

Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies

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In preclinical studies, 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') has been shown to release serotonin (5-HT), dopamine and norepinephrine. However, the role of these neurotransmitters and their corresponding receptor sites in mediating the subjective effects of MDMA has not yet been studied in humans. Therefore, we investigated the effects of three different neuroreceptor pretreatments on the subjective, cardiovascular and adverse effects of MDMA (1.5 mg/kg orally) in 44 healthy human volunteers. Pretreatments were: the selective serotonin reuptake inhibitor citalopram (40 mg intravenously) in 16 subjects, the 5-HT₂ antagonist ketanserin (50 mg orally) in 14 subjects, and the D₂ antagonist haloperidol (1.4 mg intravenously) in 14 subjects. Each of these studies used a double-blind placebo-controlled within-subject design and all subjects were examined under placebo, pretreatment, MDMA and pretreatment plus MDMA conditions. Citalopram markedly reduced most of the subjective effects of MDMA, including positive mood, increased extraversion and self-confidence. Cardiovascular and adverse effects of MDMA were also attenuated by citalopram. Haloperidol selectively reduced MDMA-induced positive mood but had no effect on other subjective effects of MDMA or the cardiovascular or adverse responses to MDMA. Ketanserin selectively reduced MDMA-induced perceptual changes and emotional excitation. These results indicate that the overall psychological effects of MDMA largely depend on carrier-mediated 5-HT release, while the more stimulant-like euphoric mood effects of MDMA appear to relate, at least in part, to dopamine D₂ receptor stimulation. The mild hallucinogen-like perceptual effects of MDMA appear to be due to serotonergic 5-HT₂ receptor stimulation. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS — MDMA; 3,4-methylenedioxymethamphetamine; Ecstasy; human; pharmacology

INTRODUCTION

While the pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') has been well studied *in vitro* and in behavioural studies in animals (Sprague *et al.*, 1998; Green *et al.*, 1995; Geyer and Callaway, 1994), little is known about the neurochemical mediators of the acute subjective effects of MDMA in humans. This paper summarises findings

from our recent mechanistic studies aimed at characterising the neurochemical mechanisms involved in the psychological effects of MDMA in humans (Liechti *et al.*, 2000a, 2000b; Liechti and Vollenweider, 2000a, 2000b).

In animals, MDMA mainly releases presynaptic serotonin (5-HT) and, to a lesser extent, norepinephrine (NE) and dopamine (DA) (Schmidt *et al.*, 1987; Rothman *et al.*, 2001). The MDMA-induced release of 5-HT is thought to be due to reversal of the 5-HT uptake transporter (Rudnick and Wall, 1992). In animals, selective serotonin reuptake inhibitors (SSRIs) blocked the MDMA-induced 5-HT and DA release (Gudelsky and Nash, 1996), reduced the behavioural effects of MDMA (Callaway *et al.*, 1990; Geyer, 1994) and provided some protection against neurotoxicity (Schmidt, 1987). These findings suggest that interaction of MDMA with the 5-HT uptake site is a primary and important mode of action of MDMA.

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Contract/grant sponsor: Heffter Research Institute.

Contract/grant sponsor: Swiss Federal Health Office.

Contract/grant number: BAG Grant 0686.

Contract/grant sponsor: Swiss National Science Foundation.

Contract/grant number: SNF Grant 31-52989.97

In humans, MDMA is also thought to mediate a large proportion of its effects via the serotonin system, and functional correlates of presumed short- and long-term 5-HT deficits or 5-HT selective neurotoxicity following Ecstasy use are increasingly reported (Schifano *et al.*, 1998; Morgan, 2000; Boot *et al.*, 2000). For example, there is a transient depression of mood in the days following MDMA use, consistent with short-term depletion of 5-HT (Parrott and Lasky, 1998; Curran and Travill, 1997). Particularly long-term Ecstasy users exhibit symptoms of depression, anxiety and sleep disorder (Topp *et al.*, 1999; McGuire *et al.*, 1994; Windhaber *et al.*, 1998; Parrott *et al.*, 2000; Gamma *et al.*, 2001). A variety of cognitive dysfunctions have also been described in Ecstasy users, including deficits in working memory, short-term and longer-term memory, and attention (Boot *et al.*, 2000; Morgan, 1998; Gouzoulis-Mayfrank *et al.*, 2000). Recreational Ecstasy use was also associated with increased impulsiveness and hostility (Morgan, 1998; Parrott *et al.*, 2000).

