

# Acute Psychological Effects of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") are Attenuated by the Serotonin Uptake Inhibitor Citalopram

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3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a recreational drug that has been shown to release serotonin (5-HT) and dopamine (DA) in animals. The effect of MDMA on 5-HT release can be blocked by 5-HT uptake inhibitors such as citalopram, suggesting that MDMA interacts with the 5-HT uptake site. It is unknown whether this mechanism is also responsible for the psychological effects of MDMA in humans. We investigated the effect of citalopram pretreatment (40 mg *iv*) on the psychological effects of MDMA (1.5 mg/kg *po*) in a double-blind placebo-controlled psychometric study in 16

healthy human volunteers. MDMA produced an emotional state with heightened mood, increased self-confidence and extroversion, moderate derealization, and an intensification of sensory perception. Most of these effects were markedly reduced by citalopram. This finding suggests that the psychological effects of MDMA are mediated via action at the 5-HT uptake site to increase 5-HT release through the carrier, as expected from animal studies.

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**KEY WORDS:** 3,4-Methylenedioxymethamphetamine; MDMA; Ecstasy; Serotonin; Citalopram; Selective serotonin reuptake inhibitors; Psychological effects

3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"), an amphetamine derivative, is a popular recreational drug that has been shown to exhibit a characteristic psychoactive profile in a controlled study (Vollenweider et al. 1998a). MDMA produced feelings of well-being and euphoria, moderate derealization, depersonalization, and cognitive disturbances, as well as

heightened sensory awareness. MDMA produced no hallucinations and only moderately increased psychomotor drive (Vollenweider et al. 1998a). The neurochemical mechanism of action of MDMA is well studied *in vitro* and in animals (for reviews see Green et al. (1996); Sprague et al. (1998); White et al. (1996). MDMA mainly releases serotonin (5-HT) (Nichols et al. 1982; Schmidt 1987) and, to a lesser extent, dopamine (DA) (Koch and Galloway 1997; Nash 1990; Yamamoto and Spanos 1988). Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and citalopram were found to block the MDMA-induced 5-HT release (Gudelsky and Nash 1996; Hekmatpanah and Peroutka 1990; Schmidt 1987) suggesting that it is carrier-mediated, possibly due to 5-HT-MDMA exchange (Rudnick and Wall 1992). It is unknown whether this mechanism is also responsible for the psychological effects of MDMA in humans. To our knowledge, there is only one case series

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reporting four Ecstasy users who had taken the SSRI fluoxetine prior to Ecstasy (McCann and Ricaurte 1993). One of the users felt an attenuation of subjective experience when fluoxetine was taken before Ecstasy while the three others felt no change compared to Ecstasy alone. This report seems to indicate that, in humans, the administration of an SSRI has very little impact on the psychological effects of MDMA. Given the uncontrolled nature and the small sample size of these reports, no firm conclusion can be drawn from this finding. Hence, the present controlled study was undertaken to determine whether pretreatment with the highly specific 5-HT uptake inhibitor citalopram would attenuate the psychoactive effects of MDMA, as measured by psychometric rating scales, in healthy human subjects. We hypothesized that 40 mg citalopram infusion would reduce the psychological effects of 1.5 mg/kg MDMA given orally.

## MATERIALS AND METHOD

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

## SUBSTANCES AND DOSING

Citalopram hydrochloride ampules, 40 mg, were kindly provided by Lundbeck, Switzerland. Citalopram (40 mg) was dissolved in 500 ml of sterile saline solution and given by perfusion over 90 minutes (330 ml/h). Dose and time parameters were chosen according to pharmacokinetic data (Baumann and Larsen 1995) and a pilot study using 40 to 80 mg citalopram infusions. Citalopram has a half-life time of 1.5 days (Baumann and Larsen 1995). Racemic MDMA hydrochloride was obtained from the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics, Berne, and prepared as capsules (10 and 50 mg) at the Pharmacy of the Kantonsspital Lucerne. Subjects received MDMA at a moderate dose of 1.5 mg/kg (mean  $\pm$  SD = 100 mg  $\pm$  10). This dose of MDMA was expected to produce robust psychological effects (Vollenweider et al. 1998a) and was carefully evaluated to minimize possible risks. While there is valid concern about possible neurotoxic effects of higher and repeated doses of MDMA in humans (McCann et al. 1998), it is extremely unlikely that administering MDMA (1.5 mg/kg) only one or two times within an experimental context will produce serotonergic dysfunction. As evidenced in non-human primates, only multiple doses of 5 mg/kg

p.o. MDMA, but not a single dose, produced depletion of serotonin (Ricaurte et al. 1988) and even after repeated administration of MDMA up to a cumulative dose of 20 mg/kg i.m., the number of 5-HT uptake sites was not significantly changed (Insel et al. 1989). For a discussion of ethical aspects see Lieberman and Aghajanian (1999) and Vollenweider et al. (1999a, 1999b).

