

Acute psychological and physiological effects of MDMA (“Ecstasy”) after haloperidol pretreatment in healthy humans

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Abstract

3,4-Methylenedioxymethamphetamine (MDMA, “Ecstasy”) releases serotonin and dopamine. The role for dopamine in mediating the effects of MDMA has not yet been examined in humans. We investigated the effect of pretreatment with the dopamine D₂ antagonist haloperidol (1.4 mg i.v.) on psychological and physiological responses to MDMA (1.5 mg/kg p.o.) in 14 healthy volunteers using a double-blind placebo-controlled within-subject design. Subjective peak effects were rated using standardised scales. The physiological effects measured were blood pressure, heart rate and body temperature. Side effects were assessed during the session, and after 1 and 3 days. Haloperidol attenuated MDMA-induced positive and mania-like mood but had no reducing effect on other subjective changes or on cardiovascular effects. Results are consistent with a partial dopaminergic mediation of the euphoriant effects of MDMA. In contrast, dopamine does not seem to contribute to the physiological effects of MDMA, indicating a role for serotonin and norepinephrine.

Keywords: 3,4-Methylenedioxymethamphetamine; MDMA; Ecstasy; Dopamine; Haloperidol; Humans

1. Introduction

MDMA (3,4-methylenedioxymethamphetamine, “Ecstasy”) is an amphetamine derivative that produces feelings of well-being, euphoria, increased extroversion, moderate derealisation and slight perceptual changes as well as a moderate activation of psychomotor drive (Liemer et al., 1992; Vollenweider et al., 1998a). The physiological responses to acute MDMA administration include elevated blood pressure, increased heart rate, and other side effects such as palpitations, sweating, jaw clenching, anorexia and insomnia (Grob, 1998; Vollenweider et al., 1998a; Mas et al., 1999). Preclinical studies suggest that these psychophysiological effects of MDMA are due to release of serotonin and dopamine. MDMA increases serotonin release via interaction with the presynaptic serotonin transporter (Hekmatpanah and Peroutka, 1990; Gu and Azmitia, 1993; Rudnick and Wall, 1992; Geyer, 1994). We have recently shown that pretreatment with the selective

serotonin reuptake inhibitor citalopram significantly reduced most of the psychological and physiological effects of MDMA, indicating that this mechanism is also relevant in humans (Liechti et al., 2000; Liechti and Vollenweider, 2000). In animals, MDMA has also been shown to increase striatal dopamine (DA) levels (Schmidt et al., 1987; Yamamoto and Spanos, 1988). This increase is probably due to both a direct interaction of MDMA with the DA-carrier (Schmidt et al., 1987; Nash and Brodtkin, 1991; Koch and Galloway, 1997) and an amplification of DA release through activation of postsynaptic 5-HT₂ receptors by MDMA-induced serotonin 5-hydroxytryptamine, 5-HT release (Nash, 1990; Schmidt et al., 1994; Yamamoto et al., 1995; Gudelsky and Nash, 1996; Koch and Galloway, 1997). Dopamine has been implicated in the mediation of euphoria induced by classical stimulants such as d-amphetamine and cocaine (Lieberman et al., 1990; Laruelle et al., 1995; Volkow et al., 1997; Schlaepfer et al., 1997). Thus, increased dopaminergic activity may also contribute to MDMA-induced euphoria. The role of dopamine in mediating responses to MDMA in humans has not yet been studied. Therefore, the present study

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examined the effect of the dopamine D₂ antagonist haloperidol (1.4 mg i.v.) on psychological and physiological responses to MDMA (1.5 mg/kg p.o.) in healthy human volunteers. We hypothesised that haloperidol would attenuate some of the stimulant-like effects of MDMA.

2. Experimental procedures

The study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich, and was conducted in accordance with the Declaration of Helsinki. The use of MDMA was authorised by the Swiss Federal Health Office Department of Pharmacology and Narcotics, Berne.

