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Psychological and Physiological Effects of MDMA ("Ecstasy") after Pretreatment with the 5-HT_2 Antagonist Ketanserin in Healthy Humans

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MDMA (3,4-methylenedioxymethamphetamine, "Ecstasy") mainly releases serotonin and dopamine. In animals, pretreatment with 5-HT_2 antagonists has been shown to attenuate neurochemical and behavioral effects of MDMA. In humans, the role of 5-HT_2 receptors in the action of MDMA has not been studied. We investigated the effect of pretreatment with the 5-$HT_{2A/C}$ antagonist ketanserin (50 mg p.o.) on subjective responses to MDMA (1.5 mg/kg p.o.) in 14 healthy volunteers using a double-blind placebo-controlled within-subject design. Subjective effects were rated by psychometric rating scales. Physiological effects measured were blood pressure, heart rate, and body temperature. Adverse effects were assessed during the sessions, and after one and three days. Ketanserin attenuated MDMA-induced perceptual changes, emotional excitation, and acute adverse responses but had little effect on MDMA-induced positive mood, well-being, extroversion, and short-term sequelae. Body temperature was lower under MDMA plus ketanserin compared to MDMA alone. The results suggest a contributing role for 5-HT_2 receptors in the action of MDMA in humans. ***[Neuropsychopharmacology 23:396–404, 2000]*** *© 2000 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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3,4-Methylenedioxymethamphetamine (MDMA) is the main component of Ecstasy tablets. In humans, MDMA produces enhanced mood with increased well-being and extroversion, moderate derealization and slight perceptual changes (Peroutka et al. 1998; Vollenweider et al. 1998a). The physiological response to MDMA includes elevated blood pressure and heart rate, a slight increase in psychomotor drive, and side effects such as jaw clenching, lack of appetite, and difficulty concentrating (Mas et al. 1999; Vollenweider et al. 1998a).

The roles of different neurotransmitters and receptors in mediating these effects of MDMA in humans are unclear. In animals, MDMA mainly releases serotonin via interaction with the serotonin (5-HT) transporter, and, to a lesser extent, also dopamine (Rudnick and Wall 1992; Yamamoto and Spanos 1988; Schmidt et al. 1987). We have recently used the 5-HT uptake inhibitor citalopram and the dopamine D_2 antagonist haloperidol as pretreatments to MDMA in healthy subjects. Citalopram largely reduced subjective (Liechti et al. 2000) as well as physiological effects of MDMA (Liechti and Vollenweider 2000a), while haloperidol pretreat-

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ment only reduced MDMA-induced positive mood and had no effect on cardiovascular stimulation or other physiological effects (Liechti and Vollenweider 2000b). These results support the hypothesis that the effects of MDMA in humans are largely dependent on 5-HT transporter-mediated enhancement of serotonergic neurotransmission. However, it is unclear which postsynaptic 5-HT receptors mediate the effects of the serotonin released by MDMA. Animal studies indicate that 5-HT_2 receptors might be involved, because 5-HT_2 antagonists reduced several effects of MDMA, such as MDMA-induced serotonergic neurotoxicity, acute hyperthermia and disruption of sensorimotor gating (Padich et al. 1996; Schmidt and Kehne 1990; Schmidt et al. 1990; Nash et al. 1988). 5-HT_{2A} receptors have been implicated in the psychological, particularly in the visual effects, of indole hallucinogens (Glennon 1990; Titeler et al. 1988; Sanders-Bush et al. 1988; Vollenweider et al. 1998b). Based on this evidence, we expected that also in humans some effects of MDMA would be reduced by pretreatment with a 5-HT_2 antagonist. In particular, we hypothesized that the slight hallucinogen-like effects of MDMA in humans may be due to 5-HT_{2A} receptor stimulation.

Therefore, the present study examined the effects of the 5-$HT_{2A/C}$ receptor antagonist ketanserin (50 mg p.o.) on psychological and physiological responses to MDMA (1.5 mg/kg p.o.) in healthy volunteers. We expected that ketanserin would attenuate some of the MDMA effects, particularly its moderate hallucinogen-like properties.