## SUBJECTS

Volunteers, 12 male and 4 female, aged between 21 and 39 years (mean  $\pm$  SD = 27.4  $\pm$  4.4) were recruited at the University Hospital and at the Medical School of the University of Zurich. All subjects had a high school education and all but one were either university students or physicians. Volunteers were 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. All gave their written consent. Subjects were healthy according to history, physical examination, 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. Of the sixteen subjects included in the study, six had previous recreational drug experience. Two had tried Ecstasy, three had tried a hallucinogen, and one had used both Ecstasy and a hallucinogen. Additional exclusion criteria were scores exceeding two standard deviations from the mean values of normative data in the "neuroticism" scale of the Freiburger Personality Inventory (FPI) (Fahrenberg et al. 1984).

## 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 (counterbalanced). The four sessions were separated by at least 14 days to prevent carry-over effects. Subjects were told not to eat or to drink coffee for two hours prior to each session. Upon arriving at the Psychiatric University Hospital (9 am or 2 pm) 40 mg citalopram in 500ml saline solution or placebo (saline solution alone) was infused over 90 minutes (330 ml/h). After removal of the intravenous catheter MDMA (1.5 mg/kg) or placebo capsules were given orally. Psychometric measurements were performed 120 minutes after MDMA/placebo intake, about 75 minutes after the anticipated onset of subjective effects.

Blood pressure, heart rate and body temperature were monitored throughout the session. Adverse effects were assessed during the session and after one and three days. In addition to the psychological measurements, sensorimotor gating of the acoustic startle reflex was assessed as previously reported (Vollenweider et al. 1999b). Side effects, cardiovascular changes and results from startle measurements will be reported separately.

## PSYCHOMETRIC RATING SCALES

The Adjective Mood Rating Scale (AM) consists of 14 scales measuring "efficiency-activation", "heightened mood", "self-confidence", "extroversion", "introversion", "apprehension-anxiety", "depressiveness", "thoughtfulness-contemplativeness", "dazed state", "tiredness", "inactivation", "sensitivity", "emotional excitability", and "aggression-anger" (Janke and Debus 1978).

The Altered States of Consciousness Rating Scale (ASC) is a visual-analog scale with 66 items (Dittrich et al. 1985; Dittrich 1998). It measures alterations in waking consciousness, including changes in mood, perception, experience of oneself and of the environment, as well as thought disorder. The ASC consists of three scales. The first scale, "Oceanic Boundlessness" (OB), measures derealization and depersonalization that are associated with positive basic mood ranging from heightened feelings to exaltation and alterations in the sense of time. The corresponding item clusters are "derealization", "depersonalization", "alterations of the sense of time", "positive basic mood" and "mania-like experience". The second scale, "Anxious Ego Dissolution" (AED), 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", "frightening derealization", and "delusion". The third scale, "Visionary Restructuralization" (VR), includes the item clusters "visual (pseudo)-hallucinations or visions", "synesthesia", "changed meaning of percepts", "facilitated recollection", and "facilitated imagination".

