placebo, placebo–MDMA, and bupropion–MDMA) that were performed in a counterbalanced order according to a Latin-square randomization design. The washout periods between 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 in Good Clinical Practice and approved by the Ethics Committee of the Canton of Basel, Switzerland, and the Swiss Agency for Therapeutic Products (Swissmedic). The study was registered at ClinicalTrials.gov (NCT01771874). The predefined primary endpoint of the study was the effect of bupropion on "good drug effects" associated with MDMA. All subjects provided written informed consent and were paid for their participation.

Subjects

Sixteen healthy white subjects (eight men and eight women) with a mean ± S.D. age of 24.3 ± 2.2 years and a body mass index of 22.7 ± 2.1 kg/m^2 were recruited from the University of Basel campus. The inclusion criterion was 18–45 years of age. Subjects with a personal or first-degree-relative history of psychiatric disorders or chronic or acute physical illness were excluded as previously described (Hysek et al., 2012a). Additional exclusion criteria were tobacco smoking (>10 cigarettes/day) and a lifetime history of using illicit drugs more than five times, with the exception of past cannabis use. Six subjects had used MDMA once previously. Drug use histories are shown in Table 1. Subjects who used any illicit drugs, including cannabis, within the past 2 months or during the study period were excluded. We performed drug tests at screening and before each test session using TRIAGE 8 (Biosite, San Diego, CA). Female participants were investigated during the follicular phase of their menstrual cycle (days

TABLE 1
Prevalence of drug use
Values are times used in life except for tetrahydrocannabinol (THC), coffee, alcohol, and smoking.

Subject	Sex	Age	MDMA	Amphetamine	Cocaine	LSD	Psilocybin	THC	Coffee	Alcohol Use	Smoking	Smoking
		yr	*pills*					*joints/yr*	*cups/day*	*drinks/wk*	*cigarettes/day*	*yr*
1	M	25	0	0	0	0	0	Never	0.0	0	0	0
2	F	23	0	0	0	0	0	<1	4.5	1	0	0
3	M	25	0	0	0	0	0	<1	0.0	0	0	0
4	F	22	1	0	0	0	0	<1	1.0	2	0	0
5	F	27	0	0	0	0	0	<1	2.0	3	0	0
6	M	27	1	0	2	0	0	10–15	1.5	3	5	10
7	M	22	0	0	0	0	0	5–10	2.0	3	0	0
8	M	25	0	0	0	0	0	Never	2.0	2	0	0
9	F	27	1	0	0	0	0	<1	2.0	3	0	0
10	F	27	1	0	0	0	0	<1	3.5	3	3	10
11	M	25	1	0	0	0	0	<1	3.0	5	0	0
12	M	25	1	0	0	0	0	5–10	2.0	3	0	0
13	M	24	0	0	0	1	1	2–4	2.5	7	0	0
14	F	20	0	0	0	0	0	<1	1.0	5	0	0
15	F	22	0	0	0	0	0	2–4	0.0	2	0	0
16	F	22	0	0	0	0	0	<1	2.0	1	0	0

LSD, lysergic acid diethylamide.

2–14) to account for cyclic changes in the reactivity to amphetamines (White et al., 2002). All subjects were genotyped (Hicks et al., 2013) and phenotyped (Trojan et al., 2012) for CYP2D6 activity. The study included 13 extensive, three intermediate, and no poor CYP2D6 metabolizers (genotyping and phenotyping congruent).

Study Outline

The study included a prescreening telephone interview, a screening visit, four whole-day test sessions with a next-day follow-up, and an end-of-study visit. Bupropion or placebo was administered daily for 7 days before each of the test sessions. The test sessions began at 7:45 AM. An indwelling intravenous catheter was placed in an antecubital vein for blood sampling, and the subjects completed baseline measurements of mood and vital signs. Bupropion (300 mg p.o.) or placebo was administered at 8:00 AM. MDMA (125 mg p.o.) or placebo was administered at 10:00 AM. A standardized lunch was served at 12:30 PM, and the subjects were sent home at 6:00 PM. On the day after each test session, the participants returned to the research ward at 10:00 AM for assessment of subjective and adverse effects and collection of the 24-hour blood sample.

Drugs

±MDMA hydrochloride ($C_{11}H_{15}NO_2$, Lipomed AG, Arlesheim, Switzerland) was prepared as gelatin capsules (100 and 25 mg). Identical-looking placebo (mannitol) capsules were prepared. MDMA was administered in a single absolute dose of 125 mg, corresponding to 1.8 ± 0.2 mg/kg body weight (mean ± S.D.). Bupropion tablets [150 mg, Wellbutrin XR 150 mg (GlaxoSmithKline, Munchenbuchsee, Switzerland) and mannitol as filler] were encapsulated within opaque gelatin capsules, and identical placebo (mannitol pill with mannitol filler) capsules were prepared. Bupropion was administered once daily at a dose of 150 mg for 3 days, followed by administration of 300 mg of bupropion once daily for 4 days before the test days. A similar regimen is used to initiate smoking cessation treatment with bupropion. The subjects were reminded by a phone text message to ingest the capsules in the morning, and medication containers were checked to confirm that the first seven doses of bupropion were administered. The last dose of bupropion (300 mg) was administered onsite under supervision 2 hours before MDMA was administered. Similar pretreatment regimens with bupropion produced 26% DA transporter occupancy as measured by [^{11}C]β-CIT-FE [*N*-(2-fluoroethyl)-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane] positron emission tomography 3 hours after the last dose of bupropion (Learned-Coughlin et al., 2003) and reduced the subjective response to methamphetamine in humans (Newton et al., 2006).