METHODS

Subjects

Subjects were recruited at the University Hospital and at the Medical School of Zurich. All subjects were screened by a semi-structured 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 substance abuse. Fourteen volunteers (13 men, 1 woman) were finally included in the study. Subjects had a mean age of 26 years (range 21–41) and were MDMA-naïve except for two who had once tried MDMA. Seven had smoked cannabis a few times and four had once tried a hallucinogen. All volunteers gave their written consent after being informed by written and oral descriptions of the aim of the study, the procedures involved, and the effects and possible risks of MDMA administration. Subjects were paid for their participation. The study was approved by the Ethics Committee of the Psychiatric University Hospital, Zurich, and the use of MDMA was authorized by the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Berne.

Study Design

This study utilized a double-blind, placebo-controlled counterbalanced within-subjects design with four experimental conditions: placebo–placebo, ketanserin–placebo, placebo–MDMA or ketanserin–MDMA. The four sessions were separated by at least 10 days to reduce carry-over effects. Test 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 took ketanserin (50 mg) or placebo capsules. After 75 min MDMA (1.5 mg/kg) or placebo was given orally. Psychometric ratings were performed before, shortly after drug onset and during the peak effect (i.e., 75 min before, and 75 min and 120 min after MDMA or placebo intake). Blood pressure, heart rate and peripheral body temperature were measured 75 min before and 0, 60, 90, 120, and 150 min after MDMA or placebo intake. 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 three days after the test session (72 h). In addition, sensorimotor gating of the acoustic startle reflex was measured (data not shown). 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.

Psychometric Ratings

The State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1970), the Adjective Mood rating scale (AM) (Janke and Debus 1978) and the Altered State of Consciousness (OAVAV) rating scale (Dittrich et al. 1985; Dittrich 1998) were used to assess psychological drug effects of the four treatment regimens. The OAVAV and the AM 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. The AM questionnaire consists of 14 scales comprised in 6 sum scales: (1) "efficiency-activation"; (2) "well-being" = "self-confidence" and "heightened mood"; (3) "anxiety" = "apprehension-anxiety," "depressiveness," and "thoughtfulness-contemplativeness"; (4) "extro- and introversion"; (5) "general inactivation" = "inactivation," "dazed state," "tiredness"; (6) "emotional excitability" = "sensitivity," "aggression-anger," and "emotional excitation."

The OAVAV rating scale is a visual-analogue scale that measures alterations in waking consciousness, including changes in mood, perception, experience of the self and of the environment, as well as thought disorder. The OAVAV questionnaire is similar to the well established OAV version but includes two additional scales AA and VIR measuring "auditory alterations" and "vigilance reduction." The five scales comprise several item clusters. (1) OB ("oceanic boundlessness") measures derealization and depersonalization associated with positive mood ranging from heightened feelings to exaltation and alterations in the sense of time. The corresponding item clusters are "derealization," "depersonalization," "alterations in the sense of time," "positive basic mood," and "mania-like experience." (2) 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," "fear of loss of thought control," "fear of loss of body control," "anxious derealization," and "delusion." (3) VR ("visionary restructuralization") includes the item clusters "elementary hallucinations," "visual (pseudo-) hallucinations," "synesthesia," "changed meaning of percepts," "facilitated recollection," and "facilitated imagination." (4) AA ("auditory alterations") mainly contains items describing auditory (pseudo-)hallucina-

Table 1. F-values for Significant and Near-significant Main Effects and Interactions of Ketanserin, MDMA and Time; $n = 14$