## STATISTICAL ANALYSIS

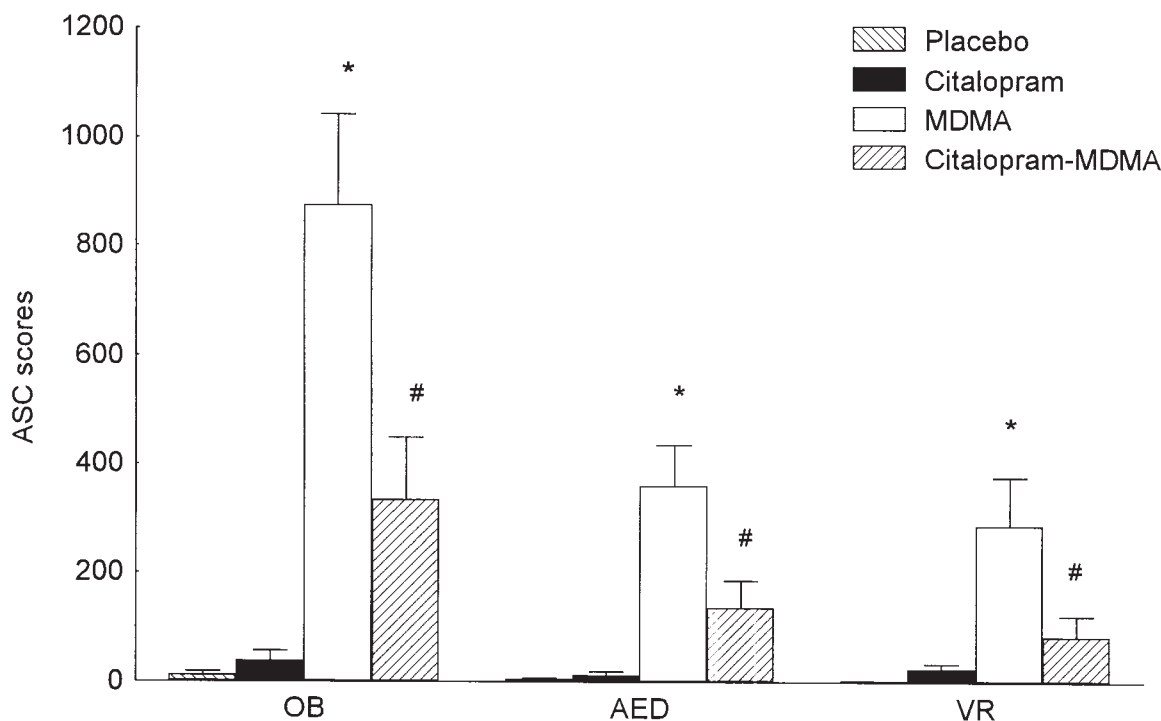
All data were analyzed with STATISTICA/w<sup>TM</sup> (StatSoft<sup>TM</sup>). Before using parametric tests, all data were checked for normal distribution by the Kolmogorov-Smirnov Test. The effect of MDMA on the scales of the ASC was assessed by MANOVA with placebo and MDMA as within-subject factors. To confirm a specific inhibiting effect of citalopram pretreatment on the

MDMA-induced psychological changes, we used two-way ANOVA with pretreatment (placebo vs citalopram) and treatment (placebo vs MDMA) as within-subject factors (repeated measures). Tukey's *post hoc* tests were done to compare changes in subscores. AM scores were assessed using nonparametric Wilcoxon matched pairs tests due to the small number of items in the different scales with discrete and non-normally distributed data. The criterion for significance was set at  $p < .05$ .

## RESULTS

MDMA (1.5 mg/kg) predominantly produced an affective state of positive mood, moderate derealization, heightened sensory awareness, and a slight increase in psychomotor drive. The subjective effect of MDMA began 20 to 120 min after drug intake (mean 45 min), reached its peak 15 to 30 min later and lasted for a mean duration of 3 hours. After pretreatment with citalopram the effect of MDMA was markedly reduced but interestingly prolonged to a mean duration of 5 hours.

