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ORIGINAL INVESTIGATION

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Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans

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Abstract *Rationale*: Prepulse inhibition of acoustic startle refers to the reduction in the startle response when the startling stimulus is preceded by a weak prepulse stimulus. This phenomenon provides an operational measure of sensorimotor gating that has been found to be reduced in patients with schizophrenia and rats treated with serotonin agonists or serotonin releasers. *Objective*: In this study, we compared the effects of a serotonin releaser, MDMA, on prepulse inhibition in laboratory rats and healthy human volunteers. In particular, we investigated whether MDMA disrupts PPI in humans as observed in animal studies. *Methods*: Rats were tested after placebo and MDMA in a counterbalanced order at an interval of 1 week, with separate groups of rats being used for each dose of MDMA (1.7, 5.4 and 17.0 mg/kg). On each test day, rats were first tested after no injections and retested 2 h later, 10 min after a subcutaneous injection of placebo or MDMA. For the human study, a placebo-controlled within-subject design and double-blind procedures were used. Subjects were examined twice at a 2 to 4 week interval after either placebo or drug administration (order being counterbalanced). On each test day, subjects underwent baseline testing including psychological and PPI measures. Ninety minutes later, subjects received placebo or MDMA (1.7 mg/kg PO) and were retested after 75 min during the peak of behavioral effects of MDMA. *Results*: As expected, MDMA decreased prepulse inhibition in a dose-related fashion in rats. In contrast, a typical recreational dose of MDMA (1.7 mg/kg, orally) increased prepulse inhibition in subjects experiencing robust psychological effects. *Conclusions*: This surprising disparity between the effects of the drug in rats and humans may reflect a species-specific difference in the mechanism of action of MDMA or in the behavioral expression of a similar pharmacological effect, or both.

Key words MDMA (3,4-methylenedioxymethamphetamine) · Serotonin · Psychopathology · Human · Rat · Prepulse inhibition · Habituation · Schizophrenia

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Introduction

The startle response is a constellation of reflex responses to a sudden intense stimulus that has been used to study homologous forms of behavioral plasticity across species. In humans, the blink reflex component of startle is measured using electromyography. In rodents, a stabilimeter is used to measure the whole-body flinch response. Prepulse inhibition (PPI) and habituation are two forms of behavioral plasticity that are studied using startle measures. PPI is the unlearned suppression of startle when the startling stimulus is preceded by a weaker prestimulus by 30–500 ms; it is not a form of conditioning and does not exhibit habituation or extinction over multiple trials. Habituation refers to the decrement in responding when the same stimulus is presented repeatedly in the absence of any contingencies and has been considered to be the simplest form of learning. PPI and startle habituation have been used as operational measures of sensorimotor gating and habituation functions, respectively, in both human and animal explorations of attentional deficits characteristic of patients with schizophrenia, Obsessive compulsive disorder (OCD), and Huntington's disease (Braff et al. 1978, 1992; Geyer and Braff 1982; Braff and Geyer 1990; Grillon et al 1992; Swerdlow et al. 1993, 1995).

Multiple neural systems have been shown to be involved in modulating PPI in rodents (Geyer et al. 1990; Swerdlow et al. 1992). For example, PPI can be disrupted by manipulations of dopaminergic systems in the nucleus accumbens, cholinergic systems in the hippocampus, and both GABAergic and serotonergic systems in the ventral pallidum (Swerdlow et al. 1992; Sipes and Geyer 1997). Converging evidence implicates central serotonergic systems in the modulation of PPI. For example, serotonin (5-HT) releasing compounds, such as 3,4-methylenedioxy-*N*-methylamphetamine (MDMA or "ecstasy"), *N*-ethyl-3,4-methylenedioxy-amphetamine (MDE or "Eve"), and alpha-ethyltryptamine (AET or "love pearls") reduce PPI in rats or mice (Mansbach et al. 1989; Dulawa and Geyer 1996; Martinez and Geyer 1997). Furthermore, direct agonists acting at multiple 5-HT receptors, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_2 subtypes, reduce PPI in rats or guinea pigs (Rigdon and Weatherspoon 1992; Sipes and Geyer 1994, 1995, 1996; Padich et al. 1996). The PPI-disruptive effects of hallucinogenic 5-HT_2 agonists (Sipes and Geyer 1994; Padich et al. 1996) appear to be mediated via actions at 5-HT_{2A} receptors within the ventral pallidum (Sipes and Geyer 1997). Similar lines of investigation in rats have demonstrated that both 5-HT releasers and 5-H_{T2} agonists consistently impair the habituation of tactile startle elicited by airpuff stimuli, but have less consistent effects on the habituation of acoustic startle (Geyer et al. 1978; Geyer and Tapson 1988; Kehne et al. 1992; Martinez and Geyer 1997). Much of the impetus for these animal studies of startle plasticity has derived from the fact that both PPI and habituation of startle have been found to be deficient in symptomatic, though medicated, patients with schizophrenia (Geyer and Braff 1982; Braff et al. 1982; Bolino et al. 1992, 1994) and in non-medicated patients with schizotypal personality disorder (Cadenhead et al. 1993).