It is unknown to what extent the release of 5-HT contributes to the acute psychoactive effects of MDMA in humans and whether SSRI treatment would reduce the acute mood effects in humans, as expected from animal studies. There are a few anecdotal reports that SSRIs, when used together with Ecstasy, dampened subjective and adverse responses to Ecstasy (Stein and Rink, 1999; McCann and Ricaurte, 1993). SSRIs have also successfully been used to treat panic disorders induced by Ecstasy (Windhaber *et al.*, 1998). In contrast, a psychotic reaction to Ecstasy has also been reported in a patient who was treated with an SSRI for years (Lauerma *et al.*, 1998). Thus, the role of the 5-HT uptake site in mediating the acute effects of MDMA remained to be clarified.

In addition to its interaction with the 5-HT transporter site, MDMA has also been shown to have moderate direct affinity for postsynaptic serotonergic 5-HT₂ receptors (Battaglia *et al.*, 1988). Stimulation of 5-HT₂ receptors has been implicated in the psychological effects, particularly in the visual effects, of indole hallucinogens (Glennon *et al.*, 1984; Vollenweider *et al.*, 1998a). For example, it has been shown that the binding affinity for a drug for the 5-HT₂ receptor site predicts its potency for evoking hallucinations in humans (Glennon *et al.*, 1984). Although the hallucinogenic potency of MDMA is generally considered to be weak, Ecstasy users have reported hallucinogenic effects of MDMA at higher doses (Solowij *et al.*, 1992). Lasting psychotic syndromes including visual illusions, hallucinations and visual 'flashbacks' have

also been noted after Ecstasy consumption (McGuire *et al.*, 1994). Taken together, these data suggest an involvement of 5-HT₂ receptors in the generation of the perceptual effects of MDMA.

Finally, MDMA releases DA by reversal of the DA uptake carrier and secondarily via 5-HT_{2A} receptor stimulation (Gudelsky *et al.*, 1994; Bankson and Cunningham, 2001). DA is known to play an important role in the mediation of euphoria and of the rewarding effects produced by classic stimulants such as d-amphetamine and cocaine (Laruelle *et al.*, 1995; Volkow *et al.*, 1997). Drug discrimination studies in animals, which are believed to model the subjective effects of drugs in humans, showed that both D₁ and D₂ dopamine agonists mimic the discriminative stimulus effects of amphetamine and that D₁ and D₂ antagonists block these effects (Brauer *et al.*, 1997). Drug discrimination studies using MDMA, however, showed only a weak dopaminergic component as compared to its serotonergic effects (Oberlender and Nichols, 1988; Schechter, 1989). Human studies using D₂ antagonists prior to amphetamine or cocaine revealed mixed results. In cocaine abusers, administration of the dopaminergic D₂ antagonist haloperidol (8 mg intramuscularly) significantly attenuated the self-rated 'high' but not the 'rush' induced by 40 mg intravenous cocaine (Sherer *et al.*, 1989). Similarly, Nurnberger and colleagues (1984) found that 0.014 mg/kg intramuscular haloperidol attenuated observer-rated 'excitation' and 'elation' responses to 0.3 mg/kg intravenous amphetamine. In contrast, Brauer and de Wit (1997) found that the D₂ antagonist pimozide had only little effect on amphetamine-induced elation, euphoria or vigour despite its reducing these ratings, compared with placebo, when given alone. Despite these disparities, these studies provide some evidence that dopaminergic D₂ receptor stimulation might contribute to the euphoric effects of classic stimulants.

The present studies aimed to investigate the following hypotheses.

1. Based on the preclinical evidence, we hypothesised that the subjective effects of MDMA in humans would primarily be due to an interaction of MDMA with the 5-HT transporter, and that the SSRI citalopram may reduce MDMA-induced psychophysiological changes.
2. We assumed that 5-HT₂ receptor stimulation might be responsible for the mild hallucinogen-like action of MDMA. Thus, we hypothesised that the serotonin 5-HT₂ antagonist ketanserin may reduce perceptual effects of MDMA in humans.

3. We speculated that DA release and/or D₂ receptor stimulation might contribute to the elevating mood effects of MDMA and that the dopamine D₂ antagonist haloperidol may reduce these effects of MDMA.