Outcome Measures

Vital Signs. Blood pressure, heart rate, and core body temperature were assessed repeatedly 2 hours and 1 hour before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours after MDMA or placebo administration as previously described (Hysek and Liechti, 2012). The cardiovascular measures were performed in duplicate after a resting time of at least 10 minutes. The averages were calculated for the analyses.

Pupillometry. Pupillometry was performed 2 hours and 1 hour before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours after drug administration. Pupil function was measured using a PRL-200 infrared pupillometer (NeurOptics, Irvine, CA) under dark-light conditions of 6.1 ± 1 lux as described previously (Hysek and Liechti, 2012). The dark-adapted pupil diameter was measured in both eyes, and the average values were used for analyses.

Endocrine Measures. Plasma levels of prolactin and cortisol were measured at baseline and 2 hours after MDMA or placebo administration using radioimmunoassays (Hysek et al., 2012b). Plasma levels of oxytocin were measured before and 1 hour and 2 hours after administration of MDMA or placebo by radioimmunoassay (Neumann et al., 2013). Concentrations of circulating catecholamines, including epinephrine and NE, were measured at baseline and 1 hour and 2 hours after administration of MDMA or placebo using ultra-performance liquid chromatography–tandem mass spectrometry (Dunand et al., 2013). Plasma epinephrine levels are mainly derived from the adrenal medulla, whereas the entrance of NE into the plasma represents an overflow by sympathetic nerves (Esler et al., 1990; Eisenhofer et al., 1995). Circulating NE is therefore considered an indicator of sympathetic system activation. DA in plasma does not derive from DA but mostly from NE neurons (Goldstein and Holmes, 2008). Nevertheless, we measured DA levels in plasma because there are no data on the effects of MDMA on DA plasma levels.

Adverse Effects. Adverse effects were assessed using the 66-item list of complaints (Zerssen, 1976) before and 5 and 24 hours after MDMA or placebo administration. The scale yields a total adverse effects score, reliably measuring physical and general discomfort.

Psychometric Scales. Subjective effects were repeatedly assessed using previously described psychometric scales. Visual Analog Scales (VASs; Hysek et al., 2011) were administered 2 hours and 1 hour before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 24 hours after administration of MDMA or placebo.

Pharmacokinetics. Blood samples for the determination of MDMA, MDA, HMMA, bupropion, hydroxybupropion, and hydrobupropion were collected 2 hours before and 0, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after MDMA or placebo administration. Plasma MDMA, MDA, and HMMA concentrations were determined using high-performance liquid chromatography–tandem mass spectrometry as described previously (Hysek et al., 2012a, 2013). Bupropion, hydroxybupropion, and hydrobupropion were included into the analytical method, and slight modifications were made. In brief, the chromolith speed ROD RP-18e (50 × 4.6 mm; Merck, Darmstadt, Germany) analytical column was replaced by a Luna PFP (2) column (50 × 2 mm; Phenomenex, Torrance, CA), and bupropion, hydroxybupropion, and hydrobupropion were added as additional analytes. Peak symmetry was improved by online dilution of the samples with water supplemented with 0.1% formic acid. Threohydrobupropion and erythrohydrobupropion were quantified together as hydrobupropion because the isomeric metabolites coeluted in chromatography and were indistinguishable in mass spectrometry. The performance of the method was monitored using quality-control samples at the lower limit of quantification (LLOQ) and at two to four other concentrations that covered the entire calibration range. The LLOQ values were 1 ng/ml for MDMA, MDA, HMMA, and hydroxybupropion, 5 ng/ml for bupropion, and 0.1 ng/ml for hydrobupropion. The interassay precision was <15% (LLOQ: 20%), and the interassay accuracy ranged from 85% to 115% (LLOQ: 80%–120%) for all the analytes.

Statistical and Pharmacokinetic Analyses

Peak effects (E_{max}) and peak changes from baseline (ΔE_{max}) were determined for repeated measures. E_{max} and ΔE_{max} values were analyzed by two-way repeated-measures analysis of variance, with MDMA (MDMA versus placebo) and bupropion (bupropion versus placebo) as within-subjects factors, using Statistica 12 software (StatSoft, Tulsa, OK). Tukey's post hoc comparisons were performed based on significant main effects or interactions. The criterion for significance was $P < 0.05$. Pharmacokinetic data were analyzed using noncompartmental models. Peak plasma concentration (C_{max}) and the time to reach maximal plasma concentration (T_{max}) were obtained directly from the observed concentration-time curves. For MDMA, HMMA, and bupropion, the terminal elimination rate constant (λ_z) was estimated by log-linear regression after semilogarithmic transformation of the data using at least three data points of the terminal linear phase of the concentration-time curve. The terminal elimination half-life ($t_{1/2}$) was calculated using λ_z and the equation $t_{1/2} = \ln 2/\lambda_z$. Determining the $t_{1/2}$ values for MDA, hydroxybupropion, and hydrobupropion was not possible because of their long $t_{1/2}$, which would require a longer sampling time. The area under the plasma concentration-time

TABLE 2

Pharmacodynamic effects

Values are mean ± S.E.M. of peak changes from baseline (ΔE_{max}) or peak effects (E_{max}) in 16 subjects.

