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The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers

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MDMA (3,4-methylenedioxymethamphetamine) or 'Ecstasy' is a widely used recreational drug that produces a state of heightened mood but also cardiovascular and vegetative side-effects. In animals, MDMA releases serotonin and, to a lesser extent, dopamine and norepinephrine. The release of serotonin can be blocked by serotonin uptake inhibitors such as citalopram. It is unknown to what extent this mechanism is also responsible for the physiological side-effects of MDMA seen in humans. We investigated the effect of citalopram pretreatment (40 mg i.v.) on vegetative and cardiovascular effects of MDMA (1.5 mg/kg p.o.) in a double-blind placebo-controlled study in 16 healthy volunteers. MDMA moderately increased blood pressure and heart rate, slightly elevated body temperature and produced a broad range of acute and short-term side-effects. Citalopram reduced all these MDMA-induced physiological changes except for body temperature. These findings suggest that physiological effects of MDMA in humans are partially due to an interaction of MDMA with the serotonin carrier and a subsequent release of serotonin.

Key words: adverse effects; cardiovascular effects; citalopram; Ecstasy; MDMA, 3,4-methylenedioxymethamphetamine; selective serotonin reuptake inhibitors; serotonin

Introduction

MDMA (3,4-Methylenedioxymethamphetamine) which is the active compound contained in 'Ecstasy' tablets has unique psychoactive effects and is widely used as a recreational drug by young adults. In the UK, 4.5–6% of 14–15-year-olds (Saunders, 1995) and 13% of second-year university students have taken Ecstasy (Webb *et al.*, 1996). In Switzerland, up to 3.5% of 15–34-year-olds have taken at least one dose of Ecstasy (SFA/ISPA, 1996; Giroud *et al.*, 1997). A typical recreational dose of 1.7 mg/kg MDMA mainly induces feelings of well-being, heightened mood, moderate derealization and slight perceptual changes (Vollenweider *et al.*, 1998). However, at this dose, MDMA also produces acute physiological and prolonged vegetative side-effects. MDMA significantly increases blood pressure and has additional sympathomimetic properties that include tachycardia, palpitations, mydriasis, tremor, sweating and diaphoresis (Grob, 1998; Vollenweider *et al.*, 1998). Other commonly reported effects are bruxism (grinding of teeth), trismus (jaw clenching) and anorexia (Vollenweider *et al.*, 1998). Frequent sequelae are fatigue, difficulty in concentrating, irritability and depressed mood lasting 1–2 days after drug intake (Solowij *et al.*, 1992; Curran and Travill, 1997; Peroutka, 1987; Vollenweider *et al.*, 1998). The neurochemical mechanism underlying these physiological effects of MDMA has not yet been studied in humans. In contrast, the pharmacology of MDMA has been well characterized *in vitro* and in behavioural animal studies (Green *et al.*, 1996; White *et al.*, 1996; Steele *et al.*, 1994; Sprague *et al.*, 1998). MDMA mainly releases presynaptic serotonin (Nichols *et al.*, 1982; Schmidt, 1987) and selective serotonin reuptake inhibitors such as fluoxetine and citalopram were found to block the MDMA-induced serotonin release in animal studies (Schmidt, 1987; Hekmatpanah and Peroutka, 1990; Berger *et al.*, 1992; Gudelsky and Nash, 1996). These studies suggest that MDMA releases endogenous serotonin via an interaction with the serotonin uptake site. However, to a lesser extent, MDMA has also been shown to release dopamine and norepinephrine (Schmidt *et al.*, 1987; Yamamoto and Spanos, 1988; Fitzgerald and Reid, 1990). It is unknown to what extent these different neurotransmitters contribute to the effects of MDMA and whether carrier-mediated release of presynaptic serotonin is also responsible for the physiological effects of MDMA observed in humans. Thus, the present study was undertaken to determine whether pretreatment with the highly specific serotonin uptake inhibitor citalopram (40 mg i.v.) would attenuate cardiovascular, hyperthermic and vegetative effects of MDMA (1.5 mg/kg p.o.) in healthy human volunteers using a double-blind placebo-controlled within-subjects design. We hypothesized that citalopram would reduce MDMA-induced physiological changes to the extent that they depend on serotonin release.