MATERIAL AND METHODS

All human studies described here were performed at the University Hospital of Psychiatry in Zurich, Switzerland, and have previously been published (Liechti *et al.*, 2000a, 2000b; Liechti and Vollenweider, 2000a, 2000b). The psychophysiological effects of MDMA were assessed in 44 human volunteers after pretreatment with three different neuroreceptor ligands. Pretreatments were the SSRI citalopram (40 mg intravenously) in 16 subjects (12 male; mean age 27 years), the serotonergic 5-HT₂ antagonist ketanserin (50 mg orally) in 14 subjects (13 male; mean age 26 years) and the dopaminergic D₂ antagonist haloperidol (1.4 mg intravenously) in 14 subjects (9 male; mean age 26 years). MDMA was given at a dose of 1.5 mg/kg (1.35–1.8 mg/kg) orally (mean absolute dose 103 mg, range 70–120 mg). Timing parameters were based on pharmacokinetic data and were as follows: MDMA/placebo capsules were administered (1) directly after citalopram or saline infusion over 90 min, (2) 75 min after oral administration of ketanserin or placebo, or (3) 10 min after intravenous haloperidol or saline injection. Psychometric ratings were performed 120 min after MDMA or placebo intake, about 60–75 min after the expected onset of subjective effects. Each of the three studies used a double-blind, placebo-controlled within-subject design. Thus, all subjects participated in four experimental sessions involving administration of placebo, pretreatment alone, MDMA alone, and pretreatment plus MDMA, with order being counterbalanced. Participants were mostly university students or physicians who had a personal scientific interest in the study. Subjects were healthy and did not meet DSM-IV criteria for substance abuse or dependence. Five participants had tried MDMA once or twice before, all other subjects were MDMA-naïve. The three studies were approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich. All participants gave their written informed consent.

The following two psychometric measures were used to assess subjective peak drug effects reported in this paper. The Altered States of Consciousness rating scale (OAV; Dittrich, 1998) is a visual analogue self-rating scale and consists of three subscales:

'oceanic boundlessness' (OB) measures positive drug effects including derealisation and depersonalisation associated with positive mood; 'anxious ego dissolution' (AED) measures negative drug effects such as thought disorder, fear of loss of thought or body control, and anxiety; 'visionary restructuralisation' (VR) measures perceptual alterations including elementary visual (pseudo-)hallucinations, synaesthesia, changed meaning of percepts, facilitated recollection and facilitated imagination. The Adjective Mood scale (AM; Janke and Debus, 1978) consists of 14 scales measuring efficiency/activation, self-confidence, heightened mood, apprehension/anxiety, depression, thoughtfulness/contemplativeness, extraversion, introversion, inactivation, dazed state, tiredness, sensitivity, aggression/anger and emotional excitation. Side effects were assessed by the List of Complaints (LC; Zerssen, 1976). Blood pressure, heart rate and peripheral body temperature were measured during each session.

Dependent measures were compared by ANOVA (simple effect test) with treatment (placebo vs MDMA) as the within-subject factor for the pooled data (n = 44). To assess the effects of pretreatments, two-way ANOVAs were used with pretreatment (citalopram, haloperidol or ketanserin vs placebo) and treatment (placebo vs MDMA) as within-subject factors. For further methodological and statistical details the reader is referred to the original publication of each study (Liechti *et al.*, 2000a, 2000b; Liechti and Vollenweider, 2000a, 2000b).

RESULTS

Subjective, cardiovascular and adverse effects of MDMA alone

The subjective effects of MDMA began 30–60 min after MDMA administration and lasted for a mean duration of 3.5 h when MDMA was given alone. MDMA significantly increased scores for all scales of the OAV rating: OB [$F_{(1,43)} = 61.24$; $p < 0.001$], AED [$F_{(1,43)} = 31.44$; $p < 0.001$], and VR [$F_{(1,43)} = 18.85$; $p < 0.001$]. Item-based analysis revealed that MDMA-induced elevation in OB scores was due to increased 'positive mood', positively experienced 'depersonalisation', and 'mania-like experience'. Subjects felt 'carefree' and experienced 'boundless joy'. Physical sensations were described as 'more pleasurable'. The increase in AED scores was due to 'thought disorder' such as difficulty concentrating, accelerated thinking, thought blocking, and impaired decision making. In addition, there was a slight 'fear

of loss of body control' and 'fear of loss of thought control'. Increases in VR scores were mainly attributable to 'changes in the meaning of percepts', 'facilitated recollection', and 'facilitated imagination'. Subjects described an intensification of sensory perception. Colours were described to be more vivid, touch was altered, and sounds seemed closer or farther away. Subjects also reported seeing flashes of light, colours and simple patterns. As described in detail elsewhere, we found highly significant correlations between the dose of MDMA (1.35–1.8 mg/kg) and VR scores after MDMA administration, particularly in women (Liechti *et al.*, 2001b).

In the AM mood rating scale, MDMA mainly increased 'heightened mood' [$F_{(1,43)} = 27.82$; $p < 0.001$], 'self-confidence' [$F_{(1,43)} = 24.21$; $p < 0.001$] and 'extraversion' [$F_{(1,43)} = 26.65$; $p < 0.001$]. There was also an increase in 'thoughtfulness-contemplativeness' [$F_{(1,43)} = 41.46$; $p < 0.001$], with subjects being in a state of dreaminess and lost in thought. MDMA-induced 'emotional excitation' [$F_{(1,43)} = 33.45$; $p < 0.001$] was due to increased restlessness, with about a third of the subjects feeling fidgety. While 'tiredness' was reduced [$F_{(1,44)} = 2.80$; $p < 0.1$] compared with placebo, there was an increase in 'dazed state' [$F_{(1,43)} = 49.45$; $p < 0.001$] that was due to about half of the subjects feeling intoxicated. MDMA also increased scores for 'inactivation' [$F_{(1,43)} = 4.70$; $p < 0.04$].