		Placebo–Placebo	Bupropion–Placebo	Placebo–MDMA	Bupropion–MDMA	Main Effect of MDMA		Main Effect of Bupropion		Bupropion × MDMA Interaction	
						$F_{1,15}$	P value	$F_{1,15}$	P value	$F_{1,15}$	P value
Vital signs											
SBP (mm Hg)	ΔE_{max}	9.3 ± 1.5	9.4 ± 1.5	33.1 ± 2.5***	27.7 ± 1.5***	91.22	<0.001	2.76	NS	2.62	NS
DBP (mm Hg)	ΔE_{max}	5.3 ± 0.9	6.1 ± 1.3	17.7 ± 1.3***	16.9 ± 1.4***	72.17	<0.001	0.00	NS	0.50	NS
Heart rate (beats/min)	ΔE_{max}	5.6 ± 1.1	6.6 ± 1.5	30.2 ± 3.1***	18.5 ± 2.2***,###	57.97	<0.001	12.38	0.003	13.97	0.002
Body temperature (°C)	ΔE_{max}	0.39 ± 0.07	0.31 ± 0.05	0.63 ± 0.09	0.66 ± 0.07*	18.26	<0.001	0.19	NS	0.71	NS
Pupillometry											
Pupil size (mm)	E_{max}	6.90 ± 0.14	6.90 ± 0.17	7.74 ± 0.13***	7.76 ± 0.14***	103.06	<0.001	0.04	NS	0.06	NS
Hormones											
Prolactin (mU/l)	ΔE_{max}	−219 ± 34	−211 ± 50	441 ± 191**	388 ± 196**	16.45	0.001	0.11	NS	0.09	NS
Cortisol (nmol/l)	ΔE_{max}	−414 ± 37	−425 ± 81	150 ± 51***	106 ± 48***	63.08	<0.001	0.20	NS	0.26	NS
Oxytocin (pg/ml)	ΔE_{max}	−0.9 ± 0.6	−1.0 ± 0.4	86 ± 15***	79 ± 17***	44.56	<0.001	0.11	NS	0.10	NS
Epinephrine (nmol/l)	ΔE_{max}	0.04 ± 0.02	0.03 ± 0.03	0.5 ± 0.1***	0.4 ± 0.07***	48.68	<0.001	0.72	NS	0.20	NS
Norepinephrine (nmol/l)	ΔE_{max}	−0.32 ± 0.13	0.10 ± 0.12	0.96 ± 0.19***	0.33 ± 0.12*,#	20.94	<0.001	1.89	NS	9.57	0.007
Dopamine (nmol/l)	ΔE_{max}	0.03 ± 0.02	−0.01 ± 0.02	0.08 ± 0.03	0.06 ± 0.03	2.61	NS	1.60	NS	0.84	NS
List of complaints (total score)											
Acute adverse effects	≤5 h	2.2 ± 0.7	2.6 ± 1.0	15.9 ± 1.8***	15.1 ± 1.0***	97.57	<0.001	0.07	NS	0.50	NS
Subacute adverse effects	≤24 h	1.3 ± 0.6	2.4 ± 0.8	8.4 ± 1.5***	7.9 ± 1.2***	33.38	<0.001	0.14	NS	1.12	NS
Subjective effects											
Visual Analog Scale (%max)											
Any drug effect	ΔE_{max}	0.3 ± 0.3	1.4 ± 1.0	75 ± 5***	84 ± 3***	508.82	<0.001	2.81	NS	2.35	NS
	$\Delta AUEC_{0-8h}$	0.2 ± 0.2	3.6 ± 3.3	191 ± 22***	261 ± 26***,#	118.97	<0.001	7.34	0.02	6.56	0.02
Good drug effect	ΔE_{max}	3.1 ± 3.1	0.9 ± 0.9	69 ± 5***	77 ± 5***	236.03	<0.001	0.93	NS	2.62	NS
	$\Delta AUEC_{0-8h}$	1.6 ± 1.6	0.5 ± 0.5	167 ± 23***	244 ± 35***,#	62.26	<0.001	6.71	0.02	6.69	0.02
Drug high	ΔE_{max}	0.0 ± 0.0	0.2 ± 0.2	63 ± 7***	76 ± 5***	167.20	<0.001	3.67	NS	3.66	NS
	$\Delta AUEC_{0-8h}$	0.0 ± 0.0	0.1 ± 0.1	131 ± 26***	188 ± 37***,#	29.43	<0.001	5.22	0.04	5.22	0.04
Drug liking	ΔE_{max}	2.4 ± 2.4	3.3 ± 3.3	72 ± 6***	76 ± 6***	242.54	<0.001	0.85	NS	0.38	NS
	$\Delta AUEC_{0-8h}$	1.2 ± 1.2	2.5 ± 2.5	173 ± 22***	245 ± 39***,#	61.50	<0.001	4.57	0.049	4.61	0.049
Stimulated	ΔE_{max}	0.0 ± 0.0	0.4 ± 0.4	61 ± 8***	68 ± 7***	102.27	<0.001	0.64	NS	0.56	NS
	$\Delta AUEC_{0-8h}$	0.0 ± 0.0	0.4 ± 0.4	144 ± 27***	193 ± 40***	28.69	<0.001	3.74	NS	3.69	NS

AUE, area under the effect-time curve; DBP, diastolic blood pressure; NS, not significant; SBP, systolic blood pressure.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with placebo-placebo; #$P < 0.05$; ###$P < 0.001$ compared with placebo-MDMA.

curve (AUC) and area under the effect-time curve (AUEC) were calculated using the linear trapezoidal rule.

Results

Autonomic Effects. Peak effects and statistics are summarized in Table 2. MDMA increased blood pressure, heart rate, and body temperature (Fig. 1, A–D). Bupropion significantly reduced the MDMA-induced increase in heart rate (Fig. 1C), but it did not significantly affect the increases in blood pressure (Fig. 1, A and B) or body temperature (Fig. 1D) induced by MDMA. Bupropion did not alter the mydriatic effect of MDMA on pupillary function (Table 2).