2.1. Subjects

Subjects were recruited at the University Hospital and at the Medical School of Zurich. All but one were university students or physicians. All subjects were carefully screened by a semistructured psychiatric interview and were healthy according to history, physical examination, electrocardiogram, and blood analysis. Exclusion criteria were as follows: personal or family history of major psychiatric disorder in first-degree relatives, somatic illness and regular alcohol or illicit drug abuse. Additional exclusion criteria were scores exceeding two standard deviations from the mean of normative data in the “neuroticism” scale of the Freiburger Personality Inventory (FPI) (Fahrenberg et al., 1984). Fourteen volunteers (nine male, five female) were finally included in the study. The mean age was 26 years (range, 21–38). All except one subject were MDMA-naïve. Seven had smoked cannabis a few times and three had once tried an hallucinogen. Two subjects were light current smokers, all others were nonsmokers. All volunteers were informed by a written and oral study description on the aim of the study, possible side effects, previous toxicology study results, and potential psychiatric risks. All participants gave their written consent.

2.2. Substances and dosing

Haloperidol, Janssen (1.4 mg) was dissolved in 5 ml of saline and injected intravenously. The intravenous dose of haloperidol used here is equivalent to an oral dose of about 2.5 mg (Froemming et al., 1989). This dose was chosen based on pilot studies and was expected to occupy about 60% of dopamine D₂ receptors (Nordström et al., 1992) while having only minor subjective effects. Racemic MDMA hydrochloride was obtained through the Swiss Federal Health Office Department of Pharmacology and Narcotics, Berne, and were prepared as gelatine capsules of 10 and 50 mg. Subjects received MDMA at a single dose of 1.5 mg/kg (mean, 100 mg; range, 70–110 mg). This dose was expected to produce robust psychological

effects (Vollenweider et al., 1998a) and was carefully evaluated to minimise possible risks. While there is valid concern about possible neurotoxic effects of high and repeated doses of MDMA in Ecstasy users, it is very unlikely that administering a moderate dose of MDMA only one or two times within an experimental context will produce lasting serotonergic dysfunction (Lieberman and Aghajanian, 1999; Vollenweider et al., 1999).

2.3. Study design

This study utilised a double-blind, placebo-controlled counterbalanced within-subjects design with four experimental conditions: placebo–placebo, haloperidol–placebo, placebo–MDMA or haloperidol–MDMA. Each of the four test sessions was separated by at least 10 days from the preceding one to minimise the influence of carry-over effects. Sessions were conducted in a calm and comfortable laboratory environment. Participants were told not to eat 2 h prior to each session. At the beginning of each session, volunteers received an i.v. injection of either haloperidol (1.4 mg) in saline or saline alone (placebo). After 10 min, MDMA (1.5 mg/kg) or placebo (lactose) capsules were given orally. Psychometric ratings were performed shortly after drug onset and during the peak effect, i.e., 75 and 120 min after MDMA or placebo intake, respectively. Blood pressure, heart rate and peripheral body temperature were measured at 0, 75 and 120 min after MDMA or placebo intake. Blood pressure and heart rate were registered by an automatic ERKA OS 90-2 device, with the volunteer in a 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 drug effects were assessed during the session, short-term sequelae the next day (24 h) and again 3 days after the test session (72 h). In addition, sensorimotor gating of the acoustic startle reflex was measured during the peak effect of MDMA and these results will be reported separately. 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.

2.4. Psychometric ratings

The State–Trait Anxiety Inventory (STAI) (Spielberger et al., 1970), the EWL mood rating scale (EWL) (Janke and Debus, 1978) and the Altered State of Consciousness (OAV-ASC) rating scale (Dittrich et al., 1985; Dittrich, 1998), were used to assess psychological drug effects of the four treatment regimens. The OAV-ASC and the EWL scale had previously been shown to be sensitive to psychological effects of MDMA in humans (Vollenweider et al., 1998a). The STAI yields a score for state and trait