As seen in Figure 1, MDMA markedly elevated scores of the three scales of the Altered States of Consciousness Rating Scale (ASC) compared to placebo [Rao R(3,12) = 7.25;  $p < .005$ ; OB ( $p < .0004$ ), AED ( $p < .0005$ ), VR ( $p < .007$ )]. Scores for the different item clusters of the ASC scale are presented in Table 1. The increase in OB scores was due to prominent increases in "positive basic mood" ( $p < .0002$ ), "derealization" ( $p < .0002$ ), and "alterations of the sense of time" ( $p < .0005$ ). Scores for "mania-like experience" ( $p < .0002$ ) and "depersonalization" ( $p < .0002$ ) were moderately elevated. The increase in AED scores was due to moderate "thought disorder" ( $p < .0001$ ), slight "frightening derealization" ( $p < .01$ ), and slight "loss of thought control" ( $p < .002$ ) and "loss of body control" ( $p < .0002$ ). The VR scale showed a marked increase in scores for "changed meaning of percepts" ( $p < .0002$ ), moderate elevation of "facilitated recollection" ( $p < .002$ ) and "facilitated imagination" ( $p < .002$ ), and slightly higher scores for "synesthesia" ( $p < .01$ ). Two-way ANOVAs for all three scales of the ASC revealed significant pretreatment-by-treatment interactions: OB [F(1,15) = 22.47;  $p < .0003$ ], AED [F(1,15) = 23.04;  $p < .0002$ ], VR [F(1,15) = 12.80;  $p < .027$ ], confirming that citalopram pretreatment significantly reduced the psychological effects of MDMA (Figure 1). Citalopram pretreatment attenuated MDMA-induced scores in all item clusters (Table 1). Significant and marked decreases were found for: "positive mood" ( $p < .0003$ ), "mania-like experience" ( $p < .0003$ ), "derealization", "depersonalization" ( $p < .007$ ), "alterations of the sense of time" ( $p < .03$ ), "thought disorder" ( $p < .0003$ ), "loss of thought-control" ( $p < .01$ ), "loss of body control" ( $p < .006$ ), "changed



**Figure 1.** Mean and SE scores of the Altered States of Consciousness Rating Scale (ASC),  $n = 16$ . Levels of OB (oceanic boundlessness), AED (anxious ego-dissolution), and VR (visionary restructuralization) during the peak effects of placebo, citalopram (40 mg iv), MDMA (1.5 mg/kg po), and citalopram-MDMA. MDMA increased scores in all scales as indicated by \* ( $p < .05$ ). Citalopram pretreatment reduced MDMA-induced increases in all scales as indicated by # ( $p < .05$ ).

meaning of percepts" ( $p < .0002$ ), and "facilitated imagination" ( $p < .01$ ). The reduction in scores for "frightening derealization" did not reach significance ( $p < .06$ ).

As seen in Figure 2 A and B, MDMA significantly increased the AM mood scores for "heightened mood" ( $p < .03$ ), "self-confidence" ( $p < .02$ ), "extroversion" ( $p < .01$ ), and "introversion" ( $p < .05$ ), as well as "emotional excitability" ( $p < .01$ ), "sensitivity" ( $p < .03$ ) and "thoughtfulness-contemplativeness" ( $p < .002$ ). "Tiredness" ( $p < .05$ ) was reduced by MDMA compared to placebo, whereas there was an increase in "dazed state" ( $p < .02$ ). MDMA did not produce any change in scores for "aggression-anger", "apprehension-anxiety", or "depressiveness". Also "efficiency-activation" was not increased compared to placebo although subjects showed a moderate increase in psychomotor drive. Citalopram pretreatment significantly reduced the MDMA-induced increases in "self-confidence" ( $p < .04$ ) and "extroversion" ( $p < .01$ ) to levels comparable to citalopram alone (Figure 2 A and B). The reduction in "heightened mood" did not reach statistical significance ( $p = .06$ ). The "efficiency-activation" score under MDMA was also significantly reduced by citalopram ( $p < .03$ ). Most other scores changed by MDMA displayed a tendency to be reversed by citalopram. In contrast, the increase in "emo-

tional excitability" and "sensitivity" induced by MDMA were not attenuated by citalopram at all.

## DISCUSSION

MDMA (1.5 mg/kg) produced a state of enhanced mood characterized by feelings of happiness, euphoria, and in some subjects mania-like experience, as well as increased self-confidence and extroversion. Moderate derealization, depersonalization, and thought disorder occurred without anxiety or panic reactions. Thought disorder included accelerated thinking, thought blocking and impaired decision making, but there was no evidence of delusional thinking. MDMA did not produce hallucinations but did elicit an intensification of visual, tactile, and acoustic perception as well as changes in the meaning of the surroundings. There was only a slight increase in psychomotor drive. In combination with other reports (Gouzoulis-Mayfrank et al. 1999; Nichols 1986; Vollenweider et al. 1998a), the present results support the classification of MDMA as an "entactogen", differentiating it from classical stimulants and hallucinogens.