Endocrine Effects. MDMA increased plasma concentrations of prolactin, cortisol, oxytocin, epinephrine, and NE compared with placebo. Bupropion significantly reduced the MDMA-induced increases in the plasma concentrations of NE but not of other hormones (Table 2). Plasma levels of DA were very low and in 75% of the measurements were below the lower limit of detection (< 0.1 nM). None of the treatments altered DA plasma concentrations.

Adverse Effects. The acute (up to 5 hours) and subacute (up to 24 hours) adverse effects of MDMA were not altered by bupropion (Table 2). Frequently reported acute adverse effects of placebo–MDMA and bupropion–MDMA were lack of appetite (n = 13 for both), perspiration (n = 11 and 12, respectively), tremor (n = 8 and 11, respectively), restlessness (n = 10 and 7, respectively), dry mouth (n = 14 and 12, respectively), and bruxism (n = 13 for both). Subacute adverse effects included headache (n = 12 and 8, respectively), tiredness (n = 9 and 10, respectively), lack of appetite (n = 8 and 9, respectively), difficulty concentrating (n = 7 and 6, respectively), dry mouth (n = 5 and 9, respectively), and bruxism (n = 6 and 10, respectively). No severe adverse effects were reported.

Subjective Effects. Peak effects and statistics are summarized in Table 2. MDMA increased VAS ratings for "any drug effect," "good drug effect," "drug high," "drug liking," and "stimulated" (Fig. 2, A–E). Bupropion enhanced the positive mood effects of MDMA, reflected by a significant increase in AUEC values and a nonsignificant increase in maximal effect ratings and in the bupropion–MDMA condition compared with the placebo–MDMA condition for VAS scales ratings for "any drug effect," "good drug effect," "drug high," and "drug liking" (Fig. 2, A–D; Table 2). MDMA-induced increases in "stimulation" were not significantly altered by bupropion (Fig. 2E).

Pharmacokinetics. The drug and metabolite concentration-time curves are shown in Fig. 3. The pharmacokinetic parameters are shown in Table 3. Bupropion pretreatment significantly increased the plasma concentration of MDMA ($C_{max,}$ $P < 0.01$; $AUC_{0–8}$, $P < 0.001$; $AUC_{0–24,}$ $P < 0.001$) and prolonged its $t_{1/2}$ ($P < 0.01$). In contrast, bupropion pretreatment significantly decreased the plasma concentrations of MDA (C_{max}, $P < 0.01$; $AUC_{0–8,}$ $P < 0.001$) and HMMA ($C_{max,}$ $P < 0.001$; $AUC_{0–8,}$ $P < 0.001$; $AUC_{0–24,}$ $P < 0.001$) and prolonged the $t_{1/2}$ and T_{max} of HMMA (both $P < 0.001$). MDMA significantly increased the plasma concentration of bupropion ($C_{max,}$ $P < 0.05$; $AUC_{0–8,}$ $P < 0.001$; $AUC_{0–24,}$ $P < 0.01$). MDMA