Materials and methods

The study was approved by the Ethics Committee of the Psychiatric University Hospital, Zurich. The use of MDMA was authorized by the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics, Bern.

Substances

Racemic MDMA hydrochloride was obtained from the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics, Bern, and prepared as capsules (10 and 50 mg) at the Pharmacy of the Kantonsspital Lucerne. Subjects received MDMA at a dose of 1.5 mg/kg (mean ± SD = 100 ± 10 mg). Citalopram hydrochloride ampoules, 40 mg, were kindly provided by Lundbeck, Switzerland. Citalopram (40 mg) was dissolved in 500 ml sterile saline solution and given by perfusion over 90 min (330 ml/h). Dose and time parameters were chosen according to pharmacokinetic data (Baumann and Larsen, 1995) and a pilot study using 40–80 mg Citalopram infusions.

Subjects

Volunteers, 12 males and four females, aged 21–39 years (mean ± SD, 27.4 ± 4.4 years), were recruited at the University Hospital and at the Medical School of the University of Zurich. All subjects were either university students or physicians. All volunteers gave their written consent after being informed by a written and oral study description on the aim of the study, the psychological properties of MDMA, possible side-effects, previous toxicology study results and potential psychiatric risks. Subjects were healthy according to medical history, clinical examination, electrocardiography and blood analysis. Subjects were screened by psychiatric interview. Exclusion criteria were as follows: personal or family history of major psychiatric disorder in first-degree relatives, history of head injury and alcohol or regular substance abuse. Four candidates were excluded by these criteria. Of the 16 subjects included in the study, six had minor previous recreational drug experience. Two had tried Ecstasy, three had tried an hallucinogen and one had used both Ecstasy and an hallucinogen. Additional exclusion criteria were scores exceeding two SD from the mean values of normative data in the 'neuroticism' scale of the Freiburger Personality Inventory (FPI) (Fahrenberg *et al.*, 1984). No subject was excluded by this criterion.

Study design

A double-blind placebo-controlled within-subject design was used with four experimental conditions: placebo-placebo, citalopram-placebo, placebo-MDMA or citalopram-MDMA (counter-balanced). Sessions were separated by 3–4 weeks to minimize the influence of any carry-over effects. The female subjects were tested only in the perimenstrual phase to reduce influences of the menstrual cycle. Upon arriving at the Psychiatric University Hospital (0900 h or 1400 h) 40 mg citalopram in 500 ml saline solution or placebo (saline solution alone) was infused over 90 min (330 ml/h). After removal of the intravenous catheter, MDMA (1.5 mg/kg) or placebo capsules were given orally. Based on a previous study, this dose of MDMA was expected to produce robust psychological and physiological effects (Vollenweider *et al.*, 1998). Blood pressure, heart rate and body temperature were measured at 0 min, 60 min and at 120 min after MDMA or placebo intake. Blood pressure and heart rate were registered by an automatic ERKA.OS 90–2 device after a resting time of 5 min with the volunteer in sitting position. Body temperature was measured with an axillary Terumo clinical thermometer C 202. Side-effects were assessed by the List of Complaints (LC) (Zerssen, 1976). This scale consists of 66 items, yielding a global score measuring physical and general discomfort. Acute effects were assessed during the session, short-term sequelae the next day (24 h) and again 3 days after the test session (72 h), and prolonged sequelae were assessed 2 weeks later using the LC scale. Psychological effects were also measured and results are shown elsewhere (Liechti *et al*., 2000a). A physician was present during the whole session. After the acute effects of MDMA had subsided, subjects remained in the hospital for another 2 h and were monitored clinically. After discharge subjects could contact the researchers at any time in case of adverse drug effects or psychological problems. At the end of the study, all subjects attended a debriefing interview including a retrospective comparative evaluation of their subjective experience of all four study sessions.