The cardiovascular response to MDMA included significant elevation of systolic blood pressure by (mean \pm SD) 30 ± 13 mm Hg [$F_{(1,43)} = 130.58$; $p < 0.001$] and of diastolic blood pressure by 16 ± 10 mm Hg [$F_{(1,43)} = 66.08$; $p < 0.001$], as well as a significant increase in heart rate by 10 ± 13 beats per min [$F_{(1,43)} = 34.92$; $p < 0.001$], compared with placebo.

The most frequent acute side effects of MDMA, as assessed by the LC, were 'difficulty concentrating' (59%), 'jaw clenching' (58%), 'lack of appetite' (54%), 'dry mouth' (53%), 'impaired balance' (49%) and 'dizziness' (38%).

Citalopram and MDMA

The SSRI citalopram markedly reduced most psychoactive effects of MDMA in humans, as evidenced by similar reductions in all scales of the OAV (Liechti *et al.*, 2000a). As shown in Figure 1, MDMA-induced positive mood (OB), thought disturbances and reduced control over thought and body (AED), as well as perceptual alterations (VR), were all significantly attenuated after citalopram pretreatment (pretreat-

ment \times treatment interactions: OB $F_{(1,15)} = 22.47$; $p < 0.001$; AED $F_{(1,15)} = 23.04$; $p < 0.001$; VR $F_{(1,15)} = 12.80$; $p < 0.03$). MDMA-induced increases in AM scores for 'extraversion' and 'self-confidence' that could be regarded as 'entactogenic' mood effects were also significantly lowered by citalopram (Wilcoxon matched pairs tests: $p < 0.01$ and $p < 0.04$, respectively) (Liechti *et al.*, 2000a).

Citalopram also reduced the acute cardiovascular response to and side effects of MDMA (Figure 2) (Liechti and Vollenweider, 2000a). Specifically, citalopram pretreatment slightly but significantly reduced the MDMA-induced rise in systolic blood pressure from (mean \pm SD) 142 ± 18 to 136 ± 17 mm Hg at 60 min [$F_{(1,15)} = 8.24$; $p < 0.01$] and from 138 ± 15 to 129 ± 14 mm Hg at 120 min [$F_{(1,15)} = 6.09$; $p < 0.03$], as confirmed by significant pretreatment \times treatment interactions. Also, diastolic pressure was significantly reduced from 87 ± 8 to 82 ± 10 mm Hg at 120 min [$F_{(1,15)} = 6.09$; $p < 0.03$], but not at 60 min. The MDMA-induced rise in heart rate was also significantly reduced by citalopram pretreatment at 60 min, from 73 ± 15 to 64 ± 12 beats/min [pretreatment \times treatment interaction: $F_{(1,15)} = 5.00$; $p < 0.04$], but not at 120 min. Citalopram not only reduced the subjective MDMA effects but also prolonged them to a mean duration of 5 h, compared with 3 h when MDMA was given alone.

Ketanserin and MDMA

Ketanserin resulted in only a moderate attenuation of the overall subjective MDMA experience. Pretreatment with ketanserin primarily and significantly reduced MDMA-induced VR scores [pretreatment \times treatment interaction: $F_{(1,13)} = 15.82$; $p < 0.01$], indicating a reduction of MDMA-induced perceptual changes, but had no significant effect on OB or AED scores (Figure 1) (Liechti *et al.*, 2000b). We also found significant pretreatment \times treatment interactions for the AM scales 'dazed state' [$F_{(1,13)} = 14.08$; $p < 0.01$] and 'tiredness' [$F_{(1,13)} = 7.43$; $p < 0.05$], and for an additional OAV scale measuring 'vigilance reduction' [$F_{(1,13)} = 4.72$; $p < 0.05$]. Thus, both ketanserin and MDMA produced increased inactivation and vigilance reduction, but this effect was significantly smaller when the two drugs were given together. In the AM scale, 'emotional excitation' was significantly lower after ketanserin plus MDMA administration, compared with MDMA alone (Figure 2) (no significant pretreatment \times treatment interaction, but significant drug effect for MDMA versus ketanserin + MDMA: [$F_{(1,13)} = 9.97$, $p < 0.008$].