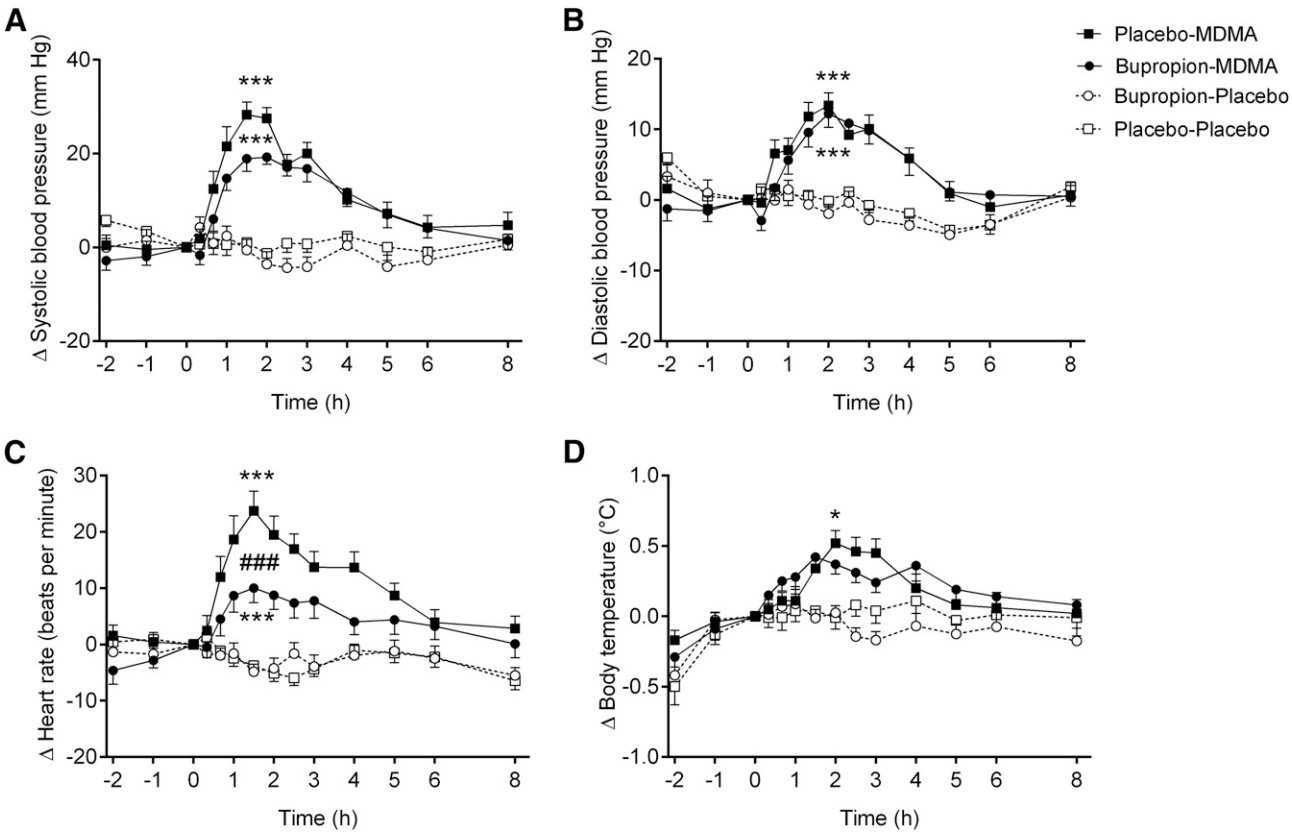

Fig. 1. Bupropion reduced the MDMA-induced an increase in heart rate (C) compared with placebo–MDMA but not in the blood pressure (A and B) or body temperature (D) response to MDMA. MDMA or placebo was administered at t = 0 hour. Data are expressed as mean ± S.E.M. in 16 subjects. $^{*}P < 0.05$; $^{***}P < 0.001$ for significant differences in the maximal effects compared with placebo-placebo; $^{###}P < 0.001$ compared with placebo–MDMA.

also slightly increased the C_{max} of hydrobupropion ($P < 0.05$), but it had no effect on the concentration of hydroxybupropion.

The MDMA concentration-effect plot (Fig. 4.) shows that higher subjective effects were reached early during the drug response in the bupropion–MDMA condition compared with the placebo–MDMA condition at similar MDMA concentrations consistent with a dynamic drug interaction. Thus, bupropion did not reduce the MDMA response taking into account any pharmacokinetic interactions.

Discussion

In the present study, bupropion reduced the heart rate response to MDMA and prolonged its subjective effects. We hypothesized that bupropion prevents the pharmacodynamic effects of MDMA to the extent that these effects depend on DA and NE release. Bupropion reduced the MDMA-induced increases in circulating NE, which is a marker of sympathetic system activation, and the cardiostimulant effects of MDMA similarly to the selective NE transporter inhibitor reboxetine (Hysek et al., 2011). The blockade of α- and β-adrenergic receptors by carvedilol reduced the heart rate and blood pressure response to MDMA (Hysek et al., 2012c). Together, these findings indicate that NE mediates the cardiostimulant effects of MDMA. In contrast, blocking the DA transporter with bupropion did not reduce and actually prolonged the positive mood effects of MDMA. Thus, DA does not appear to be a critical mediator of the subjective effects of MDMA. Otherwise, a reduction in the mood response would have been expected. Methylphenidate, which inhibits the DA transporter more potently than bupropion (Simmler et al., 2013b; Heal et al., 2014), did not attenuate the subjective effects of MDMA (Hysek et al., 2014). In contrast, several studies showed that the subjective effects of MDMA in humans are significantly reduced by 5-HT (Liechti et al., 2000; Farre et al., 2007; Tancer and Johanson, 2007) and NE (Hysek et al., 2011) transporter inhibition and almost completely blocked by dual 5-HT and NE transporter inhibition (Hysek et al., 2012d). Additionally, bupropion did not alter adverse effects of MDMA, in contrast to 5-HT (Liechti and Vollenweider, 2000) or 5-HT and NE transporter inhibitors (Hysek et al., 2012d). These clinical mechanistic studies support the view that 5-HT and NE are the primary mediators of the acute psychological effects of MDMA, whereas DA appears to be less relevant. 5-HT receptor agonists fully substituted for the discriminative stimulus effects of MDMA in rats, but methamphetamine did not (Mori et al., 2014). Unlike MDMA, methamphetamine predominantly acts on the DA system (Simmler et al., 2013a,b), and bupropion reduced the subjective effects of methamphetamine (Newton et al., 2006), consistent with a more important role for DA in the action of methamphetamine.

How bupropion prolonged the subjective response to MDMA in the present study is unclear. Bupropion has previously been shown to similarly enhance the positive subjective effects of cocaine (Oliveto et al., 2001). Bupropion increased the plasma concentration of MDMA, and this pharmacokinetic bupropion–MDMA interaction could partially explain the enhanced psychotropic effects of MDMA induced by bupropion. However, the concentration-effect relationship indicated that bupropion also increased the subjective effects of MDMA irrespective of its increasing effect on MDMA plasma concentrations.