Statistical analysis

All data were analysed with STATISTICA/w (StatSoft). Time order effects were excluded for every dependent variable. Two-way repeated measures ANOVAs with drug (placebo versus MDMA) and time (at drug intake, 60 min and 120 min later) as within-subject factors were used to assess changes in blood pressure, heart rate and body temperature. When a significant drug-by-time interaction was present, Tukey's post-hoc tests were performed to assess MDMA-induced changes compared to predrug level (0 min) and to placebo at 60 and 120 min. To assess a specific inhibiting effect of citalopram pretreatment on the MDMA-induced changes of blood pressure, heart rate and body temperature, we used two-way ANOVA at 60 min and at 120 min with pretreatment (placebo versus citalopram) and treatment (placebo versus MDMA) as within-subject factors and the pretreatment-by-treatment interaction. Differences of the global LC-scores of side-effects were compared at each time point (acute, 24 h, 72 h and 2 weeks post drug) by one-way ANOVA with the four drug conditions as within-subject factors and by Tukey's post-hoc tests. The criterion for significance was set at $p < 0.05$.

Results

As previously reported in detail (Vollenweider *et al.*, 1998; Liechti *et al*., 2000a), MDMA (1.5 mg/kg) predominantly produced a state of well-being, heightened mood, increased extroversion and moderate derealization without marked psychomotor stimulation. The subjective effect of MDMA began about 45 min after drug intake and lasted for 3–5 h.

Cardiovascular effects and body temperature

As seen in Table 1, MDMA significantly increased blood pressure. Two-way ANOVA and Tukey's post-hoc testing revealed that diastolic blood pressure was significantly elevated, both at 60 min ($p < 0.0002$) and at 120 min ($p < 0.0002$) compared to predrug values, and at 60 min ($p < 0.0004$) and at 120 min ($p < 0.0002$) compared to placebo [drug-by-time interaction $F(2,30) = 15.25$, $p < 0.0001$]. Systolic blood pressure was increased, both at 60 min ($p < 0.0002$) and at 120 min ($p < 0.0002$) compared to predrug values, and at 60 min ($p < 0.0002$) and at 120 min ($p < 0.0002$)

Table 1 Mean ± SD of blood pressure, heart rate and body temperature under MDMA, citalopram and citalopram plus MDMA (n = 16)

	Diastolic blood pressure (mmHg)			Systolic blood pressure (mmHg)		
	0 min	60 min	120 min	0 min	60 min	120 min
Placebo	69 ± 8	73 ± 9	70 ± 9	118 ± 10	115 ± 9	115 ± 7
Citalopram	72 ± 7	72 ± 8	74 ± 9	119 ± 10	120 ± 9	118 ± 9
MDMA	68 ± 6	85 ± 11***†††	87 ± 8***†††	115 ± 9	142 ± 18***†††	138 ± 15***†††
Citalopram–MDMA	69 ± 7	84 ± 9	82 ± 10#	114 ± 8	136 ± 17##	129 ± 14##
	Heart rates (Beats/min)			Body temperature (°C, axillary)		
	0 min	60 min	120 min	0 min	60 min	120 min
Placebo	60 ± 10	60 ± 11	61 ± 11	36.6 ± 0.27	36.6 ± 0.33	36.6 ± 0.37
Citalopram	64 ± 13	59 ± 9	58 ± 11	36.4 ± 0.34	36.5 ± 0.25	36.5 ± 0.25
MDMA	63 ± 13	73 ± 15**†††	73 ± 15**†††	36.5 ± 0.37	36.7 ± 0.41**	36.8 ± 0.46***†
Citalopram–MDMA	61 ± 12	64 ± 12#	66 ± 10	36.5 ± 0.38	36.6 ± 0.27	36.7 ± 0.3

* p<0.05, ** p<0.01, *** p<0.001, significant difference compared to predrug level (0 min) (Tukey's post-hoc test).
† p<0.05, †† p<0.01, ††† p<0.001, significant difference compared to placebo level (Tukey's post-hoc test).
# p<0.05, ## p<0.01, ### p<0.001, significant reduction of MDMA-induced change by citalopram (pretreatment-by-treatment interaction).

compared to placebo [drug-by-time interaction $F(2,30) = 19.87$, $p < 0.0001$]. Citalopram pretreatment reduced the MDMA-induced rise in systolic blood pressure at 60 min [$F(1,15) = 8.24$, $p < 0.01$] and at 120 min [$F(1,15) = 6.09$, $p < 0.03$] as confirmed by a significant pretreatment-by-treatment interaction. In addition, diastolic pressure was significantly reduced at 120 min [$F(1,15) = 6.09$, $p < 0.03$], but not at 60 min.