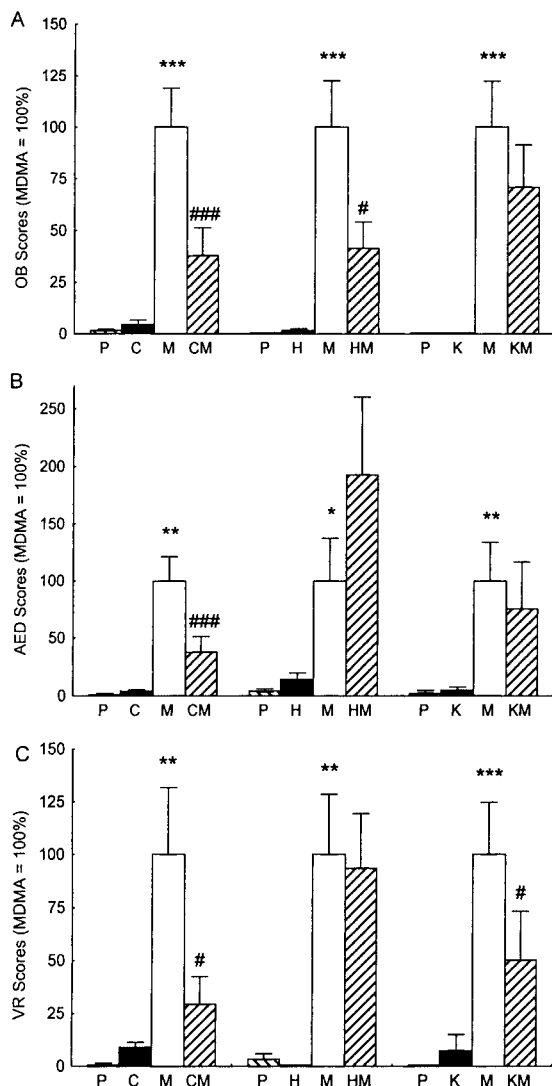


Figure 1. Scores on the 'oceanic boundlessness' (OB), 'anxious ego dissolution' (AED) and 'visionary restructuralisation' (VR) subscales of the Altered States of Consciousness Rating Scale. Drug conditions: P, placebo; M, MDMA; C, citalopram; H, haloperidol; K, ketanserin. Both citalopram and haloperidol reduced MDMA-induced changes on the OB. Only citalopram reduced MDMA-induced changes on the AED. Haloperidol increased anxious ego dissolution, compared with MDMA alone (significant increase for the anxious derealisation sub-scale). Both citalopram and ketanserin reduced MDMA-induced changes on the VR. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (simple effect test); # $p < 0.05$, ### $p < 0.001$ (two-way ANOVA, pretreatment \times treatment interaction)

However, the most typical MDMA effects in the AM scale, such as increased 'self-confidence', 'heightened mood' and 'extraversion' were not changed by ketanserin (Figure 2) (for details see Liechti *et al.*, 2000b).

Finally, ketanserin significantly reduced the total of acute adverse responses to MDMA as assessed by the LC scale (Figure 2) (global score of complaints: pretreatment \times treatment interaction: $F_{(1,13)} = 12.25$; $p < 0.01$). Adverse effects of MDMA that were reduced by ketanserin included signs of activation such as restlessness, inner tension and tremor (Liechti *et al.*, 2000b). With regard to physiological effects of MDMA, ketanserin significantly lowered diastolic blood pressure and peripheral body temperature [drug effect for MDMA versus ketanserin + MDMA: $F_{(1,13)} = 9.45$, $p < 0.05$; $F_{(1,13)} = 6.48$, $p < 0.05$, respectively] when given as a pretreatment to MDMA but also when given alone, compared with placebo (Liechti *et al.*, 2000b).

Haloperidol and MDMA

As shown in Figure 1, haloperidol reduced only the euphoric effect of MDMA, as evidenced in a decrease of MDMA-induced OB scores [pretreatment \times treatment interaction: $F_{(1,13)} = 5.89$; $p < 0.03$], but was ineffective in reducing AED or VR scores. AED scores after MDMA were even increased after haloperidol pretreatment, indicating a potentiation of dysphoric effects of MDMA, such as anxious derealisation (AED) (Liechti and Vollenweider, 2000b). In the AM scale, haloperidol only reduced MDMA-induced well-being, as expressed in reduced scores for 'heightened mood' [simple effect test: $F_{(1,13)} = 5.29$; $p < 0.04$] and 'self-confidence' (Figure 2) [$F_{(1,13)} = 6.30$; $p < 0.03$]. However, there was no pretreatment \times treatment interaction, as haloperidol also reduced these scores, compared with placebo, when given alone [simple effect test: $F_{(1,13)} = 7.02$; $p < 0.02$; $F_{(1,13)} = 4.13$; $p = 0.06$]. Haloperidol had no effect on cardiovascular parameters after MDMA. Adverse responses to MDMA were slightly but not significantly increased by haloperidol (Figure 2).