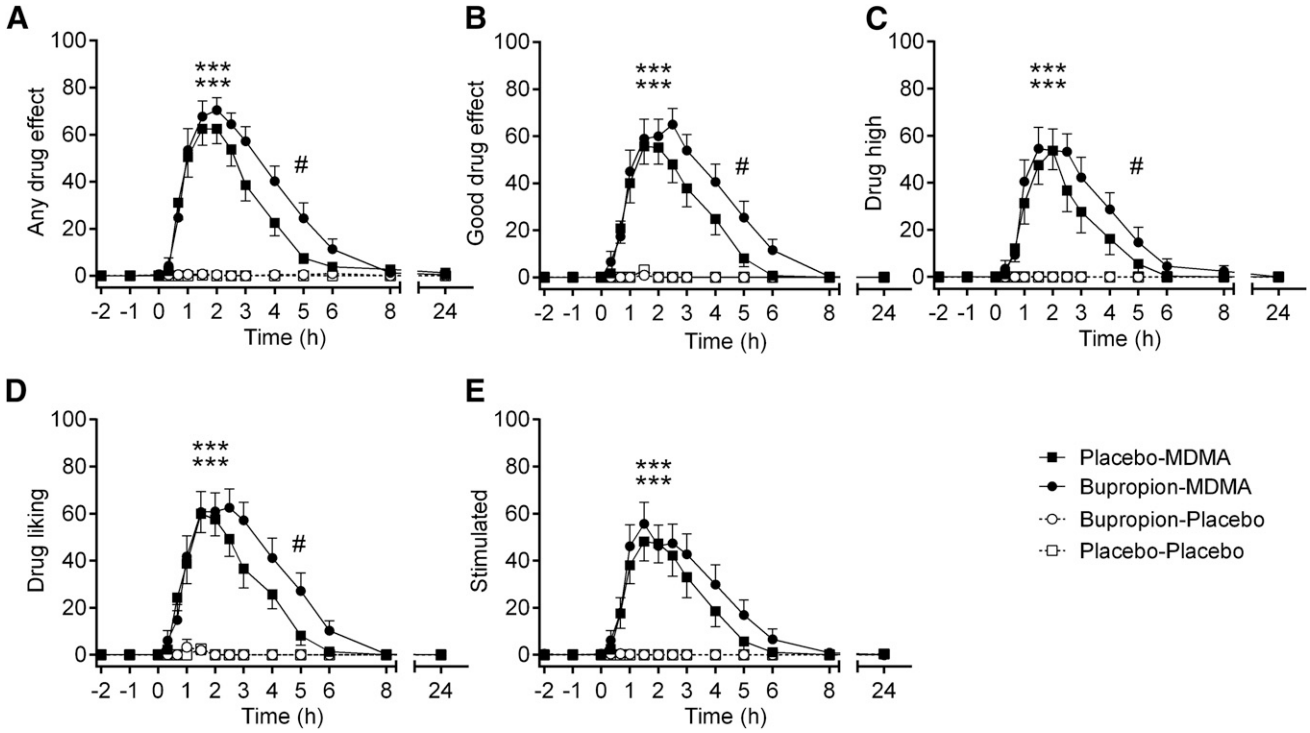

Fig. 2. Bupropion pretreatment enhanced the subjective mood effects of MDMA. The MDMA-induced area under the effect-concentration curves for VAS scale ratings for (A) "any drug effect," (B) "good drug effect," (C) "drug high," and (D) "drug liking," but not (E) "stimulation," were all significantly greater after bupropion–MDMA compared with MDMA alone ($^{\#}P < 0.05$ compared with placebo–MDMA). MDMA or placebo was administered at $t = 0$ hour. Values are expressed as mean ± S.E.M. in 16 subjects. $^{***}P < 0.001$ compared with placebo–placebo.

