Serotonin Neurotoxicity after (±)3,4-Methylenedioxymethamphetamine (MDMA; "Ecstasy"): A Controlled Study in Humans

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(±)3,4-Methylenedioxymethamphetamine (MDMA; "Ecstasy"), an increasingly popular recreational drug, is known to damage brain serotonin 5-hydroxytryptamine (5-HT) neurons in experimental animals. Whether MDMA is neurotoxic in humans has not been established. Thirty MDMA users and 28 controls were admitted to a controlled inpatient setting for measurement of biologic and behavioral indexes of central 5-HT function. Outcome measures obtained after at least 2 weeks of drug abstinence included concentrations of monoamine metabolites in cerebrospinal fluid (CSF), prolactin responses to L-tryptophan, nociceptive responses to ischemic pain, and personality characteristics in which 5-HT has been implicated (i.e., impulsivity and aggression). Subjects with a history of MDMA exposure had lower levels of CSF 5-hydroxyindoleacetic acid (the major metabolite of 5-HT) than controls (p = .001). Although they resembled controls in their prolactin response to L-tryptophan and their response to ischemic pain, MDMA users had lower scores on personality measures of impulsivity (p = .004) and indirect hostility (p = .009). The CSF findings suggest that 5-HT neurotoxicity may be a potential complication of MDMA use. Further, differences in personality support the view that 5-HT systems are involved in modulating impulsive and aggressive personality traits. Additional studies of MDMA-exposed individuals are needed to confirm and extend the present findings. Such studies could help elucidate the role of 5-HT in normal brain function as well as in neuropsychiatric disease states.

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(±)3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") is a synthetic analog of amphetamine and mescaline that has emerged as a popular recreational drug of abuse (Peroutka 1987; Anon 1991; Henry et al. 1992), and has recently been characterized as the drug of choice for use in large organized social settings (Randall 1992). Although MDMA is considered safe by most users (Eisner 1989; Randall 1992), there is compelling preclinical evidence that MDMA produces toxic effects on brain serotonin (5-hydroxytryptamine, 5-HT) neurons in animals (Stone et al. 1986; Schmidt 1987; Commins et al. 1987; Battaglia et al. 1987; Ricaurte et al. 1988a; O'Hearn et al. 1988). Furthermore, there is evidence that in nonhuman primates, the neurotoxicity

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of MDMA is prolonged (Insel et al. 1989) and possibly permanent (Ricaurte et al. 1992). Because the dose of MDMA that damages 5-HT neurons in monkeys is close to that typically taken by recreational users (Ricaurte et al. 1988b), and because the dose–response curve for MDMA neurotoxicity in the primate is steep (Ricaurte et al. 1988a), there is growing concern that MDMA neurotoxicity may generalize to humans.

At present, there are no direct methods for detecting serotonergic neurotoxicity in the living human brain. Consequently, MDMA's neurotoxic potential in humans can only be evaluated indirectly, by measuring the concentration of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF). Studies in monkeys indicate that CSF 5-HIAA can be used to detect serotonergic damage produced by MDMA, but that decreases in spinal CSF 5-HIAA underestimate the extent of serotonergic damage in the brain (Ricaurte et al. 1988c). Only two studies have measured CSF 5-HIAA in humans in an effort to screen for possible MDMA neurotoxicity. One of these found reductions in CSF 5-HIAA (Ricaurte et al. 1990), but the other did not (Peroutka et al. 1987). Given the large number of physiologic and environmental factors that can potentially influence levels of 5-HIAA in CSF (Post et al. 1980), the different findings of these two studies are not surprising, because neither study was conducted in a controlled setting.

The purpose of the present study was to measure CSF 5-HIAA in a cohort of MDMA users under controlled conditions, and to determine whether MDMA neurotoxicity, if evident in humans, was associated with changes in functional domains in which 5-HT has been implicated. These domains include neuroendocrine function, pain, and certain personality traits such as impulsivity and aggression.