DISCUSSION

Mood effects of MDMA: the role of serotonin

Confirming our primary hypothesis, pretreatment with the SSRI citalopram markedly attenuated the overall MDMA experience, including subjective, cardiovascular and acute adverse responses. Extending these findings, citalopram, but not haloperidol or ketanserin, significantly reversed the effect of MDMA on sensorimotor gating of the acoustic startle reflex in our citalopram study subjects (Liechti *et al.*, 2001a). These results are in line with data from *in vitro* and animal studies and with uncontrolled reports of recreational

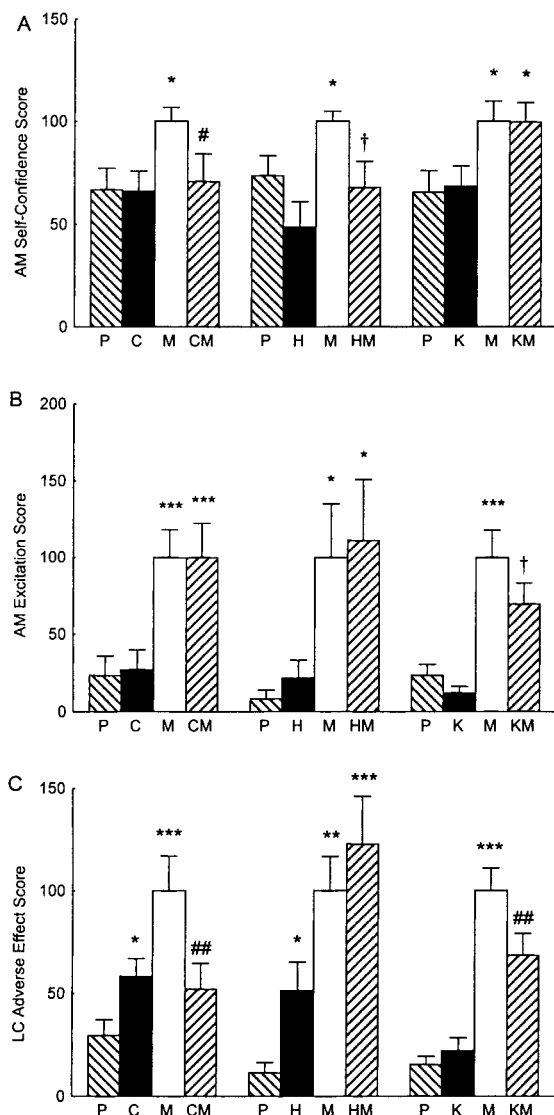


Figure 2. Scores on the self-confidence, excitement and adverse effect subscales of the Adjective Mood scale. Drug conditions: P, placebo; M, MDMA; C, citalopram; H, haloperidol; K, ketanserin, (MDMA = 100%). MDMA increased self-confidence in all three studies, compared with placebo. Citalopram and haloperidol reduced MDMA-induced changes on the self-confidence score. However, there was no pretreatment \times treatment interaction since haloperidol also reduced self-confidence, compared with placebo. MDMA increased excitement scores in all three studies, compared with placebo, and ketanserin reduced MDMA-induced changes. MDMA increased adverse effect scores in all three studies, and both citalopram and ketanserin reduced MDMA-induced changes. Haloperidol non-significantly increased MDMA-induced adverse effects. $^{\dagger}p < 0.05$ (simple effect test) $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (simple effect test); $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ (two-way ANOVA, pretreatment \times treatment interaction)

Ecstasy users who co-administered MDMA with an SSRI and experienced a reduction of their subjective and adverse responses (McCann and Ricaurte, 1993). *In vitro* studies suggest that MDMA interacts with the 5-HT uptake site, causing 5-HT release that might be due to 5-HT-MDMA exchange through the uptake carrier (Rudnick and Wall, 1992). Thus, it can be assumed that the SSRI citalopram also prevented the interaction of MDMA with the 5-HT transporter and thereby reduced the efflux of 5-HT in humans. Citalopram reduced the overall effect of MDMA more potently than haloperidol or ketanserin. This reduction also included mood effects typically attributed to MDMA, such as increased extraversion and self-confidence. In sum, the present data suggest that the psychophysiological effects of MDMA in humans and particularly its effect on mood primarily depend on carrier-mediated release of 5-HT.

Another source of pharmacological interaction between SSRIs and MDMA is at the level of metabolic P450 liver enzymes. We observed a prolongation of the subjective MDMA effect by about 2 h after citalopram pretreatment as compared to MDMA alone (Liechti *et al.*, 2000a). This finding could be explained by a pharmacokinetic interaction, since citalopram is an inhibitor of the CYP2D6 enzyme, which is involved in the metabolism of MDMA (Tucker *et al.*, 1994). This inhibition of the breakdown of MDMA could prolong its central availability and thus its subjective effects. Given the high prevalence of depressive symptoms among Ecstasy users (Parrott and Lasky, 1998; Boot *et al.*, 2000), co-use and potential pharmacological interactions of SSRIs and MDMA might be frequent and should be more thoroughly investigated (Hegadoren *et al.*, 1999).