anxiety levels. The trait scale was administered prior to entering the study. The state scale was used during each session at 75 and 120 min after MDMA or placebo administration. From the EWL questionnaire, the following five scales were used: “efficiency–activation”, “inactivation”, “extro-/introversion”, “well-being” and “emotional excitability”. The EWL was administered at 120 min after drug intake. The OAV-ASC rating scale is a visual-analog scale measuring altered states of consciousness (ASC). It yields three scales comprising several item clusters. The first scale, OB (“oceanic boundlessness”), measures derealisation and depersonalisation with positive mood ranging from heightened feelings to exaltation and alterations in the sense of time. The corresponding item clusters are “derealisation”, “depersonalisation”, “alterations in the sense of time”, “positive basic mood” and “mania-like experience”. The second scale, AED (“anxious ego dissolution”), measures ego-disintegration and loss of autonomy and self-control associated with arousal and anxiety. The item clusters are “thought disorder”, “loss of thought control”, “loss of body control”, “anxious derealisation” and “delusion”. The third scale, VR (“visionary restructuralization”), includes the item clusters “illusions”, “visual (pseudo)-hallucinations”, “synesthesia”, “changed meaning of percepts”, “facilitated recollection” and “facilitated imagination”. OAV-ASC ratings were performed at the end of each session.

2.5. Data analysis

Data were analysed using Statistica 5.5 for Windows (StatSoft, Tulsa, OK, USA). Scores of OAV-APZ and EWL ratings were analysed separately for each scale using two-way repeated measures ANOVA with haloperidol (placebo vs. haloperidol) and MDMA (placebo vs. MDMA) as factors. State anxiety scores of the STAI were analysed using three-way repeated-measures ANOVA with haloperidol, MDMA and time (75 and 120 min after drug intake) as factors. Drug effects on blood pressure, heart rate and body temperature were analysed using three-way repeated measures ANOVAs with haloperidol, MDMA and time (0, 75 and 120 min after drug intake) as factors. Differences of the global LC-scores of side effects were compared at each time point (on day of drug intake, next day, third day) using two-way repeated measures ANOVA with haloperidol and MDMA as factors. Tukey’s post hoc tests or simple effect tests were performed based on significant main effects or interactions. P -values <0.05 were considered to be statistically significant.

3. Results

3.1. Psychological effects

MDMA (1.5 mg/kg) predominately produced an affective

state of well-being associated with increased extroversion and sociability. MDMA also induced moderate depersonalisation and derealisation, an altered perception of time, slight changes in sensory perception and moderate psychomotor activation. Subjective effects began about 60 min after drug intake and lasted for 3.5 to 4 h.

3.2. OAV-ASC rating

Fig. 1 shows scores of the Altered State of Consciousness scale (OAV-ASC). MDMA significantly increased the three OAV-ASC scores OB, AED and VR [OB: $F(1,13)=25.96$; $P<0.001$; AED: $F(1,13)=14.41$; $P<0.002$; VR: $F(1,13)=16.73$; $P<0.001$]. The increase in OB scores was due to increases in the item clusters “positive mood” ($P<0.001$), “mania-like experience” ($P<0.001$), “derealisation” ($P<0.001$) and “alterations in the sense of time” ($P<0.01$). The increase in AED scores was mainly due to moderately elevated “thought disorder” ($P<0.0002$) and slight non-significant increases in “loss of thought control” and “loss of body control”. The increase in VR scores was mainly attributable to “changes in the meaning of percepts” ($P<0.03$). Haloperidol pretreatment reduced the effect of MDMA on OB scores [two-way ANOVA, haloperidol $\times$ MDMA interaction: $F(1,13)=5.89$; $P<0.03$]. Post hoc analysis of the corresponding item clusters revealed that haloperidol significantly reduced scores for “positive mood” ($P<0.02$) and “mania like experience” ($P<0.01$). Haloperidol did not attenuate the effect of MDMA on AED and VR scores. In contrast, we found a marked increase in “anxious derealisation” (AED) ($P<0.001$) under haloperidol plus MDMA compared to