As shown in Table 1, MDMA increased heart rate both, at 60 min ($p < 0.009$) and at 120 min ($p < 0.002$) compared to predrug values, and at 60 min ($p < 0.0005$) and at 120 min ($p < 0.0006$) compared to placebo [drug-by-time interaction $F(2,28) = 4.66$, $p < 0.018$]. This increase was reduced by citalopram pretreatment at 60 min [pretreatment-by-treatment interaction $F(1,15) = 5.00$, $p < 0.04$], but not at 120 min.

As shown in Table 1, MDMA administration slightly increased body temperature at 60 min ($p < 0.008$) and at 120 min ($p < 0.001$) compared to predrug values, and compared to placebo ($p < 0.04$) at 120 min, but not at 60 min [drug-by-time interaction $F(2,30) = 5.26$, $p < 0.011$]. Citalopram pretreatment did not reduce the slight increase in body temperature induced by MDMA.

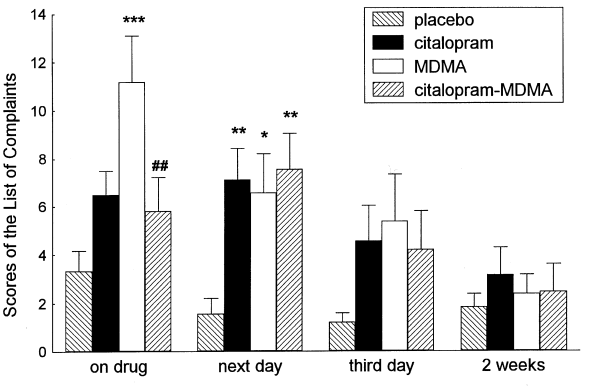

Figure 1 Mean (+ SE) global scores of side-effects assessed by the List of Complaints (n = 16). Side-effects were assessed during the experimental session on drug, the next day, the third day and 2 weeks later. Significant increases of side-effects under MDMA and citalopram compared to placebo are indicated by *p < 0.05, **p < 0.01, ***p < 0.001. Citalopram significantly reduced MDMA-induced acute side-effects as indicated by #p < 0.01

Acute side-effects

Global scores of the List of Complaints are shown in Fig. 1. One-way ANOVA for side-effects of the four treatment conditions [$F(3,45) = 8.64$, $p < 0.0001$] and post-hoc testing revealed that MDMA significant increased scores for complaints compared to placebo ($p < 0.0002$), while citalopram alone had no significant effect. Pretreatment with citalopram significantly reduced side-effects of MDMA ($p < 0.008$) (Fig. 1). As shown in Table 2, the most frequently observed acute side-effects of MDMA were difficulty concentrating (10/16), dizziness or vertigo (8/16) with impaired balance and gait control (8/16), signs of psychomotor activation and agitation such as feelings of restlessness (7/16), restless legs (7/16), and inner tension (3/16). A lack of appetite (8/16), thirst (6/16) and jaw clenching (7/16) were reported by approximately half the subjects. During the citalopram infusion, subjects became increasingly tired (11/16) and nausea (6/16) without vomiting occurred as well as headaches (5/16). Although citalopram reduced most of the acute side-effects of MDMA, it increased inner tension (8/16) (Table 2).

Subacute effects after 24 h and 72h

The subacute effects of MDMA and citalopram are summarized in Fig. 1 and Table 3. A few acute effects of MDMA, such as a lack of appetite (6/16) and a difficulty concentrating (4/16), were still present the next day or up to 3 days later. Newly occurring the next day were headaches (7/16), fatigue (6/16), exhaustibility (5/16), weakness (3/16) and a lack of energy (3/16), which lasted up to 3 days in a few subjects. Signs of depressed mood, including irritability (4/16), brooding (4/16) and gloomy thoughts (3/16), were observed in approximately one-third of the subjects within 3 days after MDMA administration. However, citalopram alone also produced comparable adverse effects lasting up to 3 days. One day after drug intake, we found no difference in global scores for complaints among the three conditions citalopram, MDMA or citalopram-MDMA. However, all three treatments produced significantly more short-term effects compared to placebo [one-way ANOVA $F(3,45) = 6.14$, $p < 0.001$; post-hoc tests all $p < 0.02$]. Finally, after 3 days, and also after 2 weeks, there was no

Table 2 Acute side-effects of citalopram, MDMA and citalopram plus MDMA (n = 16)