Our present data, in line with anecdotal reports from Ecstasy users who took MDMA while under therapy with a SSRI (Stein and Rink, 1999; McCann and Ricaurte, 1993), indicate that the use of MDMA after administration of the SSRI is unlikely to result in an adverse drug reaction. In contrast, adverse responses to pure MDMA were attenuated in our controlled study (Liechti and Vollenweider, 2000a). Whether the use of MDMA prior to administration of the SSRI leads to an amplification or the MDMA effect, or even to a serotonin syndrome (Green *et al.*, 1995), cannot be inferred from our data.

Hallucinogenic effects: the role of 5-HT₂ receptors

In contrast to citalopram, the 5-HT₂ antagonist ketanserin had little effect on the most characteristic MDMA effects, increased positive mood, self-

confidence and extraversion. However, ketanserin significantly decreased the perceptual (VR) effects of MDMA, as was also observed in a previous study where ketanserin was administered prior to the serotonergic hallucinogen psilocybin (Vollenweider *et al.*, 1998a). In a pooled analysis of all 74 MDMA experiments conducted in our laboratory, the dose of MDMA in the range of 1.35–1.8 mg/kg was found to positively correlate with the intensity of MDMA-induced perceptual changes (Liechti *et al.*, 2001b). Thus, higher doses of MDMA produced more hallucinogen-like effects. This finding is in line with reports from Ecstasy users that MDMA had more hallucinogenic effects at higher doses (Solowij *et al.*, 1992). At low doses, a preferential stimulation of 5-HT₁ receptors by released 5-HT can be expected, since the affinity of 5-HT for 5-HT₁ receptors is higher than for 5-HT₂ receptors (Barnes and Sharp, 1999). At higher doses of MDMA, however, the probability of 5-HT₂ receptor stimulation increases as either the released 5-HT or especially MDMA itself can bind to 5-HT₂ receptors. Taken together, these results demonstrate that 5-HT₂ receptor stimulation mediates the hallucinogen-like perceptual effects of higher doses of MDMA in humans.

Stimulant effects: the role of the dopamine system

Haloperidol pretreatment changed the subjective MDMA effects from a pleasurable state of well-being and euphoria to a more dysphoric state with slightly increased anxiety. The finding that haloperidol significantly reduced the euphoric effect of MDMA is in agreement with the view that dopamine D₂ receptor stimulation partially contributes to the euphoria produced by MDMA. However, haloperidol also produced a mood-lowering effect when given alone. It is possible that this dysphoric effect of haloperidol, rather than specific D₂ antagonism, may account for the reduced euphoria seen after haloperidol and MDMA. Indeed, it may be that similar sedating side effects of the D₂ antagonists haloperidol or pimozide reduced the euphoric effects of classic stimulants such as cocaine or amphetamine in earlier studies (Brauer and de Wit, 1997; Nurnberger *et al.*, 1984; Sherer *et al.*, 1989). In contrast to its effect on euphoria, haloperidol did not lessen cardiovascular responses to MDMA, indicating that dopamine D₂ receptor stimulation does not contribute to the physiological effects of MDMA. Emotional excitation and activation produced by MDMA were also not reduced by haloperidol, indicating a role for the NE or 5-HT systems (see below) or dopaminergic D₁ receptors. Dopaminergic

D₁-like receptors have previously been found to mediate the 'high' and 'good drug effect' of cocaine in humans (Romach *et al.*, 1999).

Hyperactivity: the role of 5-HT_{1B} and 5-HT_{2A} receptors

Indirect 5-HT_{1B} receptor stimulation is known to play a role in the mediation of MDMA-induced hyperactivity in animals. 5HT_{1B} agonists elicit similar behavioural responses in animals to those from low doses of MDMA (Rempel *et al.*, 1993). 5-HT_{1B} but not 5-HT_{1A} antagonists completely reversed hyperactivity caused by low doses of MDMA (McCreary *et al.*, 1999). In contrast, 5-HT_{2A} antagonists blocked the hypermotility induced by high doses of MDMA (20 mg/kg), but hyperactivity elicited by a low dose of MDMA (3 mg/kg) was unaffected (Bankson and Cunningham, 2001). 5-HT_{2A} receptors are thought to play a permissive role in the MDMA-induced activation of the DA system. In particular, DA release and hyperactivity evoked by high doses of MDMA can be blocked by 5-HT_{2A} antagonists (Gudelsky *et al.*, 1994; Kehne *et al.*, 1996). These data indicate that MDMA-induced locomotor hyperactivity partially results from 5-HT_{1B} receptor stimulation at low doses and from 5-HT_{2A} receptor-mediated DA stimulation at higher doses of MDMA. In our human studies, MDMA produced some stimulant-like effects, including increased emotional excitation, inner tension, restlessness and tremor, that could be regarded as a correlate of MDMA-induced hyperactivity in animals. These effects of MDMA in humans were reduced by the 5-HT₂ antagonist ketanserin (Liechti *et al.*, 2000b) but not by the SSRI citalopram (Liechti *et al.*, 2000a). Thus, it appears that the activating, stimulant-like properties of MDMA in humans might, at least to some extent, be directly related to 5-HT_{2A} receptor activation.