Psychometric Ratings	Ket	MDMA	Time	Ket × MDMA	Ket × Time	MDMA × Time	Ket × MDMA × Time
OAVAV[a]	F(1,13)	F(1,13)		F(1,13)			
OB	NS	19.58***		NS			
AED	NS	5.45*		NS			
VR	3.8†	11.98**		15.82**			
AA	NS	3.62†		NS			
VIR	NS	13.07**		4.72*			
STAI[b]	F(1,13)	F(1,13)	F(2,26)	F(1,13)	F(2,26)	F(2,26)	F(2,26)
Stait anxiety	NS	NS	NS	NS	NS	NS	2.89†
Adjective Mood scale[b]	F(1,13)	F(1,13)	F(2,26)	F(1,13)	F(2,26)	F(2,26)	F(2,26)
Efficiency-activation	NS	NS	NS	NS	NS	NS	NS
Self-confidence	NS	7.04*	3.96*	NS	NS	5.07*	NS
Heightened mood	NS	15.54**	2.97†	NS	NS	8.84***	NS
Apprehension-anxiety	NS	7.08*	5.03*	NS	NS	5.32**	NS
Depressivenes	NS	NS	NS	NS	NS	NS	NS
Thoughtfulness-contemplativeness	NS	14.62**	10.79***	3.91†	4.2*	5.63**	4.68*
Extroversion	6.99*	13.67*	5.67**	NS	3.27*	5.67**	NS
Introversion	NS	4.21†	NS	NS	NS	6.85**	NS
Inactivation	NS	NS	19.68***	3.76†	NS	3.7*	3.38*
Dazed state	NS	18.41***	36.14***	14.08**	NS	38.34***	5.61**
Tiredness	NS	NS	2.72†	7.43*	NS	NS	NS
Sensitivity	NS	17.78***	7.55**	NS	NS	7.72**	NS
Aggression-anger	NS	NS	NS	NS	NS	NS	NS
Emotional excitation	14.41**	22.86***	13.3***	NS	3.31*	10.49***	NS
Physiological measures[c]	F(1,13)	F(1,13)	F(5,65)	F(1,13)	F(5,65)	F(5,65)	F(5,65)
BP systolic	97.61***	3.02†	24.43***	NS	2.88*	36.81***	NS
BP diastolic	9.45**	25.03***	15***	NS	2.77*	11.05***	NS
Heart rate	24.85***	NS	3.56**	NS	NS	16.33***	NS
Body temperature	7.94*	15.08**	5.15***	NS	10.18**	9.68***	NS
List of Complaints[d]	F(1,13)	F(1,13)	F(2,26)	F(1,13)	F(2,26)	F(2,26)	F(2,26)
Global score of complaints, all time points	NS	26.64***	35.93***	NS	3.07†	11.12***	5.65**
Acute side effects	5.22*	61.15***		12.25**			
Sequelae after 24 hours	NS	7.8*		NS			
Sequelae after 72 hours	NS	4.43†		NS			

[a] Ratings 150 min after MDMA administration.
[b] Ratings 75 min before and 75 and 120 min after MDMA administration.
[c] Measurements 75 min before and 0, 60, 90, 120, and 150 min after MDMA administration.
[d] Ratings 150 min, 24 and 72 hours after MDMA administration.
† $p < .1$, * $p < .05$, ** $p < .01$, *** $p < .001$.

tions. (5) VIR ("vigilance reduction") describes a clouding of consciousness, tiredness and somnolence.

Drugs and Dosing

Ketanserin was kindly provided by Janssen-Cilag AG Switzerland and was prepared as gelatine capsules of 50 mg. A similar dose has previously been shown to robustly antagonize the psychological effects of the 5-$HT_{2/1}$ agonist psilocybin using a comparable design (Vollenweider et al. 1998b). Racemic MDMA was obtained through the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Bern, and prepared as gelatine capsules of 10 and 50 mg. Subjects received MDMA at a single dose of 1.5 mg/kg (mean 110 mg, range 80–120 mg). This dose has robust psychological and physiological effects and was carefully evaluated to minimize possible risks (Vollenweider et al. 1999; Lieberman and Aghajanian 1999).