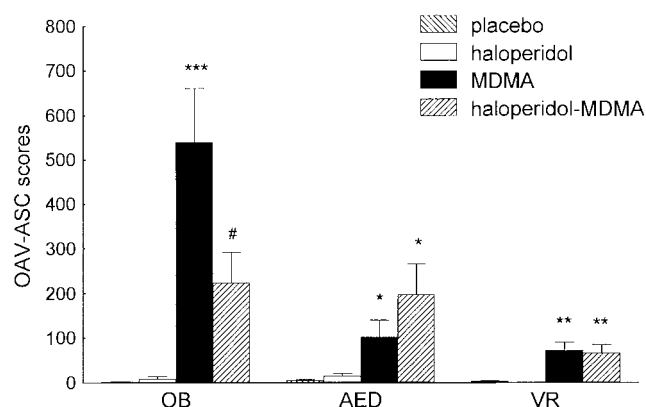


Fig. 1. Mean and S.E. scores of the Altered States of Consciousness Rating Scale (OAV-ASC), $n=14$. Levels of OB (oceanic boundlessness), AED (anxious ego-dissolution) and VR (visionary restructuralization) during the peak effects of placebo, haloperidol (1.4 mg i.v.), MDMA (1.5 mg/kg p.o.), and haloperidol plus MDMA. MDMA increased scores in all scales compared to placebo as indicated by * for $P<0.05$, ** for $P<0.01$ and *** for $P<0.001$ (Tukey’s post hoc tests). Haloperidol pretreatment reduced MDMA-induced positive mood (OB) compared to MDMA alone, as indicated by # for $P<0.05$ (two-way ANOVA, haloperidol $\times$ MDMA interaction). MDMA-induced levels of AED and VR remained significantly elevated after haloperidol pretreatment.

placebo, while haloperidol or MDMA alone had no effect on this scale.

3.3. STAI rating

The mean trait anxiety was 33 ± 5 (mean $\pm$ S.D.). There were no correlations between trait and state anxiety scores. Fig. 2 shows state anxiety scores. There was a significant haloperidol $\times$ MDMA $\times$ time interaction [$F(1,13)=6.43$; $P<0.02$] for state anxiety scores, which was further analysed using Tukey's post hoc tests: MDMA alone had no effect on anxiety at 75 min after drug intake, but significantly decreased state anxiety compared to placebo at 120 min ($P<0.03$), indicating an anxiolytic property of MDMA. Haloperidol alone increased state anxiety both at 75 min ($P<0.03$) and at 120 min ($P<0.02$). Interestingly, haloperidol together with MDMA increased state anxiety at 75 min ($P<0.001$ compared to placebo) to a level higher than after haloperidol alone ($P<0.004$). At 120 min, the level of state anxiety after haloperidol plus MDMA was significantly lower than after 75 min ($P<0.001$), reflecting the anxiolytic effect seen under MDMA alone.

3.4. EWL rating

Fig. 3 shows scores of the EWL mood rating. MDMA increased "well-being" [$F(1,13)=4.83$; $P<0.05$] and haloperidol reduced scores on this scale [$F(1,13)=19.22$; $P<0.001$]. Although there was no haloperidol $\times$ MDMA interaction, "well-being" scores after haloperidol and MDMA were significantly lower than after MDMA ($P<0.03$, post hoc, based on significant main effect). MDMA increased "emotional excitability" [$F(1,13)=8.78$; $P<0.01$], which was not reduced by haloperidol pretreatment. While "efficiency-activation" and "extro-/introversion"

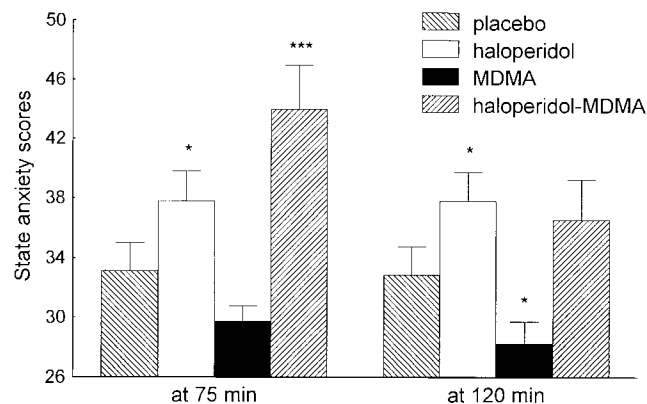


Fig. 2. Mean and S.E. scores for state anxiety of the State-Trait Anxiety Inventory (STAI), $n=14$. Differences compared to placebo are indicated by * for $P<0.05$, ** for $P<0.01$ and *** for $P<0.001$ (three-way ANOVA and Tukey's post hoc tests). Haloperidol alone slightly increased state anxiety, while MDMA alone slightly reduced scores compared to placebo. Haloperidol plus MDMA induced higher anxiety scores than haloperidol alone.