METHODS

Subjects

Fifty-eight subjects participated in the study: 30 experimental (MDMA-exposed) subjects and 28 controls. The demographics of the study groups are shown in Table 1 and discussed below (see Results). The MDMA subjects were self-referred; they called one of the investigators (GAR) after learning about ongoing MDMA research at the Johns Hopkins Medical Institutions. Controls were either referred by MDMA subjects or recruited from the greater Baltimore/Washington, DC metropolitan area. All participants were screened first for eligibility in telephone interviews. For inclusion in the MDMA group, individuals had to be in good health, they had to have used MDMA on at least 25 occasions, and they could not have any of the exclusionary criteria (see below). To be in the control group, subjects had to meet the same health criteria and have no history of MDMA exposure, although prior use of other drugs was allowed, because most MDMA users had also used other drugs at some time. Information about MDMA use was obtained in several ways: (1) a preliminary telephone interview; (2) an MDMA questionnaire that asked about the number of times MDMA had been used, the usual amount of MDMA taken, the frequency of MDMA use, the last time MDMA had been used, and the highest dose of MDMA ever taken; (3) a standardized drug history questionnaire; and (4) the Scheduled Interview for DSM-III-R (Spitzer and Williams 1982). Characteristics of MDMA use are listed in Table 2, and characteristics of drug exposure other than MDMA are listed in Table 3. Exclusionary criteria for both groups included past or present major medical illness (neurologic, renal, endocrine, or hematologic), pregnancy, positive human immunodeficiency virus status, history of psychosis, current major depressive disorder, or current alcohol or drug dependence. All subjects agreed to refrain from any recreational drug use for at least 2 weeks prior to the study and understood that they would undergo a urine and blood drug screen upon arrival at the clinical research center. Subjects who passed the initial telephone screen underwent further screening at the time of inpatient admission. Potential subjects were given a detailed physical and neurologic examination, a structured psychiatric interview using the Scheduled Interview for DSM-III-R (Spitzer and Williams 1982), and laboratory tests including a blood chemistry panel, complete blood count, platelet count, urinalysis, urine drug screen, and human immunodeficiency virus screen. Subjects admitted to the clinical research center were maintained on a low monoamine diet for the duration of the study. The study was approved by the local institutional review board.

Outcome Measures

CSF Monoamine Metabolites. Lumbar punctures were performed as described (Ricaurte et al. 1990) between 8 AM and 10 AM on the third morning of the subjects' stay at the clinical research center, after an overnight fast and complete bed rest. Concentrations of monoamine metabolites in CSF were determined by high-performance liquid chromatography coupled with electrochemical detection using the method of Kilpatrick et al. (1986) for 5-HIAA and homovanillic acid (HVA), and the method of Sharpless (1986) for MHPG. Samples of CSF from control and MDMA subjects were processed and assayed in tandem without awareness of the drug condition of each subject.

Prolactin Responses to L-Tryptophan. The prolactin response to L-tryptophan, which is thought to provide a measure of central 5-HT function in humans (Price et al. 1990), was used to evaluate central 5-HT function in MDMA users. Neuroendocrine challenge with L-tryp-

Table 1. Demographics[a]

	Age (yr)	Height (cm)	Weight (kg)	Education (yr)
Group				
Control (n = 28)	27.8 ± 7.8	175.4 ± 9.5	70.4 ± 10.7	16.5 ± 2.8
MDMA (n = 30)	32.3 ± 13.6	174.8 ± 9.2	69.9 ± 14.9	15.2 ± 2.0
Subgroups				
Control male (n = 17)	27.3 ± 5.6	181.4 ± 6.2	75.1 ± 6.4	17.2 ± 2.6
MDMA male (n = 18)	31.4 ± 13.9	180.5 ± 6.1	76.8 ± 14.9	14.8 ± 1.6[2]
Control female (n = 11)	28.6 ± 10.9	166.2 ± 5.7[1]	63.3 ± 12.3[1]	15.4 ± 2.9
MDMA female (n = 12)	33.7 ± 12.9	166.4 ± 6.2[1]	59.0 ± 5.9[1]	15.7 ± 2.4

[a] Values are means (± SD).
[1] Significant gender difference ($p < .05$).
[2] Significant difference from male controls ($p < .05$).

Table 2. Characteristics of MDMA Use

Number of exposures	94.4 ± 90.6 (range: 25 to 300)
Duration of use	4.98 ± 2.96 years (range: 0.5 to 16)
Frequency of use	4.16 ± 4.79 per month (range: 0.15 to 20)
Usual dose[a]	170 ± .82 mg (range: 0.5 to 4)
Time since last dose	17.9 ± 24.7 weeks (range: 2 to 104)

[a] Estimate based on number of capsules or tablets taken on a given day.