Data Analysis

Data were analyzed using Statistica 5.5 for Windows (StatSoft, Tulsa, OK). After confirming normal distribution by Kolmogorov-Smirnov tests, data were subjected to a repeated measures analysis of variances (ANOVA) with MDMA (MDMA versus placebo), ketanserin (ketanserin versus placebo) and time as within-subject factors. Scores of the OAVAV and the LC ratings at each time point were analyzed using ANOVA with MDMA and ketanserin as within-subject factors. If there was no significant ketanserin × MDMA × time interaction, but significant interactions of both drugs and time, then additional post hoc repeated measure ANOVAs with drug (MDMA versus ketanserin-MDMA) and time were conducted. Tukey's post hoc tests were performed based on significant main effects or interactions. p-values $< .05$ were considered statistically significant.

RESULTS

F- and p-values for significant main effects and interactions are presented in Table 1. Subjective effects of MDMA (1.5 mg/kg) began about 60 min after drug intake and lasted for a mean duration of 3.5 h after MDMA and 3 h after MDMA plus ketanserin. MDMA produced robust effects on all measures, except for state-anxiety which was not significantly changed. Mean trait anxiety was 34 ± 7 (mean ± S.D.).

Figure 1 shows scores of the Altered State of Consciousness questionnaire (OAVAV). MDMA significantly increased scores in all five scales. The increase in OB scores was due to a marked increase in the item cluster "positive mood" ($p < .001$), moderate changes in "mania-like experience" ($p < .01$), "derealization" ($p < .001$), "depersonalization" ($p < .05$), and "alterations in the sense of time" ($p < .01$). The increase in AED scores was mainly due to moderately elevated "thought disorder" ($p < .001$) and "fear of loss of body control" ($p < .001$). The increase in VR scores was mainly attributable to "changes in the meaning of percepts" ($p < .001$), and non-significant increases in "elementary hallucinations" and "synesthesia." There were no complex hallucinations, however, subjects reported an increased vividness of perception including an intensification of colors and tactile awareness. MDMA also induced a significant, although slight, increase in auditory alterations. Auditory perception was qualitatively changed (e.g., sounds appeared closer or farther away), but no hallucinations were reported. Ketanserin pretreatment significantly reduced the effect of MDMA on VR scores. MDMA-induced OB scores were not significantly changed by ketanserin. Vigilance was reduced by MDMA and interestingly, this effect was less pronounced after ketanserin.

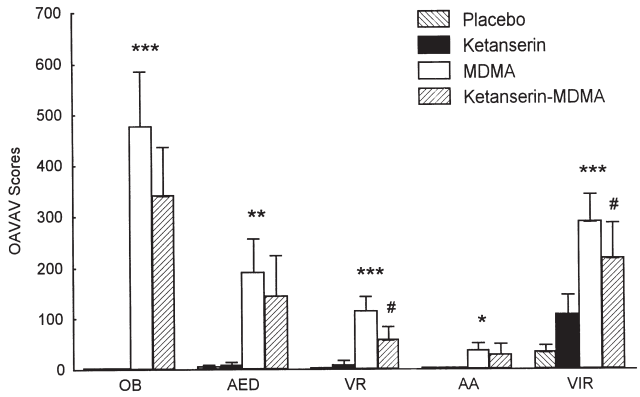

Figure 1. Mean and S.E. scores of the Altered States of Consciousness Rating Scale (OAVAV), $n = 14$. Levels of OB (oceanic boundlessness), AED (anxious ego-dissolution), VR (visionary restructuralization), AA (auditory alterations), and VIR (vigilance reduction) during the peak effects of placebo, ketanserin (50 mg p.o.), MDMA (1.5 mg/kg p.o.), and ketanserin plus MDMA. MDMA increased scores in all scales compared to placebo as indicated by * for $p < .05$, ** for $p < .01$, *** for $p < .001$ (Tukey's post hoc tests). Ketanserin pretreatment reduced MDMA-induced VR and VIR as indicated by # for $p < .05$ (two-way ANOVA, ketanserin × MDMA interaction).