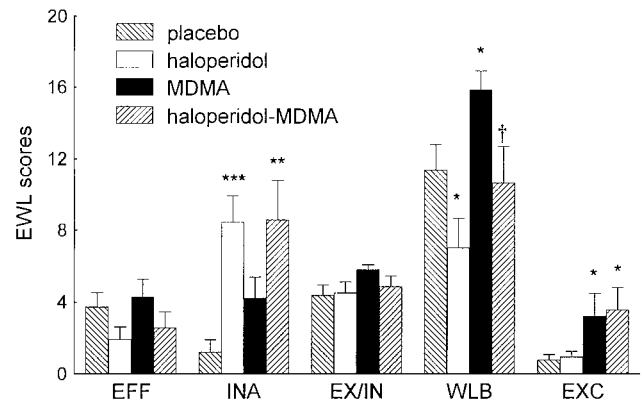


Fig. 3. Mean and S.E. scores of the adjective mood scale (EWL) rated 120 min after drug intake, $n=14$. EFF=efficiency-activation, INA=inactivation, EX/IN=extro-/introversion, WLB=well-being, EXC=emotional excitability. Differences compared to placebo are indicated by * for $P<0.05$, ** for $P<0.01$ and *** for $P<0.001$. Haloperidol significantly reduced MDMA-induced scores for "well-being" indicated by † for $P<0.05$ (Tukey's post hoc or simple effect tests).

were not significantly affected by any treatment, haloperidol increased "inactivation" [$F(1,13)=30.11$; $P<0.001$], both when given alone ($P<0.001$) or in combination with MDMA compared to placebo ($P<0.01$) or MDMA alone ($P<0.05$).

3.5. Debriefing interview

In the debriefing interview performed after completion of the study, subjects retrospectively reported that MDMA-induced positive feelings were markedly reduced by haloperidol pretreatment. Feelings of discomfort and anxiety were reported when haloperidol was given in combination with MDMA but not when MDMA or haloperidol were given alone. When both drugs were given, anxiety was mainly increased at the onset of drug effects and disappeared within 1 h, changing into a more pleasurable MDMA-like state. Eight of the fourteen subjects could not distinguish haloperidol from placebo. Overall, 13 of 14 subjects considered the study as a positive experience. One subject reacted with marked anxiety and tiredness to haloperidol. Seven subjects reported that they would consider taking MDMA again in a controlled setting. Except for the one subject previously experienced with MDMA, none of the participants expressed an interest in taking MDMA in a recreational setting.

3.6. Physiological effects

3.6.1. Blood pressure, heart rate and body temperature

Table 1 shows values for systolic and diastolic blood pressure, heart rate and body temperature. MDMA increased systolic and diastolic blood pressure [MDMA $\times$ time interaction: $F(2,26)=20.41$; $P<0.001$; $F(2,26)=21.32$; $P<0.001$, respectively]. Haloperidol pretreatment

Table 1

Mean±S.D. values of diastolic and systolic blood pressure, heart rate and body temperature under MDMA, haloperidol and haloperidol plus MDMA, $n=14$

	Diastolic blood pressure (mm Hg)			Systolic blood pressure (mm Hg)		
	0 min	75 min	120 min	0 min	75 min	120 min
Placebo	76±9	75±10	76±11	116±13	117±16	116±15
Haloperidol	72±10	72±9	74±15	115±15	115±13	117±17
MDMA	75±11	86±13***†††	84±11**†††	118±15	135±21***†††	141±20***†††
Haloperidol–MDMA	71±12	84±11***†††	86±11***†††	112±15	128±17***††	134±18***†††
	Heart rate (beats/min)			Body temperature (°C, axillary)		
	0 min	75 min	120 min	0 min	75 min	120 min
Placebo	66±10	64±11	63±8	36.7±0.3	36.7±0.4	36.6±0.4
Haloperidol	66±11	59±13	58±9	36.7±0.3	36.3±0.3	36.5±0.6
MDMA	64±13	74±21*†	73±20†	36.8±0.4	36.8±0.6	36.9±0.4
Haloperidol–MDMA	64±12	65±17	63±19	36.4±0.4	36.3±0.3	36.4±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.

had no effect on the MDMA-induced increases in systolic and diastolic blood pressure as confirmed by the lack of significant haloperidol×MDMA×(time) interactions. MDMA increased heart rate [$F(2,26)=5.3$; $P<0.01$].