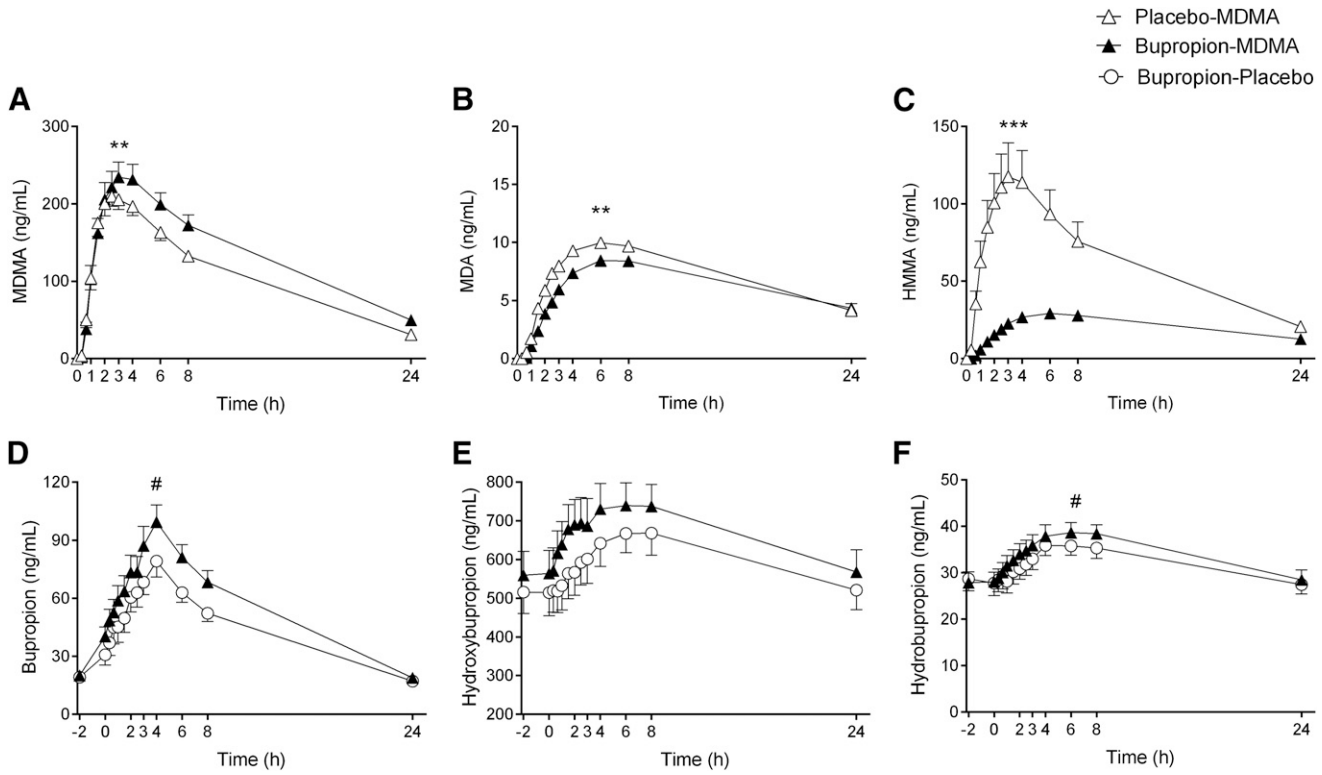

Fig. 3. Plasma concentration-time profiles. (A) Bupropion significantly increased the plasma concentration of MDMA (C_{max}, $AUC_{0–8}$, and $AUC_{0–24}$) and (B) significantly decreased the plasma concentrations of the MDMA metabolites MDA (C_{max} and AUC_{0-8}) and HMMA (C) (C_{max}, $AUC_{0–8}$, and $AUC_{0–24}$). (D) MDMA significantly increased the plasma concentrations of bupropion (C_{max}, $AUC_{0–8}$, and $AUC_{0–24}$) and hydrobupropion (F) (C_{max}) but had no significant effect on hydroxybupropion concentration (E). The pharmacokinetic parameters are shown in Table 2. MDMA or placebo was administered at $t = 0$ hour, and the last pretreatment administration of bupropion occurred at $t = -2$ hours. Values are expressed as mean ± S.E.M. in 16 subjects. $^{**}P < 0.01$ and $^{***}P < 0.001$ indicate significant differences between placebo–MDMA and bupropion–MDMA. $^{\#}P < 0.05$ indicates significant difference between bupropion-placebo and bupropion–MDMA.

Bupropion increased the C_{max} of MDMA by 15%, increased the $AUC_{0–24h}$ of MDMA by 30%, and decreased the C_{max} and $AUC_{0–24h}$ of the MDMA metabolite HMMA by 75% and 66%, respectively. Because MDMA is primarily metabolized to HMMA by CYP2D6 (Segura et al., 2005; de la Torre et al., 2012), the effects of bupropion on the pharmacokinetics of MDMA and HMMA are explained by CYP2D6 inhibition. Bupropion, and particularly erythro-hydrobuprion and threo-hydrobupropion have previously been shown to inhibit CYP2D6 (Jefferson et al., 2005; Kotlyar et al., 2005; Reese

TABLE 3
Pharmacokinetic parameters of MDMA and bupropion and metabolites
Values are mean ± S.E.M. in 16 healthy subjects.

	C_{max} (ng/ml)	$AUC_{0–8}$	$AUC_{0–24}$	$t_{1/2}$	T_{max}
		ng/ml·h			*h*
MDMA					
Placebo–MDMA	231 ± 14	1262 ± 72	2576 ± 156	7.4 ± 0.4	2.5 ± 0.2
Bupropion–MDMA	264 ± 13**	1535 ± 67***	3428 ± 144***	9.2 ± 0.7**	3.1 ± 0.2
MDA					
Placebo–MDMA	10.3 ± 0.5	59.2 ± 3.1	170 ± 11		6.1 ± 0.3
Bupropion–MDMA	8.8 ± 0.5**	46.8 ± 2.7***	149 ± 8.5		6.8 ± 0.3
HMMA					
Placebo–MDMA	123 ± 22	711.2 ± 99	1482 ± 247	8.5 ± 0.5	3.5 ± 0.3
Bupropion–MDMA	29.6 ± 3.3***	169 ± 18***	492 ± 54***	15.1 ± 1.1***	6.0 ± 0.3***
Bupropion					
Bupropion–placebo	93.2 ± 7.5	486 ± 36	1030 ± 69	10.3 ± 0.9	5.1 ± 0.5
Bupropion–MDMA	110 ± 8.3#	615 ± 40###	1313 ± 84##	8.7 ± 0.8	5.8 ± 0.4
Hydroxybupropion					
Hydroxybupropion–placebo	748 ± 63	4976 ± 337	14490 ± 1273		7.3 ± 0.6
Hydroxybupropion–MDMA	793 ± 62	5613 ± 486	16056 ± 1336		7.1 ± 0.6
Hydrobupropion					
Hydrobupropion–placebo	37.4 ± 2.1	267 ± 18	769 ± 51		7.0 ± 0.6
Hydrobupropion–MDMA	40.9 ± 2.0#	287 ± 17	822 ± 47		7.7 ± 0.5

$^{**}P < 0.01$; $^{***}P < 0.001$ compared with placebo–MDMA; $^{\#}P < 0.05$; $^{\#\#}P < 0.01$; $^{\#\#\#}P < 0.001$ compared with bupropion–placebo.