The present studies compared the effects of a 5-HT releaser, MDMA, on PPI and habituation of acoustic startle in normal laboratory rats versus healthy human volunteers. To maximize the comparability of doses between species, the rat study examined an order of magnitude dose-range beginning at the same dose used in humans. To the extent possible, identical test parameters and procedures were used in both human and rat studies. Based on previous studies in rats and mice, the hypothesis was that MDMA would disrupt PPI in both rats and humans.

Materials and methods

Study design

In rats, a mixed design was used, with drug dose as a between-subject factor and placebo versus drug being a repeated measure. Thus, each rat was tested after placebo and drug in a counterbalanced order at an interval of 1 week, with separate groups of rats being used for each dose of MDMA. Based on previous studies of both locomotor activity and PPI , three doses of MDMA were tested in rats: 1.7 (n = 10); 5.4 (n = 9); and 17.0 mg/kg (n = 11). On each test day, rats were first tested after no injections and retested 2 h later, 10 min after a subcutaneous injection of placebo or MDMA when robust effects of MDMA on both locomotor and startle behaviors have been observed in rats (Kehne et al. 1992; Geyer and Callaway 1994). For the human study, a placebo-controlled within-subject design and double-blind procedures were used. Subjects were examined twice at a 2 to 4-week interval after either a placebo or drug administration (order being counterbalanced). On each test day, subjects were also tested in a baseline session. Human subjects received 1.7 mg/kg MDMA orally, a typical dose taken for recreational use (Greer and Tolbert 1986). Upon arriving at the hospital (noon), fasting subjects were examined using the rating scales described below and the baseline startle session was administered. Placebo or MDMA was then given orally in capsules (1330 hours). The rating scale and PPI measures were repeated 75 min later, to coincide with the peak effects of MDMA (Helmlin et al. 1996).

Animal subjects

Rat studies were conducted in San Diego, Calif., USA and used 30 male Sprague-Dawley rats (275–300 g, Harlan, San Diego, Calif., USA), housed in pairs on a reversed 12/12 h light/dark cycle (lights off 0700–1900 hours), with food and water provided ad libitum. Testing occurred between 0900 and 1500 hours because rats are nocturnal. Rats were handled within 3 days of arrival and daily thereafter.

Human subjects

The study was approved by the Ethics Committee of the Psychiatric University Hospital Zürich (PUK); the use of MDMA was approved by the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Bern. All subjects were examined at the Research Department of the PUK. Ten male and three female healthy volunteers (age: 23–47 years) were recruited from university and hospital staff. Written consent was obtained. The subjects were screened by psychiatric interview to exclude those with personal or family (first-degree relatives) histories of major psychiatric disorders or a history of illicit drug abuse. Subjects were healthy according to physical examination, electrocardiogram, blood, and urine analysis.

Drugs

For rat studies, racemic MDMA was obtained from the National Institute on Drug Abuse with approval from the US Drug Enforcement Agency and the State of California Research Advisory Panel. MDMA was dissolved in saline vehicle and injected subcutaneously (1 ml/kg). For human studies, racemic MDMA was obtained through the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Bern, from EPROVA AG, Schaffhausen, and prepared as capsules (10 and 50 mg) at the Pharmaceutical Institute of the University of Bern, Switzerland.

Acoustic startle

Animal apparatus

Each of the four startle chambers (SR-LAB, San Diego Instruments, San Diego, Calf., USA) consisted of a Plexiglas cylinder 8.2 cm in

diameter, resting on a Plexiglas frame in a sound-attenuated, ventilated enclosure. Acoustic noise bursts were presented via a loudspeaker mounted 24 cm above the rat. A piezoelectric accelerometer mounted below the frame detects and transduces the motion of the cylinder produced by the whole-body startle response of the rat. Stabilimeter readings were rectified and recorded by a microcomputer and interface ensemble, with 100, 1-ms readings collected beginning at stimulus onset. Startle amplitude was defined as the average of the 100 readings.