Cardiovascular effects: the role of the norepinephrine system

Rothman and colleagues (2001) determined the neurochemical mechanism of action of various stimulants, including d-amphetamine, ephedrine and racemic MDMA, using *in vitro* methods. They found that the most potent effect of these stimulants was to release NE. In addition, the reported oral dose of these stimulants that produced stimulant-like subjective effects in humans correlated with their potency in releasing NE, not DA. For MDMA, IC₅₀ for release of 5-HT, NE and DA was 56.6 nM, 77.4 nM and 376 nM, respectively (Rothman *et al.*, 2001). Thus,

in this assay, MDMA released 5-HT and NE with about the same potency. In animals, the blood pressure response to MDMA has recently been shown to involve α_1 and, possibly, α_2 adrenoceptors and 5-HT₂ receptors (McDaid and Docherty, 2001). In humans, activation of the NE system produces sympathomimetic effects, including elevated blood pressure. In humans, MDMA produces such cardiovascular stimulation, including increases in diastolic and systolic blood pressure, as well as in heart rate (Lester *et al.*, 2000; Liechti *et al.*, 2001b; Vollenweider *et al.* 1998b). Of note, the SSRI citalopram significantly reduced these cardiovascular responses to MDMA, indicating that these physiological effects of MDMA are partially due to an interaction of MDMA with the 5-HT carrier and subsequent release of 5-HT (Liechti and Vollenweider, 2000a). In addition, the 5-HT₂ antagonist ketanserin, which also has α_1 adrenergic antagonistic properties, lowered diastolic blood pressure when given as a pretreatment to MDMA but also when given alone, compared with placebo (Liechti *et al.*, 2000b). It could be speculated that MDMA-induced 5-HT release might activate the NE system. In addition, MDMA has direct affinity for α_2 adrenergic receptors (Battaglia *et al.*, 1988). The role of NE in the mediation of the physiological and psychological effects of MDMA in humans remains to be elucidated. Studies using NE uptake inhibitors and postsynaptic NE receptor antagonists prior to MDMA could clarify this issue.

The role of acetylcholine and histamine

MDMA has recently been shown to release acetylcholine (ACh) from rat striatal slices (Fischer *et al.*, 2001) or *in vivo* as measured by microdialysis (Acquas *et al.*, 2001). Given that MDMA itself has considerable affinity for histamine (H) H₁ receptors (Battaglia *et al.*, 1988) and that only a H₁ antagonist reduced the MDMA-induced ACh release (Fischer *et al.*, 2001), direct MDMA–H₁ receptor interaction is likely to be responsible for the MDMA-induced ACh release. Furthermore, MDMA itself has moderate affinity for muscarinic M₁ receptors (Battaglia *et al.*, 1988). Yet, the significance of ACh and H in the mechanism of action of MDMA in humans is unknown. ACh and H are involved in the regulation of arousal, motor activity and memory, and various interactions with the monoamine systems are known. With regard to our human studies, we observed a significant interaction of MDMA and ketanserin (5-HT₂ but also H₁ antagonist) on scales measuring inactivation ('dazed state' and 'tiredness')

and vigilance reduction (Liechti *et al.*, 2000b) that might be due to the common affinity for H₁ receptors.

Conclusion

The present findings from our mechanistic studies with MDMA in humans are in line with results from animal studies. However, only human studies can directly assess the various subjective effects of MDMA and their underlying neurochemical basis. At present, available evidence suggests that the psychological effects of MDMA in humans primarily depend on carrier-mediated release of 5-HT. Positive mood effects of MDMA may be related in part to dopaminergic D₂ receptor stimulation. The mild hallucinogen-like perceptual effects of MDMA appear to be due to 5-HT₂ receptor stimulation. The significance of other neurotransmitters, particularly NE, and of recognition sites such as the dopamine D₁ and 5-HT₁ receptors in the action of MDMA in humans deserves further investigation.

ACKNOWLEDGEMENTS

These studies were supported by the Heffter Research Institute, Santa Fe, NM, USA, the Swiss Federal Health Office (BAG Grant 0686) and the Swiss National Science Foundation (SNF Grant 31-52989.97). The authors thank Alex Gamma for critical comments on the manuscript.

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