**Table 1.** Percent Scores for Item Clusters of the ASC Rating Scale

|                                  | Placebo | Citalopram | MDMA              |     | Citalopram-MDMA   |     |
|----------------------------------|---------|------------|-------------------|-----|-------------------|-----|
|                                  | Mean %  | Mean %     | Mean %            | SE  | Mean %            | SE  |
| Derealization                    | 0.4     | 1.3        | 32.7 <sup>a</sup> | 7.0 | 12.6 <sup>b</sup> | 5.0 |
| Depersonalization                | 0.0     | 1.2        | 24.5 <sup>a</sup> | 6.7 | 10.5 <sup>b</sup> | 4.0 |
| Alterations of the sense of time | 0.8     | 1.8        | 30.9 <sup>a</sup> | 7.6 | 13.1 <sup>b</sup> | 5.2 |
| Positive basic mood              | 0.6     | 2.3        | 40.1 <sup>a</sup> | 6.6 | 16.4 <sup>b</sup> | 5.3 |
| Mania-like experience            | 0.3     | 0.4        | 26.6 <sup>a</sup> | 6.2 | 6.7 <sup>b</sup>  | 2.8 |
| Frightening derealization        | 0.0     | 1.1        | 8.5 <sup>a</sup>  | 3.7 | 2.1               | 1.2 |
| Thought disorder                 | 0.0     | 2.2        | 24.8 <sup>a</sup> | 6.0 | 8.6 <sup>b</sup>  | 3.7 |
| Delusion                         | 0.0     | 0.1        | 10.4              | 5.6 | 1.5               | 0.8 |
| Loss of thought control          | 0.0     | 1.2        | 14.1 <sup>a</sup> | 5.6 | 2.8 <sup>b</sup>  | 2.0 |
| Loss of body control             | 0.2     | 1.2        | 11.9 <sup>a</sup> | 3.6 | 5.3 <sup>b</sup>  | 2.3 |
| Hallucinations                   | 0.1     | 0.3        | 9.7               | 3.1 | 3.6               | 1.7 |
| Synesthesia                      | 0.0     | 0.1        | 12.8 <sup>a</sup> | 4.6 | 8.0               | 3.3 |
| Changed meaning of percepts      | 0.6     | 1.7        | 37.3 <sup>a</sup> | 7.2 | 14.1 <sup>b</sup> | 5.5 |
| Facilitated recollection         | 0.0     | 0.6        | 18.4 <sup>a</sup> | 6.2 | 7.6               | 3.9 |
| Facilitated imagination          | 0.7     | 1.4        | 27.2 <sup>a</sup> | 8.7 | 6.6 <sup>b</sup>  | 2.6 |

Scores for the item clusters of the three scales of the Altered States of Consciousness Rating Scale (ASC) are presented in percent of maximal scores for each item cluster and are the mean and SE,  $n = 16$ .

<sup>a</sup>  $p < .05$ , indicates that compared to placebo, MDMA increased scores in most clusters.

<sup>b</sup>  $p < .05$ , indicates that citalopram pretreatment reduced MDMA-induced scores in most clusters.

Abbreviations: OB = oceanic boundlessness; AED = anxious ego-dissolution; VR = visionary restructuralization.