Human apparatus

In humans, the eyeblink component of the acoustic startle response was measured using electromyographic recordings (EMG-SR, San Diego Instruments) of the orbicularis occuli muscle. Two silver/silver chloride electrodes were placed below and to the right of the subjects' right eye, as described by Braff et al. (1992). A ground electrode was placed on the mastoid behind the right ear. Startle stimuli were presented binaurally through Maico headphones (Model TDH-39-P), while subjects lay in a reclined position with eyes directed upwards. Amplifier settings (low cutoff: 100 Hz; high cutoff: 1 kHz) ensured that eye movements other than blinking were excluded. Electrode impedance was below 3 h Ω for all subjects.

PPI test session

For both rats and humans, each test session started with a 5-min acclimation period consisting of background broad-band noise at 70 dB[A] SPL (which continued throughout the session), followed by 52 startle trials consisting of three conditions: (1) a 115-dB[A], 40-ms noise burst presented alone; (2) this same burst preceded by a 20-ms duration prepulse either 30 or 120 ms before either 8 or 16 dB[A] above background noise, yielding four types of prepulse trials (30_8, 30_16, 120_8, 120_16); and (3) no-stimulus trials. The first and last blocks of trials consisted of five pulse-alone trials each and were not used in the calculation of PPI. Between these blocks were 42 mixed trials presented in a pseudorandom order: 12 pulse-alone trials; 24 prepulse trials (six of each type); and six no-stimulus trials. Because no consistent effects were observed on no-stimulus trials, these data are not shown. Intertrial intervals ranged from 4 to 22 s, averaging 13 s. The entire test session took about 15 min.

Psychometric scales

The Adjective Mood Rating Scale (AM) and the Altered State of Consciousness (ASC) rating scale, a visual-analog scale and slightly modified version of the original ASC rating scale (66 instead of 72 items), were used to assess drug effects under placebo and drug conditions (Dittrich 1994, 1996). The AM mood rating consists of six scales (factors) measuring efficiency, inactivation, extroversion-introversion, feelings of well-being, emotional excitability, and anxiety. The well-being scale yields the two subscale scores "self-confidence" and "heightened mood". The anxiety scale consists of the three subscales "thoughtfulness-contemplativeness", "apprehension-anxiety", and "dejection" (Janke and Debus 1978).

The ASC rating scale yields three dimensions (factors) comprised of several item clusters. The first subscale, OB ("oceanic boundlessness"), measures derealization and depersonalisation phenomena associated with a positive basic mood ranging from heightened feelings to sublime happiness, and alterations in the sense of time and space. The second subscale, VR ("visionary restructuralization"), assesses illusions, (pseudo-) hallucinations, synaesthetic phenomena, as well as changes in the meaning and interpretation of various percepts. The third subscale DE ("dread of ego-dissolution"), measures thought disorder, anxious ego-disintegration, loss of control over body and thought, and derealization phenomena associated with arousal and anxiety. The ASC dimensions OB, VR and DE have been shown to be altered consistently in a manner that is independent of the particular treatment, disorder, or condition that led to the altered state of consciousness (Dittrich et al. 1981; Dittrich 1994).

Statistical analysis

Variables used in the analyses were the startle magnitude (pulse alone), percent prepulse inhibition (%PPI), and percent habituation. The %PPI was calculated for each prepulse condition (30_8, 30_16, 120_8, 120_16) as the reduction in startle magnitude in the presence of the prepulse compared to the magnitude in the absence of the prepulse: %PPI = [pulse alone − (prepulse + pulse trials)/ pulse alone] × 100. The percent habituation was calculated as the reduction in startle magnitude between the first and last blocks of pulse-alone trials: %HAB = [(first block magnitude – last block magnitude)/ first block magnitude] × 100. Absolute difference scores for both PPI and habituation were also analyzed and yielded very similar results (data not shown). For the data from rats, initial overall analyses with order of treatment and dose of MDMA being between-subjects factors, placebo versus drug as a within-subject factor, and with or without the baseline data as covariates, confirmed the absence of order interactions and the presence of treatment effects (data not presented). For the sake of brevity and to maximize the comparability between the analyses of rat and human data, the different doses of MDMA were then analyzed separately. The effects of MDMA on startle reactivity were analyzed with two-way ANOVAs with treatment (each dose of MDMA versus the respective placebo) and block as repeated measures. The effects of MDMA on percent or absolute PPI were analyzed with two-way ANOVAs with treatment and prepulse condition as repeated measures. The effects of each dose of MDMA on percent or absolute habituation were analyzed with one-way ANOVAs with treatment as a repeated measure. The startle data from humans were analyzed using similar designs, after confirming the absence of order effects or interactions. The effects of MDMA on psychological measures (ASC and AM dimensions) were analyzed by two-way ANOVAs with treatment (MDMA versus placebo) and psychological dimensions as repeated measures factors. The Greenhouse-Geisser adjustment was applied to correct for the multiple levels of the repeated measure factor. Based on significant main effects or interactions, post-hoc comparisons were done using either ANOVA or Tukey's tests as appropriate. Analyses of the rat data were performed using BMDP ; the human data were analyzed using STATISTICA/w, version 5.1 (Statsoft 1995).