Figure 2 shows peak scores of all scales of the AM mood rating. Ketanserin did not affect aspects of "well-being" ("self-confidence and heightened mood") increased by MDMA. Similarly, MDMA-induced extroversion was not significantly changed. In contrast, ketanserin attenuated MDMA-induced "emotional excitability" [ketanserin × MDMA interaction $F(1,13) = 3.90$; $p < .08$], which summarizes the three scales "emotional excitation," "sensitivity," and "aggression." There was no significant ketanserin × MDMA × time interaction but strong main effects of the drugs on "emotional excitation." An additional post hoc repeated measures

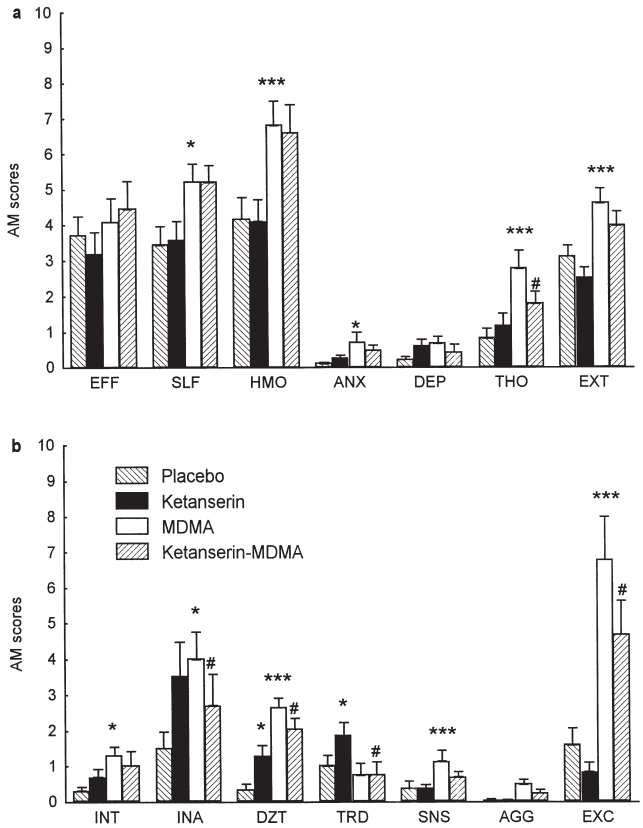

Figure 2. Mean and S.E. scores of the adjective mood rating scale (AM) during peak drug effects, $n = 14$. **A** EFF = efficiency-activation, SLF = self-confidence, HMO = heightened mood, ANX = apprehension-anxiety, DEP = depressiveness, THO = thoughtfulness-contemplativeness, EXT = extroversion. **B** INT = introversion, INA = inactivation, DZT = dazed state, TRD = tiredness, SNS = sensitivity, AGG = aggression-anger, EXC = emotional excitation. Differences compared to placebo are indicated by * for $p < .05$, ** for $p < .01$, *** for $p < .001$. # for $p < .05$ indicates significantly lower scores under MDMA plus ketanserin compared to MDMA or a significant ketanserin × MDMA interaction.

ANOVA with drug (MDMA and ketanserin-MDMA) and time as factors yielded a significant drug effect [$F(1,13) = 9.97$, $p < .008$] confirming that "emotional excitation" was significantly lower after ketanserin plus MDMA administration compared to MDMA alone. "General inactivation" ("inactivation," "dazed state," "tiredness") was also lower when ketanserin was given with MDMA compared to either drug alone [ketanserin × MDMA interaction $F(1,13) = 21.27$; $p < .02$]. Finally, also the dreamy state under MDMA described by the scale "thoughtfulness" was significantly reduced by ketanserin.

As shown in Table 1 and Figure 3, MDMA significantly increased blood pressure, heart rate and peripheral body temperature. Although, ketanserin alone markedly reduced these physiological measures, there were no ketanserin × MDMA interactions. Post hoc repeated measures ANOVAs with drug (MDMA and MDMA-ketanserin) and time as factors revealed that diastolic blood pressure and body temperature were significantly lower after MDMA plus ketanserin compared to MDMA alone [drug main effect, respectively $F(1,13) = 9.45$, $p < .05$; $F(1,3) = 6.48$, $p < .05$]. As seen in Figure 3, levels of peripheral body temperature were lowered to levels of placebo when MDMA and ketanserin were given together.