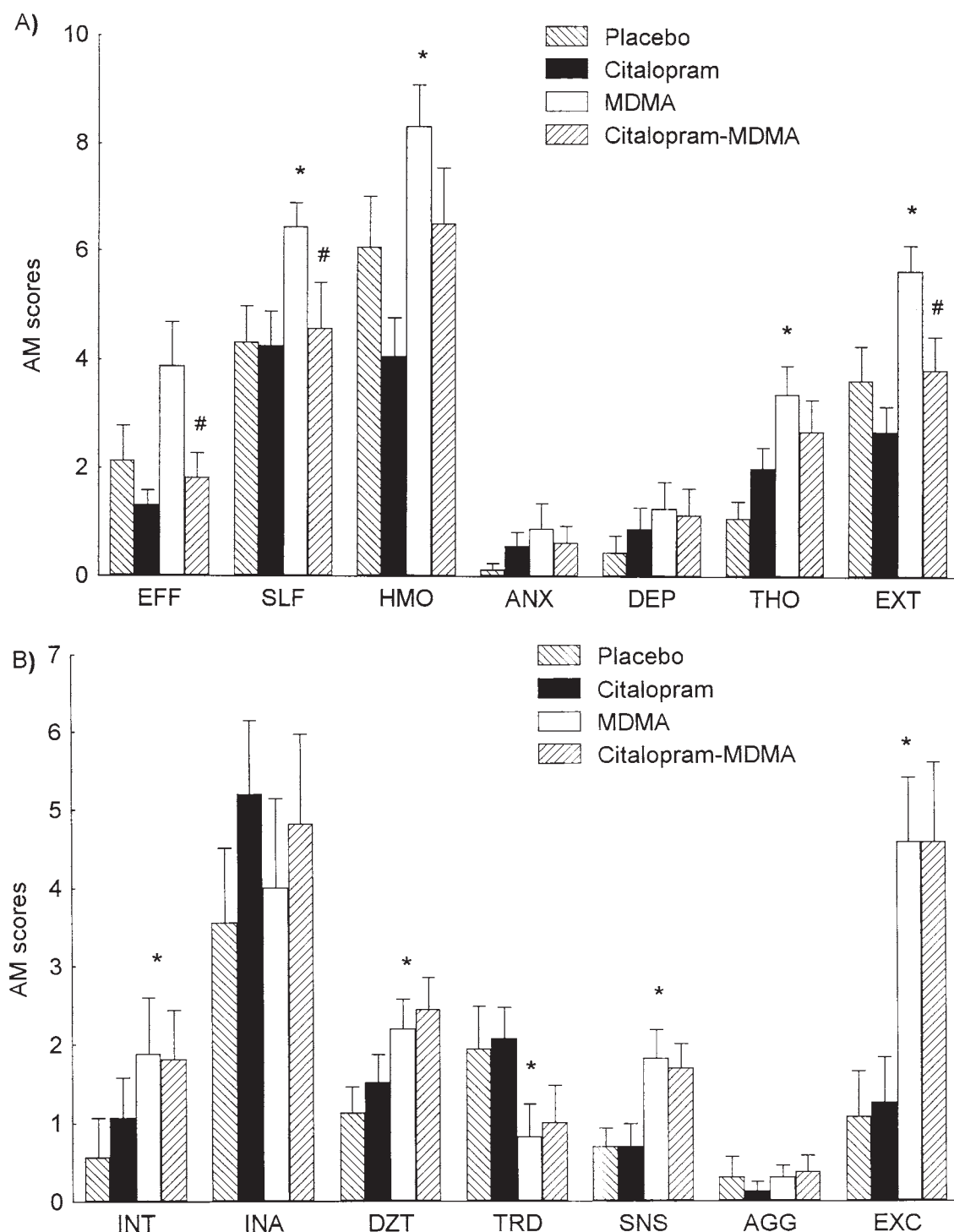
The main result of this study is that the psychoactive effects of 1.5 mg/kg MDMA were substantially attenuated by pretreatment with the SSRI citalopram (40 mg iv). Citalopram inhibited most of the psychological effects of MDMA. MDMA-induced increases in positive mood, derealization and depersonalization phenomena, thought disorder, and the loss of thought and body control were all attenuated by citalopram pretreatment. MDMA-evoked intensification of sensory perception, changes in the meaning of percepts, and subjectively facilitated imagination were also inhibited by citalopram as compared to MDMA alone. Citalopram alone also lowered scores on some scales compared to placebo. Most of these changes, however, were clearly due to side effects of citalopram such as fatigue, headache, and nausea, which influenced the mood rating. MDMA also produced marked increases in emotional excitability and sensitivity that, however, were not reduced by citalopram.

To our knowledge, this is the first controlled study in humans investigating the potential inhibition of psychological MDMA effects by a selective serotonin uptake inhibitor. McCann and Ricaurte published a case series of four Ecstasy users, three of whom reported no appreciable change in subjective experience when fluoxetine was taken before Ecstasy (McCann and Ricaurte 1993). A possible explanation for the discrepancy between that finding and our results may be due to the fact that we used a high dose of citalopram, 40 mg iv, compared to 20 mg fluoxetine orally. At the same time our dose range of MDMA was 80 to 120 mg, compared

to an estimated dose of 100 to 250 mg in the report of McCann and Ricaurte. In addition, one of the subjects from this series viewed fluoxetine as a "buffer" for the effect of Ecstasy, which indicates a reducing effect similar to our findings. Finally, these retrospective reports are limited given their uncontrolled nature, the small sample size, and the lack of drug identification.