	Placebo	Citalopram	MDMA	Citalopram – MDMA
Difficulty concentrating	2	5	10	7
Impaired balance/gait	0	3	8	5
Lack of appetite	2	4	8	6
Dizziness or vertigo	0	5	8	4
Palpitations	1	2	7	4
Feelings of restlessness	1	2	7	5
Jaw clenching (bruxism)	0	0	7	3
Being cold	1	1	6	1
Thirst	0	1	6	3
Hot flashes	1	0	5	1
Paresthesias	0	0	5	1
Fatigue	9	11	3	0
Nausea	1	6	3	3
Tremor	0	1	3	0
Inner tension	1	2	3	8
Fear	1	0	2	0
Headache	3	5	1	3

Table 3 Subacute effects of citalopram, MDMA and citalopram plus MDMA (n = 16)

	Placebo		Citalopram		MDMA		Citalopram – MDMA	
	24 h	72 h	24 h	72 h	24 h	72 h	24 h	72 h
Headache	2	2	7	4	7	2	6	3
Fatigue	1	3	10	4	6	2	6	3
Lack of appetite	1	0	2	2	6	2	8	3
Difficulty concentrating	0	0	2	2	4	4	4	0
Brooding	1	0	2	2	3	4	4	3
Decreased libido	0	0	4	0	3	3	0	1
Bad dreams	0	0	0	1	3	2	2	0
Thirst	2	0	0	0	3	1	4	3
Forgetfulness	0	0	3	1	3	2	1	1
Inner tension	1	1	3	5	2	3	5	2
Gloomy thoughts	1	0	1	2	2	3	0	2
Insomnia	0	0	6	3	2	2	6	1
Increased need to sleep	0	1	2	0	2	3	4	1
Dizziness or vertigo	0	0	3	1	2	1	4	0
Jaw clenching (bruxism)	0	0	2	1	2	2	0	0
Palpitations	0	0	2	1	1	0	3	3
Private/job related worries	1	0	2	3	1	2	1	2
Tremor	0	0	4	1	1	0	3	1
Irritability	0	1	0	0	1	4	2	1
Nausea	0	0	6	2	0	1	3	2

statistical difference between the adverse effects of any of the treatments.

Debriefing interview

In the debriefing interview performed after completion of the study, all subjects retrospectively reported that the acute psychological and somatic effects of MDMA were reduced by citalopram pretreatment. Eight of 16 subjects could not distinguish citalopram from placebo. All but one subject distinguished MDMA from placebo. Overall, 14 of 16 subjects had a mostly positive experience. Two subjects reacted with moderate anxiety, one to MDMA, one to citalopram. Seven subjects reported that they would consider taking MDMA again in a controlled setting. None of the participants expressed increased interest in taking MDMA in a recreational setting.

Discussion

The main finding of the present study is that MDMA produced cardiovascular and vegetative side-effects that were mostly reduced by citalopram pretreatment.

MDMA alone produced sympathomimetic symptoms, including elevated blood pressure and heart rate, palpitations, feelings of restlessness, and tremor, as well as other side-effects such as disturbance of balance and gait, dizziness and difficulty concentrating. These effects were experienced without marked discomfort by most subjects. Moderate increases in blood pressure and heart rate were also found in a pilot-study (Downing, 1986) and in placebo-controlled studies in healthy volunteers using comparable doses of MDMA (Vollenweider *et al.*, 1998; Mas *et al.*, 1999) or its analogue MDE (Gouzoulis *et al.*, 1993; Gouzoulis-Mayfrank *et al.*, 1999). In contrast, no significant increase in blood pressure was observed with lower doses of MDMA (0.25–1.0 mg/kg) (Grob *et al.*, 1996). These data indicate that the cardiovascular effects of MDMA are dose-dependent. Similarly, as observed in Ecstasy users (Curran and Travill, 1997; Parrott and Lasky, 1998), MDMA produced prolonged side-effects lasting 1–3 days. Of particular interest are signs and symptoms of depression, that were found in approximately one-third of the present subjects. Thus, it appears that the symptoms of depression seen in our subjects, and in Ecstasy users in general, might be attributable to MDMA and reflect a transient depletion of serotonin (Schmidt *et al.*, 1986). Although, in the present study in healthy volunteers, after a single moderate dose of MDMA, sequelae largely abated within 3 days and completely disappeared after 2 weeks, it is important to note that lasting psychiatric complications have been reported in vulnerable persons after regular Ecstasy use (McCann and Ricaurte, 1991; McGuire *et al.*, 1994; Windhaber *et al.*, 1998). In accordance with our hypothesis, citalopram pretreatment significantly reduced the cardiovascular response and acute vegetative effects of MDMA. Furthermore, coadministration of MDMA and citalopram produced prolonged sequelae that were similar to and not greater than those produced by administration of either drug alone. Given this fact, no significant reduction by citalopram of prolonged MDMA sequelae could be demonstrated.