Results

Effects of MDMA on startle in rats

The data regarding startle reactivity (pulse-alone magnitude) and percent habituation for placebo and the three different doses of MDMA tested in rats are summarized in Table 1. The 5-HT releaser MDMA had no significant effects on startle reactivity at 1.7 or 17.0 mg/kg, but significantly reduced reactivity in the first block of trials at 5.4 mg/kg [treatment by block interaction $F(2,16) = 5.34$; $P < 0.02$]. There were no significant differences in percent habituation scores after any dose of MDMA. In keeping with previous reports of disruptions in PPI by 5-HT releasers in rodents, MDMA significantly reduced %PPI at

Table 1 Startle reactivity and habituation for: *A* rats receiving systemic 0.9% saline, 1.7 mg/kg, 5.4 mg/kg, or 10 mg/kg MDMA; and *B* humans receiving placebo or 1.7 mg/kg MDMA. In rats, the middle dose of MDMA significantly decreased startle reactivity in the first block. In humans, MDMA increased startle reactivity about 20–30% with a significant increase in the middle block (32.2%). MDMA had no significant effect on percent habituation in either rats or humans. An *asterisk* (*) indicates a statistically significant difference in startle magnitude relative to the startle magnitude of the same MDMA-treated rats or humans as revealed by post hoc analyses

	Test session	Startle magnitude			Habitution
		Block #1	Block #2	Block #3	% Decrease
		Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
A Rats dose					
1.7 mg/kg	Placebo	862.0 ± 130	429.6 ± 69.2	312.0 ± 39.5	55.2 ± 7.3
(n = 10)	Drug	716.6 ± 110	426.5 ± 75.2	408.6 ± 98.4	35.9 ± 12.5
5.4 mg/kg	Placebo	749.8 ± 180	418.8 ± 82.0	374.9 ± 78.4	42.6 ± 11.2
(n = 9)	Drug	398.2 ± 65*	278.6 ± 45.7	285.5 ± 50.2	22.5 ± 11.3
17.0 mg/kg	Placebo	679.4 ± 112	385.7 ± 60.5	442.1 ± 98.4	32.0 ± 9.5
(n = 11)	Drug	711.1 ± 58	508.1 ± 46.2	397.8 ± 43.2	41.9 ± 5.9
B Humans dose					
1.7 mg/kg	Placebo	112.2 ± 16.5	82.2 ± 14.7	73.0 ± 14.9	37.9 ± 7.7
(n = 13)	Drug	127.4 ± 16.4	100.8 ± 15.9*	88.2 ± 17.6	37.4 ± 6.8

5.4 mg/kg [$F(1,8) = 9.89$; $P < 0.02$] and 17.0 mg/kg [$F(1,10) = 13.46$; $P < 0.005$]. With 17.0 mg/kg MDMA, a significant interaction between treatment and prepulse condition was also observed [$F(3,30)] = 10.94$; $P < 0.0001$]. The low dose of MDMA had no effect on %PPI. As indicated in Fig. 1, poshoc analyses indicated that these effects of MDMA were most pronounced when the prepulses were presented 120 ms prior to the pulses. Analyses of absolute difference scores for PPI produced identical results (data not shown).