Haloperidol decreased heart rate [$F(2,26)=5.07$; $P<0.01$], but there was no haloperidol×MDMA interaction. Body temperature was not significantly affected by any treatment.

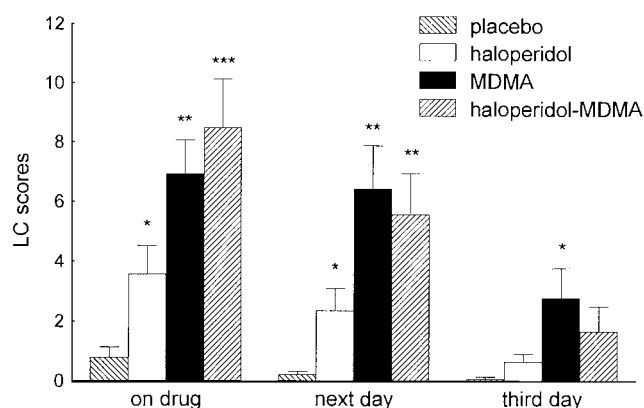


Fig. 4. Mean and S.E. global scores of the List of Complaints (LC), $n=14$. Two-way ANOVAs for each time point and Tukey's post hoc tests * for $P<0.05$, ** for $P<0.01$ and *** for $P<0.001$. MDMA significantly increased scores for both acute and subacute side effects. Haloperidol failed to reduce MDMA-induced effects.

3.7. Side effects

Fig. 4 shows global scores of the List of Complaints (LC) at different time points. Acute side effects are listed in Table 2. Both MDMA and haloperidol produced significant acute side effects [$F(1,13)=18.45$; $P<0.0009$ and $F(1,13)=6.87$; $P<0.02$, respectively]. When both drugs were given together, the highest scores were reached. However, haloperidol reduced some typical acute side effects of MDMA, such as jaw clenching, thirst/dry mouth, and lack of appetite, as seen in Table 2. MDMA also produced significant subacute side effects 1 and 3 days after drug intake [$F(1,13)=14.10$; $P<0.002$ and $F(1,13)=4.99$; $P<0.04$, respectively]. The main complaints the day after MDMA intake were: fatigue (7/14), lack of appetite (7/14), thirst/dry mouth (5/14), insomnia (5/14), difficult concentrating (4/14), weakness (4/14) and headache (4/14). The main complaints 3 days after

Table 2

Selected acute side-effects of MDMA, haloperidol and haloperidol plus MDMA ($n=14$)

	Placebo	Haloperidol	MDMA	Haloperidol–MDMA
Jaw clenching (bruxism)	0	0	10	7
Thirst/dry mouth	1	0	8	3
Lack of appetite	0	0	7	4
Difficult concentrating	1	3	7	12
Impaired balance and gait	0	1	6	6
Fatigue	2	11	4	7
Restlessness	0	3	4	8
Palpitations	0	0	3	3
Vertigo	0	1	3	5
Tremor	0	0	2	4
Inner tension	0	1	2	7

MDMA intake were: fatigue (4/14), lack of appetite (4/14) and lack of energy (3/14). Haloperidol pretreatment had no significant effect on these sequelae of MDMA at any time point compared to MDMA alone.

4. Discussion

The main finding of the present study is that haloperidol pretreatment changed the pattern of subjective MDMA effects from a pleasurable state of well-being and euphoria to a more dysphoric state with slightly increased anxiety, while having no effect on the cardiovascular response to MDMA.