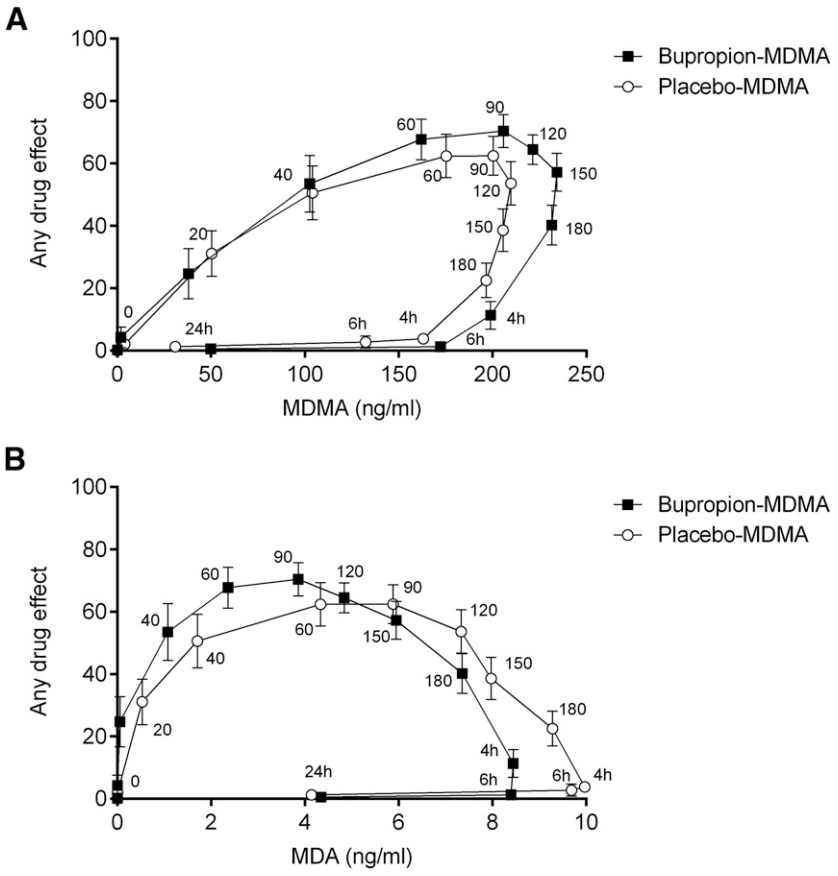

Fig. 4. Subjective effects of (A) MDMA and (B) MDA plotted against plasma concentrations of MDMA. The values are expressed as the means and S.E.M. values in 16 subjects. The time of sampling is noted next to each point in minutes or hours after MDMA administration. (A) Up to the peak response to MDMA, slightly higher subjective drug effects were reported after bupropion–MDMA compared with placebo–MDMA at a given MDMA concentration. Contrary to our hypothesis bupropion did not reduce the subjective response to MDMA. Note the rapid acute tolerance to the subjective effects of MDMA.

et al., 2008). Other CYP2D6 inhibitors, including paroxetine, reboxetine, and duloxetine (Farre et al., 2007; Hysek et al., 2011, 2012d), also increased the plasma levels of MDMA and lowered HMMA concentrations (Farre et al., 2007; Hysek et al., 2012d) to an extent similar to that of bupropion in the present study. Interestingly, bupropion also decreased plasma levels of MDA in the present study. Pure CYP2D6 inhibition would shift MDMA metabolism from HMMA formation to MDA formation, resulting in higher plasma MDA levels as previously reported after reboxetine or duloxetine pretreatment (Hysek et al., 2011, 2012d). Thus, in the present study, the minor metabolic pathway of MDMA to MDA by CYP2B6, CYP3A4, and CYP1A2 (Kreth et al., 2000) was also inhibited, possibly via competitive CYP2B6 inhibition by bupropion (Hesse et al., 2000).

MDMA also altered the pharmacokinetics of bupropion. Specifically, MDMA increased the C_{max} of bupropion by 18% and AUC_{0-24} by 27%, together with slight increases in hydrobupropion and hydroxybupropion. Hydrobupropion is formed by nonmicrosomal carbonyl reductase, and hydroxybupropion is formed by CYP2B6 (Hesse et al., 2000; Jefferson et al., 2005). How MDMA increased the plasma levels of bupropion and its metabolites is unclear. CYP2B6 inhibition by MDMA could explain the increase in plasma concentration of bupropion, but a decrease in hydroxybupropion would be expected. The effects of MDMA on the pharmacokinetics of bupropion could be clinically relevant because MDMA enhanced the exposure to bupropion and its metabolites, and all the metabolites of bupropion are also pharmacologically active (Damaj et al., 2004; Jefferson et al., 2005; Zhu et al., 2012).

The present study had a few limitations. First, only one dose regimen for bupropion and one single, relatively high dose of MDMA were used. Second, bupropion treatment produced DA transporter occupancy in the human striatum of only 26% (Learned-Coughlin et al., 2003). This occupancy may not have been sufficient to prevent MDMA from interacting with the DA transporter. It was important, however, to use a DA transporter inhibitor with no psychoactive effects, as shown for bupropion in the present study and previously (Peck and Hamilton, 1983; Oliveto et al., 2001) and in contrast to methylphenidate (Hysek et al., 2014; Schmid et al., 2014). Third, both MDMA and bupropion exhibit stereoselective metabolism (Kharasch et al., 2008; Steuer et al., 2014). The analytical method used in the present study was not stereoselective. The analytical methods are currently being developed to further address interactions between MDMA and bupropion enantiomers.

In conclusion, bupropion–MDMA coadministration resulted in prolonged positive mood effects but lower cardiostimulant effects than MDMA alone. Bupropion increased the plasma concentration of MDMA and vice versa. These findings indicate that NE contributes to the cardiovascular effects of MDMA, with no evidence that DA mediates the subjective effects of MDMA.

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Authorship Contributions

Participated in research design: Schmid, Rickli, Hysek, Liechti.

Conducted experiments: Schmid, Rickli, Schaffner, Duthaler, Grouzmann, Hysek.

Performed data analysis: Schmid, Rickli, Liechti.

Wrote or contributed to the writing of the manuscript: Schmid, Liechti.

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