Effects of MDMA on startle in humans

The startle reactivity and percent habituation data for placebo and MDMA are summarized in Table 1. The 5-HT releaser MDMA increased startle reactivity in all three blocks by about 20–30% [main effect of drug $F(1,12) = 6.69$; $P < 0.024$]. Posthoc analysis revealed a significant increase in the middle block of the session (32.2%). Although robust habituation was observed in both the placebo and MDMA conditions, MDMA had no significant effect on percent or difference score measures of habituation (Table 1).

Surprisingly, MDMA increased %PPI in humans (Fig. 2). A two-way ANOVA revealed main effects of drug [$F(1,12) = 6.12$; $P < 0.03$] and prepulse condition [$F(3,36) = 15.99$; $P < 0.0001$], and a significant interaction of drug × prepulse condition [$F(3,36) = 3.01$; $P < 0.04$]. As seen in Fig. 2, %PPI was increased about 28% in the 120_16 condition. Because the %PPI in the 120_16 condition was lower than in the 120_8 condition in the placebo condition, we also analyzed the baseline data (Fig. 2). A $2 \times 2 \times 4$ within-subjects ANOVA (day, drug, and prepulse condition) yielded a significant triple interaction [$F(3,36) = 4.98$; $P < 0.005$]. Tukey's HSD comparisons confirmed that the PPI induced by 120_16 after MDMA was significantly greater than that after placebo or either of the two baseline tests. Identical results were obtained using difference score measures of PPI.

Effects of MDMA on psychological measures in humans

As previously reported in detail, MDMA produced significant changes in mood, small-to-moderate derealization phenomena, and stimulant-like effects in this experiment. The psychic and stimulant effects of MDMA began about 30 min after MDMA administration, peaked at about 60 min after ingestion, and lasted for 1–2 h. Thus startle testing, which occurred from 90 to 110 min after drug administration, was done during the peak drug effect. Stimulant effects were paralleled by increased heart rate, increased blood pressure, increased alertness, dry mouth, and sometimes jaw clenching (for details see Vollenweider et al. 1998). A repeated measures ANOVA with Greenhouse-Geisser adjustments revealed significant main effects of treatment [$F(1,12) = 25.3$, $P < 0.0001$], AM dimension [$F(2.62,31.4 = 25.6$, $P < 0.0001$], and a significant treatment × AM dimension interaction [$F(2.63,31.5=3.91$, $P < 0.021$]. Post hoc analysis of the treatment × dimension interaction with Tukey's tests revealed that MDMA significantly increased the AM scores for extroversion-introversion, well-being, heightened mood, emotional excitability, and thoughtfulness-contemplativeness, a subscale of the state anxiety scale (Table 2). Subjects also reported feelings of enhanced insightfulness, self-confidence, and closeness to others.