We are not aware of any previous description of the pharmacodynamic interaction of MDMA with haloperidol or any mechanistic investigation into the role of dopamine in mediating MDMA effects in humans. However, the present results can be compared to those from studies that tested the effects of dopamine antagonists including haloperidol on subjective responses to classical stimulants such as d-amphetamine and cocaine in human volunteers. In line with our results, Nurnberger and colleagues found that haloperidol (0.014 mg/kg i.m.) attenuated excitation and elation in response to d-amphetamine in normal volunteers but did not affect pressor responses (Nurnberger et al., 1984). In cocaine users, pretreatment with a high dose of haloperidol (8 mg i.m.) reduced subject ratings of “high” and “pleasant sensations” but had no effect on the drug “rush” induced by cocaine (40 mg i.v.) (Sherer et al., 1989). More recently, Brauer and de Wit conducted a series of studies aimed at examining the effect of different doses of the selective dopamine D₂ antagonist pimozide (1, 2, 4 and 8 mg p.o.) on subjective responses to d-amphetamine (10 and 20 mg p.o.) in healthy volunteers (Brauer and de Wit, 1995; Brauer and de Wit, 1996; Brauer and de Wit, 1997). Pimozide had little effect on d-amphetamine-induced elation, euphoria or vigour or any other ratings despite having a reducing effect on these ratings compared to placebo when given alone (Brauer and de Wit, 1997). Although all of these studies found that D₂ antagonists attenuated stimulant-induced euphoria to various degrees, the studies of Brauer and de Wit raise the question of whether or not this reduction might be due to non-specific dysphoric reactions to the blocking agent. This view is also relevant for the present study, since haloperidol given alone caused several symptoms of discomfort and reduced EWL ratings for well-being. The use of lower doses of haloperidol or of dopamine antagonists, producing less dysphoria, could address this question. However, there is the unexpected finding that haloperidol plus MDMA resulted in a potentiation of anxiety (STAI), anxious derealisation (OAV-ASC), inner tension and difficult concentrating (LC) and these findings are unlikely to be explained by simple additive drug effects. There is a striking similarity of these findings to a mechanistic human study using the same rating scales and

haloperidol (0.021 mg/kg i.v.) prior to the mixed 5-HT_{2/1} serotonin agonist psilocybin (0.25 mg/kg p.o.). As in the present study, haloperidol potentiated anxious derealisation in combination with psilocybin without having an effect by itself (Vollenweider et al., 1998b). It can be hypothesized that dysphoria and anxiety after haloperidol and serotonergic agonists such as MDMA or psilocybin might reflect increased serotonergic and/or D₁ dopaminergic activity with concomitantly reduced dopaminergic D₂ tone. There is further evidence supporting this hypothesis. First, in a manner similar to that in the present study, haloperidol also reduced psilocybin-induced euphoria (OB) and increased discomfort in humans (Vollenweider et al., 1998b). Second, a recent human PET study, using [¹¹C]raclopride to assess dopamine release in psilocybin subjects, demonstrated an increase in endogenous dopamine and a correlation between [¹¹C]raclopride binding potential in the ventral striatum and depersonalisation associated with euphoria (Vollenweider et al., 1998c). These results also support the view that positive mood and elation induced by MDMA may in part be mediated by dopamine.

In contrast to its effect on euphoria, haloperidol failed to antagonise the physiological effects of MDMA. Since citalopram significantly reduced the cardiovascular response to MDMA (Liechti and Vollenweider, 2000), the release of serotonin appears to be more relevant for the mediation of these physiological effects. In addition, the β -adrenergic and the serotonergic 5-HT₁ antagonist propranolol, but not haloperidol, reduced d-amphetamine-induced pressor responses (Nurnberger et al., 1984). These results indicate a role for serotonin and norepinephrine but not for dopamine in mediating MDMA-induced cardiovascular stimulation.

In conclusion, pretreatment with the dopaminergic D₂ antagonist haloperidol mainly reduced the MDMA-induced state of positive mood and euphoria. Although nonspecific dysphoric effects of haloperidol might account for these findings they are also consistent with a partially dopaminergic mediation of euphoric effects of MDMA. In contrast, dopamine does not seem to contribute to the physiological effects of MDMA, indicating a role for serotonin and norepinephrine.

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