The overall attenuation of the psychological profile of MDMA by citalopram in our study is in agreement with a large number of preclinical investigations suggesting that MDMA primarily produces a carrier-mediated 5-HT release. MDMA releases 5-HT *in vitro* from synaptosomes (Berger et al. 1992; Hekmatpanah and Peroutka 1990; McKenna et al. 1991; Nichols et al. 1982) and from cultured neurons (Gu and Azmitia 1993), as well as *in vivo* (Brodin et al. 1993; Schmidt 1987). MDMA-induced 5-HT release is blocked by different 5-HT uptake inhibitors *in vitro* (Gu and Azmitia 1993; Hekmatpanah and Peroutka 1990) and *in vivo* as demonstrated by microdialysis (Gudelsky and Nash 1996; Koch and Galloway 1997). Moreover, MDMA has been shown to inhibit [<sup>3</sup>H] serotonin transport into vesicles and to inhibit competitively the binding of [<sup>3</sup>H] imipramine to platelet membrane vesicles containing the imipramine-sensitive serotonin carrier (Rudnick and Wall 1992). These results 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 carrier (Rudnick and Wall 1992).

Non-specific untoward effects of citalopram such as nausea in some subjects (6/16) might have reduced



**Figure 2A & B.** Mean and SE scores of the Adjective Mood Rating Scale (AM),  $n = 16$ . Significant changes induced by MDMA compared to placebo are indicated by \* ( $p < .05$ ). Citalopram pretreatment reduced MDMA-induced changes in most scales. Significant reductions are indicated by # ( $p < .05$ ). EFF = efficiency-activation, SLF = self-confidence, HMO = heightened mood, ANX = apprehension-anxiety, DEP = depressiveness, THO = thoughtfulness-contemplativeness, EXT = extroversion, INT = introversion, INA = inactivation, DZT = dazed state, TRD = tiredness, SNS = sensitivity, AGG = aggression-anger, EXC = emotional excitability.

some of the pleasurable MDMA effects but are unlikely to explain the reduction of the different psychological MDMA-effects seen in all subjects in this study. Furthermore, in the same subjects, citalopram also signifi-

cantly reduced cardiovascular responses to MDMA and its effect on sensorimotor gating, but had no effect when given alone (Liechti ME, Vollenweider FX (2000) The serotonin uptake inhibitor citalopram reduces

acute cardiovascular and vegetative effects of MDMA (Ecstasy) in healthy volunteers, submitted) (Liechti ME, Geyer MA, Hell D, Vollenweider FX (2000) Effects of MDMA (Ecstasy) on prepulse inhibition and habituation of startle in humans after pretreatment with citalopram, haloperidol, or kertsanserin, submitted). Therefore, the fact that we could partially block the psychological effects of MDMA with citalopram seems to indicate a specific interaction of citalopram and MDMA at the 5-HT uptake site. Citalopram is presently the most selective SSRI available. It competitively binds to the 5-HT uptake site with high affinity ( $K_i = 0.7 - 1.8$  nM) and exhibits very low affinity for other receptors (Hyttel et al. 1995; Milne and Goa 1991). We can assume that citalopram either prevented the interaction of MDMA with the 5-HT uptake site or, alternatively, blocked the efflux of 5-HT through the carrier. However, citalopram only attenuated the effects of MDMA by about 60% in this study. This finding does not appear to be due to an insufficient dose because we gave 40 mg citalopram to all subjects regardless of their body weight and found no correlation between the dose of citalopram per kg and its inhibiting effect on the MDMA experience. Second, in a pilot study, doses of 60 and 80 mg citalopram were administered prior to MDMA in two candidates and both doses blocked the psychological effects of MDMA to a degree comparable to 40 mg. Therefore, we conclude that citalopram blocked only part of the MDMA effect, suggesting that MDMA has actions in addition to its effects at the 5-HT uptake site. Based on preclinical evidence several other mechanisms of action should be taken into account.