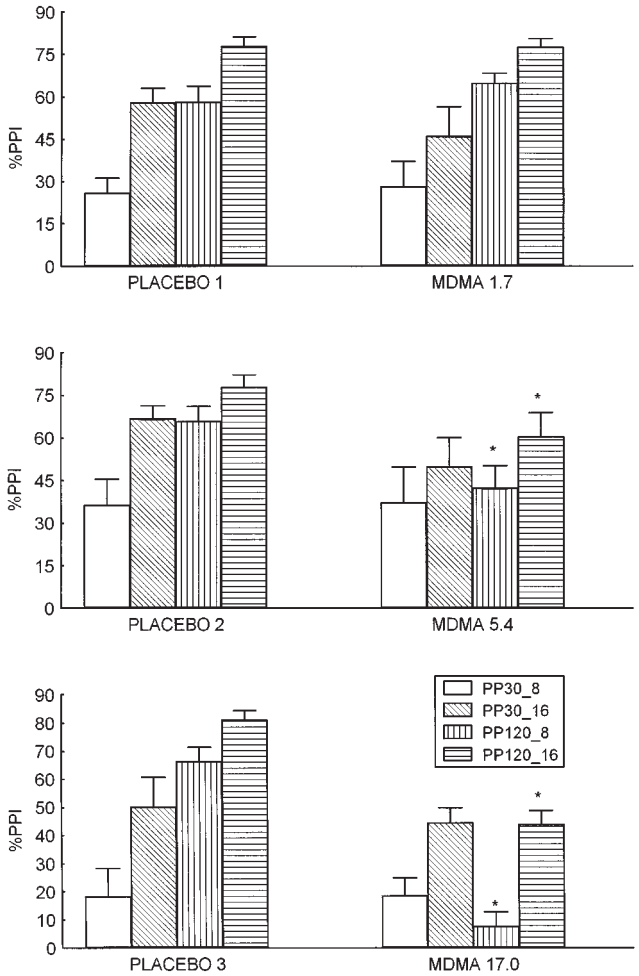

Fig. 1 Prepulse inhibition (*PPI*) disruption in rats. Group means (± SEM) are displayed for percent PPI for the three independent groups of rats tested after administration of either placebo or 1.7 (*top*), 5.4 (*middle*), or 17.0 (*bottom*) mg/kg MDMA. PPI was produced by 8 dB prepulses presented 30 (PP30_8) or 120 (PP120_8) ms before the startle stimulus or 16 dB prepulses presented 30 (PP30_16) or 120 (PP120_16) ms before the startle stimulus. In the *left and right of each panel* are the individual group means for the placebo and the MDMA test sessions, respectively. MDMA disrupted PPI, especially with 120-ms prepulses. The %PPI was calculated for each prepulse condition as the reduction in startle magnitude in the presence of the prepulse compared to the magnitude in the absence of the prepulse: %PPI = [pulse alone – (prepulse + pulse trials)/pulse alone] *100. An *asterisk* (*) indicates a statistically significant difference in %PPI in the MDMA-treated rats relative to the corresponding placebo test of the same rats, as revealed by post hoc analyses

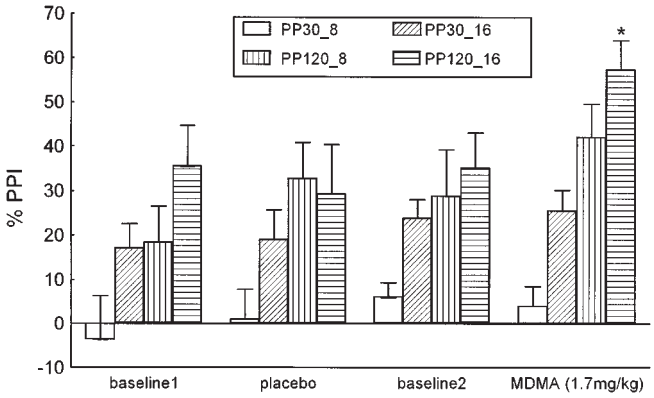

Fig. 2 Prepulse inhibition (PPI) facilitation in humans. Group means (± SEM) are displayed for percent PPI exhibited by healthy humans tested at baseline and after administration of either placebo or 1.7 mg/kg MDMA. Placebo and MDMA were tested in the same subjects in a counterbalanced order on different days. PPI was produced by 8 dB prepulses presented 30 (PP30_8) or 120 (PP120_8) ms before the startle stimulus or 16 dB prepulses presented 30 (PP30_16) or 120 (PP120_16) ms before the startle stimulus. MDMA increased the amount of PPI, especially with 120-ms prepulses. An *asterisk* (*) indicates a statistically significant difference in %PPI after the MDMA treatment relative to any of the other tests of the same subjects, as revealed by post hoc analyses

MDMA also produced small-to-moderate derealization and discrete depersonalisation phenomena as indicated by increased OB, VR, and DE scores (Table 2). A repeated measures ANOVA with Greenhouse-Geisser adjustments for multiple levels of the repeated measure factor yielded significant main effects of treatment [$F(1,12) = 24.6$, $P < 0.0001$], ASC dimension [$F(1.29,15.5 = 28.9$, $P < 0.0001$], and a significant treatment × ASC dimension interaction [$F(1.31,15.7 = 32.9$, $P < 0.0001$]. Post hoc analysis of the treatment × ASC dimension interaction revealed that the increase in OB, VR, and DE was significant. The increase in the OB score was due to a prominent increase in the "positive basic mood" items and moderate increases in the "derealization", "depersonalization", and "alterations in the sense of time and space" item clusters. The increase in the VR score was attributable to "changed meaning of percepts", "illusions", "facilitated recollection", and "imagination" items. None of the subjects reported hallucinations or paranoia. The increase in the DE score was due to the "thought disorder" and "loss of body" control items. Scores for "frightening derealization", "delusion", and "loss of thought control" were not changed by MDMA (for details see Vollenweider et al. 1998).