Acute side effects and short-term sequelae are listed in Table 2. Ketanserin significantly reduced the total of acute adverse responses to MDMA, but not short-term sequelae, as assessed after 24 and 72 h. Ketanserin alone produced very little adverse effects.

A debriefing interview after completion of the study revealed that only 5 of 14 subjects could distinguish ketanserin from placebo. Nine of 14 subjects retrospectively reported that their MDMA experience was clearly less intense after ketanserin pretreatment. Five participants subjectively felt little difference between MDMA and MDMA plus ketanserin and were therefore not sure when they had received which treatment.

DISCUSSION

The principal finding of the present study was that pretreatment with the 5-$HT_{2A/C}$ antagonist ketanserin significantly reduced MDMA-induced perceptual changes, emotional excitation, and acute adverse effects, while having little effect on positive basic mood and well-being.

Perceptual changes elicited by MDMA were moderate and mainly included a changed experience of the environment ("changed meaning of percepts"), an intensification of visual, tactile and acoustic perception, but no hallucinations. Ketanserin pretreatment robustly reduced these MDMA-induced perceptual changes (VR scores) by 50%. This finding is consistent with several lines of evidence that indole hallucinogens exert their effects via agonist action at 5-HT_{2A} receptors (Glennon 1990; Titeler et al. 1988; Sanders-Bush et al. 1988; Vollenweider et al. 1998b). For example, it has been shown that the binding affinity for a drug for the 5-HT_{2A} receptor site predicts its potency for evoking hallucinations in humans (Glennon et al. 1984). In humans, a smaller dose of ketanserin (40 mg) has previously also been shown to block most subjective effects of the hallucinogen and mixed 5-$HT_{2/1}$ agonist psilocybin in a comparable experimental design (Vollenweider et al. 1998b). Ketanserin is about 1000-fold more selective for the 5-HT_{2A} compared to the 5-HT_1 receptors, and about 100-fold more selective for the 5-HT_{2A} relative to the 5-HT_{2C} receptor (Leysen et al. 1981). Ketanserin has also