The pharmacological profile of MDMA demonstrates a broad range of affinities for various brain recognition sites (Battaglia and De Souza 1989). MDMA has highest affinity for the 5-HT uptake site ( $<1\mu\text{M}$ ) with lower but comparable affinities at 5-HT<sub>2</sub>,  $\alpha_2$ -adrennergic, M<sub>1</sub> cholinergic and H<sub>1</sub> histamine receptors ( $K_i$  values  $< 6\mu\text{M}$ ) (Battaglia et al. 1988). S(+) and R(-) MDMA both possess activity at 5-HT<sub>2C</sub> receptors and R(-) MDMA also at 5-HT<sub>2A</sub> receptors (Nash et al. 1994). First 5-HT<sub>2A</sub> receptor stimulation has been implicated in the psychological and particularly in the visual effects of indole hallucinogens (Sanders-Bush and Conn 1987; Vollenweider et al. 1998b). Therefore, part of the effects of MDMA on perception, such as the intensification of colors, might be mediated by direct activation of these receptors. In addition, 5-HT<sub>2C</sub> receptors are involved in mediating some of the effect of the serotonin releaser fenfluramine, another amphetamine derivative (McCann et al. 1996). Second, MDMA has been shown to induce the release of striatal DA (Schmidt et al. 1987; Yamamoto and Spanos 1988). This release is probably due in part to a direct interaction of MDMA with the DA-carrier (Koch and Galloway 1997; Nash and Brodtkin 1991; Schmidt et al. 1987), but there is also evidence

that the concomitant MDMA-induced release of 5-HT amplifies DA release through activation of postsynaptic 5-HT<sub>2</sub> receptors (Gudelsky and Nash 1996; Koch and Galloway 1997; Nash 1990; Schmidt et al. 1992; Schmidt et al. 1994; Yamamoto et al. 1995). If these mechanisms extend to humans, then citalopram in our study would be expected to block this amplification by preventing 5-HT release, while having no effect on MDMA-induced carrier-mediated DA release and its psychological manifestations. Third, MDMA has considerable affinity for the norepinephrine (NE) uptake site. Indeed, its potency at the NE uptake site is comparable to that at the 5-HT uptake site (Steele et al. 1987) and MDMA has been shown to induce NE release from hippocampal slices (Fitzgerald and Reid 1990). Moreover, MDMA produced EEG frequency band changes very similar to the NE uptake inhibitor tandamine (Frei E, Gamma A, Vollenweider FX (2000) Localization of MDMA-induced electric brain activity in healthy volunteers using Low Resolution Brain Electromagnetic Tomography (LORETA), submitted). In the present study elevated "emotional excitability" produced by MDMA might be a manifestation of MDMA-induced DA or NE release since it was not prevented by citalopram pretreatment. In sum, several receptors and biological interactions may be involved in mediating the unique psychological profile of MDMA. Hence considerably more research is needed to clarify the mechanisms and sites of action of MDMA in humans.

Another interesting finding is that in this study citalopram attenuated the acute psychological effects of MDMA, but at the same time prolonged them by up to two hours compared to MDMA alone. This finding might be explained by a metabolic interaction, since citalopram and MDMA are both substrates of the cytochrome P450 (CYP) isoenzymes in the liver (Hegadoren et al. 1999). Citalopram is an inhibitor of CYP2D6 (Baumann 1996), which is involved in the metabolism of MDMA (Tucker et al. 1994). Citalopram could have prolonged the presence of MDMA in the blood, thereby delaying subjective effects. This argument is weakened, however, by the report that doses of 1.5 mg/kg MDMA produced peak blood levels of 330 ng/ml after 120 min and levels of 150 ng/ml lasting over nine hours (Helmelin et al. 1996). Thus, effective plasma levels of MDMA appear to outlast its psychological effects. Therefore, citalopram might also simply delay the release of 5-HT by competition with MDMA at the uptake site. In addition, there is also recent evidence that citalopram interacts with psychostimulants at the level of 5-HT transporter phosphorylation and sequestration (Ramamoorthy and Blakely 1999) that regulate 5-HT transporter capacity.

In conclusion, the present double-blind placebo-controlled study demonstrated that pretreatment with the SSRI citalopram attenuated the acute psychological effects of MDMA in healthy humans by about 60 percent.

This finding suggests that the psychoactive properties of MDMA are largely dependent on an action at the 5-HT uptake site, a finding in line with preclinical evidence. However, 5-HT release is only one of the actions of MDMA and the involvement of postsynaptic sites such as 5-HT and DA receptors in mediating the psychological effects of MDMA remain unclear. Further investigations in humans using specific receptor ligands are necessary especially to assess the contribution of postsynaptic 5-HT<sub>2</sub>, DA and NE receptors in the mediation of MDMA effects. Finally, our findings suggest that human studies with MDMA and specific receptor ligands are useful to elucidate the neurochemical mechanisms underlying the serotonergic regulation of mood and its role in affective disorders.

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