Discussion

The two major findings of the present experiments were: (1) MDMA decreased PPI of acoustic startle in a dose-related fashion in rats, as expected from previous studies; and (2) a typical recreational dose of MDMA (1.7 mg/kg) increased PPI measured under comparable conditions in humans. The rat and human experiments utilized the same within-subject design and the same parameters for both prepulse and startle stimuli. The multiple doses of MDMA used in rats ranged from the same 1.7 mg/kg dose used in humans to one order of magnitude higher, in keeping with the typical differences in effective doses between these species. This dose range for MDMA has been shown to be effective in rats using a variety of behavioral

Table 2 Psychological peak effects of MDMA (1.7 mg/kg PO) as measured *A* by the mood rating scale AM and *B* by the Altered State of Consciousness Questionnaire ASC (mean ± SE, $n = 13$). Post hoc analysis revealed statistically significant differences in AM and ASC scores in the same human subjects treated with MDMA as indicated by *asterisks*

Rating scales	Placebo		MDMA	
	Mean	SE	Mean	SE
A AM mood rating				
Efficiency	4.1	1.0	6.0	0.9
Inactivation	5.5	1.6	6.4	1.4
Extroversion-introversion	4.5	0.6	7.3**	0.5
Well-being:	11.7	1.4	17.4**	0.5
Self-confidence	5.5	0.7	7.2	0.3
Heightened mood	6.2	0.9	10.3**	0.3
Emotional excitability	2.6	0.9	10.2**	1.6
Anxiety:	1.5	0.5	4.5**	0.9
Apprehension-anxiety	0.2	0.2	0.7	0.3
Dejection	0.2	0.1	0.5	0.2
Thoughtfulness-Contemplativeness	1.2	0.5	3.3**	0.6
B ASC rating				
OB (oceanic boundlessness)	9.2	7.6	774.2***	138.9
VR (visionary restructuralisation)	15.3	6.8	307.1***	77.5
DE (dread of ego-dissolution)	11.8	6.8	164.9*	57.6

*For $P < 0.05$; ** for $P < 0.01$; and *** for $P < 0.001$

(e.g. locomotor and PPI) and neurochemical endpoints (e.g. brain 5-HT levels) (Kehne et al. 1992; Geyer and Callaway 1994; Nichols 1994). As detailed elsewhere (Vollenweider et al. 1998) and summarized in Table 2, the dose of MDMA used in this human study was found to have substantial psychological effects, characterized by feelings of relaxation, heightened mood, euphoria, increased sensory awareness, and elevated psychomotor drive. The time between administration and testing was selected to be at or near the time of peak effects observed in rats and humans, given the respective routes of administration (subcutaneous injection versus oral). Thus, despite attempts to maximize the comparability of the experiments in rats and humans, MDMA produced opposite effects on PPI.

It remains possible, however, that the observed difference in the effects of MDMA on PPI in rats and humans could be related to procedural differences between the experiments rather than to species differences. For example, different muscle groups were measured to quantitate startle responses, different routes of administration were used, and different, though overlapping levels of PPI were obtained using the similar stimulus parameters. Further studies using alternative procedures, stimulus parameters, drug treatments, and measures are warranted to establish the generality of this observation. It should be noted, however, that the field of preclinical psychopharmacology rests on cross-species comparisons based on studies having many fewer commonalities than those found in the present study.

In both rats and humans, MDMA had only weak effects on startle reactivity and no effect on habituation. In rats, the 5.4 mg/kg dose of MDMA decreased startle reactivity at the beginning of the test session. Nevertheless, no significant changes in startle reactivity were seen with either the lower or higher doses tested in the present experiment. Thus, the disruption in PPI produced by 17.0 mg/kg MDMA in rats was observed in the absence of any change in the magnitude of responses to the pulse-alone condition. In humans, 1.7 mg/kg MDMA slightly but significantly increased startle reactivity. This small increase in startle reactivity is unlikely to be related to the observed increase in PPI, because many studies have demonstrated that drug-induced changes in reactivity and PPI are typically independent (Mansbach et al. 1988; Geyer et al. 1990). Furthermore, the effects of MDMA on PPI were confirmed using both percent and difference score analyses. MDMA had no significant effect on the habituation of acoustic startle in rats or humans. Although MDMA and related 5-HT releasers have been shown to impair the habituation of tactile (airpuff-elicited) startle in rats (Kehne et al. 1992; Martinez and Geyer 1997), they do not affect acoustic startle habituation consistently, even when the two modalities are tested in the same subjects (e.g. Martinez and Geyer 1997). Thus, the present finding of no effect of MDMA on acoustic startle habituation in humans is consistent with previous studies in rats.