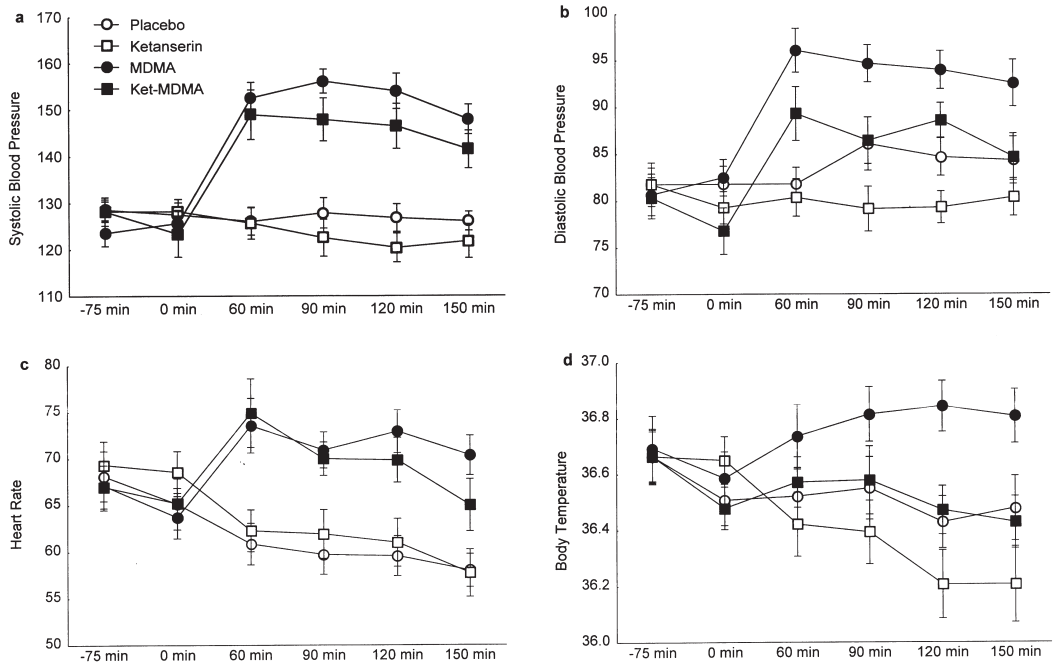

Figure 3. Mean and S.E. values of measures for **(a)** systolic and **(b)** diastolic blood pressure, **(c)** heart rate and (**d)** peripheral body temperature, $n = 14$. Both diastolic blood pressure and body temperature were significantly lower after ketanserin plus MDMA compared to MDMA alone, $p < .05$ (ANOVAs). Ketanserin alone also lowered values compared to placebo.

moderate affinity for H_1 histaminergic and α_1-adrenergic receptors. MDMA is predominately a serotonin releaser and has relatively weak affinity for the α_1-adrenergic receptor (K_i = 18.4 μM) compared to its affinity for the serotonin uptake site (K_i = 0.61 μM) or the 5-HT_2 (K_i = 5.1 μM) receptor (Battaglia et al. 1988). In addition, we are not aware of any evidence that H_1 histaminergic and α_1-adrenergic receptor stimulation has appreciable mind-altering effects in humans comparable to those produced by hallucinogens or psychostimulants. Thus, we can assume that the slight hallucinogen-like effects of MDMA are due to 5-HT_{2A} receptor stimulation.

We have recently shown that the selective serotonin uptake inhibitor citalopram markedly reduced both psychological and physiological responses to MDMA in healthy volunteers (Liechti et al. 2000; Liechti and Vollenweider 2000a). These results indicate that MDMA effects are largely dependent on transporter-mediated release of serotonin. In comparison with the present results, citalopram caused a more pronounced reduction of responses to MDMA than the postsynaptic 5-$HT_{2A/C}$ antagonist ketanserin. In the OAVAV scale, citalopram reduced MDMA-induced OB, AED, and VR scores, while ketanserin only produced a significant reduction in VR scores measuring perceptual changes. This failure to block all effects of MDMA could be due to an insufficient dose of ketanserin. We cannot address this possibility because we used only one dose of ketanserin which, however, has proved to be effective in psilocybin subjects (Vollenweider et al. 1998b). The fact that ketanserin showed a relative selectivity in reducing alterations in the OAVAV scale compared to citalopram supports the involvement of 5-HT_2 receptors in mediating perceptual changes induced by released serotonin. On the other hand, only citalopram (Liechti et al. 2000), but not ketanserin attenuated MDMA-induced positive mood and well-being, raising the question whether other serotonin receptors might play a role in the action of MDMA. Indeed, behavioral studies in animals indicate an important role for 5-HT_{1B} receptors in the effects of MDMA and other serotonin releasers (Geyer 1994; Geyer and Callaway 1994).

Emotional excitation in the present study was reduced by ketanserin pretreatment. In contrast, pretreatment with the D_2 antagonist haloperidol failed to reduce MDMA-induced emotional excitation in an identical study design (Liechti and Vollenweider 2000b). Pretreatment with citalopram was also ineffective in this regard (Liechti et al. 2000). These findings suggest that MDMA-induced emotional excitation is not primarily dependent on release of endogenous serotonin or D_2 receptor stimulation. There are several possible explanations for this unexpected result. First, because MDMA binds directly to 5-HT_2 receptors (Ki = 5.1 μM) as evidenced by radioligand binding assays us-

Table 2. Acute and Subacute Effects of Ketanserin, MDMA, and Ketanserin Plus MDMA