At the dose tested in the present study, MDMA produced a slight but significant increase in body temperature (0.3 °C). Similarly, a small increase in body temperature in humans has been reported with MDE (Gouzoulis-Mayfrank *et al.*, 1999), while similar, but non-significant increases (up to 0.5 °C) were observed with MDMA using smaller or comparable doses than were used in this study (Grob *et al.*, 1996; Grob, 1998; Vollenweider *et al.*, 1998). In rodents, MDMA produced hyperthermia in a dose-dependent manner (Schmidt *et al.*, 1990; O'Shea *et al.*, 1998) and hyperthermic reactions have been reported in Ecstasy users (Woods and Henry, 1992). Thus, higher doses of MDMA might be responsible for these hyperthermic reactions in humans. The rise in body temperature elicited by MDMA in the present study was not affected by citalopram at all. Similarly, in animal studies, selective serotonin uptake inhibitors such as MDL 27 777 or fluoxetine did not affect hyperthermia produced by high doses of MDMA (Schmidt *et al.*, 1990; Malberg *et al.*, 1996). Therefore, hyperthermia does not seem to be directly related to MDMA-induced serotonin release, but may reflect direct interaction of MDMA with postsynaptic receptors such as 5-HT_2 receptors (Schmidt *et al.*, 1990; Liechti *et al.*, 2000b).

To our knowledge, this is the first controlled study investigating the neuropharmacological interaction of MDMA with a selective serotonin uptake inhibitor in humans. The present results are consistent with anecdotal reports (McCann and Ricaurte, 1993) of four ecstasy users who took the serotonin uptake inhibitor fluoxetine (20 mg orally) prior to Ecstasy and found that typical side-effects of Ecstasy such as jaw clenching and dry mouth were attenuated by fluoxetine.

Citalopram competitively binds to the serotonin uptake site with high affinity (K_I = 0.7–1.8 nM) and exhibits low affinity for other receptors or transporters (Milne and Goa, 1991; Hyttel *et al.*, 1995). The overall attenuation of acute physiological effects of MDMA by citalopram in our study is in accordance with preclinical studies demonstrating that MDMA-induced serotonin release is blocked by different serotonin uptake inhibitors (Hekmatpanah and Peroutka, 1990; Gu and Azmitia, 1993; Gudelsky and Nash, 1996; Koch and Galloway, 1997). Moreover, pretreatment with fluoxetine inhibited MDMA-induced locomotor hyperactivity in rats (Callaway *et al.*, 1990). Based on these data, it is conceivable that, in the present study, citalopram either prevented the interaction of MDMA with the serotonin uptake site or, alternatively, blocked the efflux of serotonin through the carrier.

Citalopram did not completely block the physiological effects of MDMA. This might be due to an insufficient dose of citalopram. Studies using different and higher doses of citalopram could address this possibility. Moreover, some effects of MDMA may also be mediated by norepinephrine or dopamine (Liechti and Vollenweider, 2000). For example, norepinephrine uptake inhibitors attenuated MDMA-induced behavioural effects in rats, although not as effectively as serotonin uptake inhibitors (Callaway *et al.*, 1991; Geyer and Callaway, 1994).

In conclusion, the present double-blind placebo-controlled study demonstrated that pretreatment with the selective serotonin uptake inhibitor citalopram attenuated side-effects of MDMA in healthy volunteers. This finding confirms data from animal studies suggesting that the physiological properties of MDMA are partially due to an action at the presynaptic serotonin uptake site. However, the role of dopamine and norepinephrine in mediating the specific physiological effects of MDMA in humans remains to be elucidated in mechanistic studies.

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