Previous studies in rats have demonstrated that the PPI-disruptive effects of MDMA and related drugs are attributable to the drug-induced release of presynaptic 5-HT. Specifically, the effects of MDMA-like drugs on PPI are prevented by pretreatment with 5-HT-selective reuptake blockers given at doses that have no effects by themselves (Kehne et al. 1992; Martinez and Geyer 1997). These reuptake blockers prevent access of MDMA to the presynaptic serotonergic terminal and thereby prevent MDMA-induced 5-HT release (Geyer and Callaway 1994; Nichols 1994). It has been widely assumed that the psychological effects of MDMA in

humans are due to its actions as an indirect 5-HT agonist, based largely on the many mechanistic studies in animals (Geyer and Callaway 1994). Hence, it is somewhat surprising that MDMA has opposite effects on PPI in rats versus healthy human volunteers. Differences in dosage alone do not appear to explain why MDMA produces increased PPI in humans, because the low dose of MDMA (1.7 mg/kg) did not increase or have any other effect on PPI in rats. There is some precedent for species-specific effects of serotonergic agonists on PPI. Although a variety of 5-HT_{1A} agonists dose-dependently disrupt PPI in rats (Rigdon and Weatherspoon 1992; Sipes and Geyer 1994), the diametrically opposite effect has been reported in mice (Dulawa et al. 1997). It may also be relevant to note that the hallucinogen psilocybin produces a small increase in PPI in healthy human volunteers (Gouzoulis-Mayfrank et al. 1998). The effects of psilocybin on PPI in rodents have not been reported. Thus, in the absence of mechanistic studies, no firm conclusions can be drawn regarding the mediation of the observed MDMA effects in humans. Hence, considerably more research is needed to clarify the mechanisms and sites of action of MDMA on PPI in humans. For example, it will be important to determine whether the MDMA-induced increase in PPI observed in humans in the present study is prevented by pretreatment with 5-HT reuptake inhibitors, as would be expected if this effect is due to a drug-induced release of presynaptic 5-HT as the opposite effect appears to be in rats.

Sensorimotor gating, as reflected in measures of PPI (Braff and Geyer 1990), has been thought to serve as a largely preattentive, protective buffer for information processing and attentional operations by preventing the intrusion of irrelevant sensory information which can increase demands on attentional allocation. Based on theoretical and experimental grounds, deficits in sensorimotor gating have been associated with the sensory flooding and cognitive fragmentation seen in psychotic disorders such as schizophrenia. Indeed, a number of studies demonstrated that schizophrenia-spectrum patients (Braff et al. 1978, 1992; Grillon et al. 1992; Cadenhead et al. 1993; Bolino et al. 1994) and psychosis-prone normals (Swerdlow et al. 1995a) exhibit deficient PPI. That the present study demonstrated the opposite effect is consistent with the fact that MDMA and related 5-HT releasers have not been considered to be psychotomimetic in humans and have been discriminated from other putative psychotomimetics, including both psychostimulants and classical hallucinogens, on the basis of psychological and neuroendocrine effects in humans (Gouzoulis et al. 1993) as well as behavioral and mechanistic studies in rats (Geyer and Callaway 1994; Nichols 1994). Indeed, the MDMA-treated subjects in the present study were not psychotic, but instead experienced a peculiar emotional state with an enhanced sense of well being, an expanded mental perspective, and an increase in arousal and vigilance at the same time. At the dose tested, MDMA was not frankly hallucinogenic, but what was typically described during the peak effects of MDMA were an intensification of sensory awareness, changes in the meaning of percepts, changes in the sense of time, and first signs of loosening of ego-boundaries. The slight loosening of ego-boundaries was experienced by most of the subjects with pleasure (high OB scores), while 5 of 13 subjects responded to the associated first signs of loss of body control with transient concern as measured by the DE scale. Thus, the effects of MDMA on both psychological and startle plasticity measures observed in humans in this study differ qualitatively from the behavior characteristic of patients with schizophrenia.

In conclusion, the present study demonstrated opposite behavioral effects of MDMA in rats versus humans, using a measure of sensorimotor gating that is thought to have a high degree of cross-species homology (Ison 1984; Geyer and Markou 1995). Considerably more research will be required to determine whether this disparity between drug effects in rats and humans reflects procedural differences, a species-specific difference in the mechanism of action of MDMA, or a different behavioral expression of a similar pharmacological effect. Furthermore, these findings demonstrate the importance of conducting mechanistic studies of pharmacological agents in healthy humans as well as in experimental animals.

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