	Placebo			Ketanserin			MDMA			Ketanserin-MDMA		
	Acute	24h	72h	Acute	24h	72h	Acute	24h	72h	Acute	24h	72h
Difficulty concentrating	2	1		4	1		10	2		8	2	
Dry mouth/increased thirst				1			10	5	1	8	4	2
Impaired balance				2			8			6		
Dizziness	1			2			8			4		
Jaw clenching/trismus							8	3	1	4	2	
Lack of appetite							7	4		7	6	
Restlessness							7	2	1	6	2	1
Drowsiness	7	1		8	2	2	6	4	2	7	4	3
Palpitations				2			6			1		
Being cold	1						6			3	1	1
Inner tension							6	1	1	3	2	1
Nausea	1						5			1	1	2
Transpiration							5	1		2	2	
Weakness				2			5	3		6	3	2
Lack of energy	2	1		3	1		4	3	1	5	3	2
Brooding							4	3	1	2	1	2
Tremor							3					1
Anxiety							2		1	1		
Insomnia	–			–			–	2		–	2	
Hypersomnia	–	1		–	2		–	2	1	–	4	2

Numbers indicate number of subjects (total $n = 14$).
– = not assessed.

ing [^{3}H]ketanserin (Battaglia et al. 1988), direct interaction of MDMA with 5-HT_2 receptors rather than indirect agonist effects via released serotonin might contribute to the emotional excitation induced by MDMA. Second, 5-HT_2 antagonists such as M100,907 (formerly MDL 100,907) and ketanserin attenuated MDMA-induced striatal dopamine release, suggesting a permissive role for 5-HT_2 receptors in the MDMA-induced activation of the dopamine system (Schmidt et al. 1994, 1992; Nash 1990). Dopamine is generally thought to be involved in the euphoriant and arousing effects of stimulants such as d-amphetamine and cocaine (Vollenweider et al. 1998c; Laruelle et al. 1995; Volkow et al. 1997; Schlaepfer et al. 1997; Sherer et al. 1989; Nurnberger et al. 1984). Thus, the stimulant-like properties of MDMA may be attributed partially to 5-HT_2-mediated increase of dopamine activity. In particular, such indirect dopamine activation might have contributed to emotional excitation induced by MDMA in the present study. Since the dopamine D_2 antagonist haloperidol did not reduce MDMA-induced emotional excitation, dopaminergic D_1 receptors might be involved in these MDMA effects. A role for D_1-like receptors has also been suggested for the mediation of the acute mood altering effects of cocaine in humans (Romach et al. 1999).

Several subjects in the present study reported that dysphoric effects of MDMA coexisted or alternated with its pleasurable effects. Indeed, MDMA also increased scores for vigilance reduction, dazed state, inactivation, apprehension-anxiety, and produced several adverse effects. Although ketanserin alone also slightly produced these unpleasant symptoms, it reduced them as a pretreatment to MDMA compared to MDMA alone. Both MDMA and ketanserin have moderate affinity for H_1 histaminergic receptors (Battaglia et al. 1988; Brogden and Sorkin 1990). H_1 antagonists are well known for their adverse effects including sedation and dizziness. Thus, H_1 receptors are likely to be involved in the mediation of such unpleasant responses to MDMA and ketanserin.

Ketanserin lowered diastolic blood pressure and body temperature when given as a pretreatment to MDMA but also when given alone compared to placebo. Ketanserin is clinically used as an antihypertensive drug and the reduction of diastolic blood pressure can be explained by the antihypertensive effectiveness of ketanserin probably due to α_1-adrenergic antagonistic action (Brogden and Sorkin 1990). Although there was no statistical interaction of MDMA and ketanserin in the present study, the complete reduction of MDMA-induced increases in body temperature is consistent with animal studies demonstrating that 5-HT_2 antagonists such as MDL 11,939 or ketanserin block the hyperthermic effect of MDMA in rats (Schmidt et al. 1990; Nash et al. 1988).

In conclusion, pretreatment with the serotonergic 5-$HT_{2A/C}$ antagonist ketanserin mainly reduced MDMA-

induced perceptual changes, emotional excitation, and some of its physiological effects. In particular, our results indicate that the mild hallucinogen-like perceptual effects of MDMA in humans may be mediated via 5-HT_2 receptors.

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