Table 3. Other Recreational Drug Exposure

Drug Class	MDMA (n = 30)[a]	Control (n = 28)[a]
Non-MDMA amphetamines	13 (43%)	4 (14%)
Cocaine	24 (80%)	8 (29%)
Benzodiazepines	18 (60%)	6 (21%)
Sedative hypnotics	10 (33%)	1 (4%)
LSD & other hallucinogens	26 (87%)	9 (32%)
Cannabis	28 (93%)	22 (73%)
Organic solvents/inhalents	8 (27%)	8 (29%)
Opiates	16 (53%)	9 (32%)
PCP and related drugs	4 (13%)	2 (7%)

[a] Values are the number and percentage of individuals within each experimental group that reported any prior exposure to a drug in the listed drug class.

tophan was performed following the protocol of Price et al. (1990) with minor modification. Briefly, L-tryptophan (7 g) dissolved in 500 ml 0.45% normal saline was infused through an indwelling intravenous catheter over a 20-minute period and blood for prolactin was collected through the catheter 15 and 0.5 minutes before and 30, 40, 50, 60, 70, 90, and 120 minutes after L-tryptophan administration. Values from −15 and −0.5 minutes were averaged to provide basal prolactin concentrations. Peak change scores were determined by subtracting the baseline value from the highest prolactin value after L-tryptophan infusion. The prolactin area under the curve was calculated using the trapezoidal rule. Serum prolactin was determined by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA).

Pain Measurements. Because 5-HT has been implicated in central pain (see Richardson 1992), and because impairments in 5-HT function have been associated with alterations in nociception (see Messing and Lytle 1977), pain measures were also examined in MDMA users. Nociceptive function was assessed by the submaximum-effort tourniquet technique for inducing ischemic pain in humans (Smith et al. 1966). Three pain measures were obtained: (1) the subject's first self-rating of pain was used as a measure of pain "sensitivity;" (2) the time from the start of the test until the subject chose to abort testing was used as a measure of a subject's pain "endurance" (with a maximum score of 20); and (3) the total pain score (the sum of all the values taken at 30-second intervals for the duration of the test) was used as a measure of a subject's pain "tolerance."

Personality Assessments. Decreased CSF 5-HIAA levels have been found in individuals with impulsive and hostile personality traits (Linnoila et al. 1983; Roy et al. 1988; Coccaro et al. 1992). To determine whether MDMA

users had alterations in these personality traits, subjects were asked to complete the Multidimensional Personality Questionnaire (Tellegen 1982), the Buss Durkee Hostility Inventory (Buss and Durkee 1957), and the Eysenck Personality Questionnaire (Eysenck 1976).

Statistical Analysis

In CSF studies, analysis of covariance was initially used to analyze the concentrations of monoamine metabolites in the CSF of MDMA and control subjects. Age and height were used as covariates in these analyses because these factors have been reported to influence CSF monoamine metabolite levels (Bowers and Gerbode 1968; Gottfries et al. 1971; Wode-Helgodt and Sedvall 1978; Stanley et al. 1985). In addition, it has been reported that the season of the year (i.e., summer, winter, spring, or fall) can influence CSF monoamine metabolite levels (Brewerton et al. 1987). For this reason, the CSF data were also analyzed with a 2 × 4 (group × season) analysis of covariance (ANCOVA), again covarying for age and height. Because the raw data suggested a possible effect of gender on CSF monoamine metabolite levels, the CSF data were further analyzed with a 2 × 2 (group × gender) ANCOVA, with age and height as covariates.

In functional studies, analysis of covariance was used to analyze the prolactin response to L-tryptophan, using age, basal prolactin levels, and plasma tryptophan levels as covariates. Pain study results were analyzed with a 2 × 2 (group × gender) analysis of variance (ANOVA), and personality measures were analyzed with a multivariate 2 × 2 ANCOVA, with age and education as covariates. For the personality measures, the Bonferroni method for computing multivariate intervals was used.

In the case of either significant main effects of group or significant group × gender interactions, post-hoc comparisons were performed using Duncan's multiple range test. Correlations were assessed by Pearson's product moment. All tests were two tailed; significance was set at $p \leq .05$.

RESULTS

Demographics

Control and experimental groups were well matched for age, height, weight, and relative proportion of males and females in each group (Table 1). Although MDMA subjects were slightly older than controls, ANOVA indicated that the age difference was not statistically significant ($F[1,54] = 2.31$, $p = .13$). There were also no significant socioeconomic, ethnic, racial, or occupational differences between the two groups, although a 2 × 2 (group × gender) ANCOVA with age as a covariate revealed a significant group × gender interaction for education ($F[1,53] = 4.4$, $p = .04$), with post hoc tests indicating that control males had more years of education than MDMA males (Table 1).

CSF Monoamine Metabolites

5-HIAA. Concentrations of CSF 5-HIAA in control subjects in this study (15.2 ± 7.9 ng/ml [mean ± SD]; range: 4.8 to 37.3 ng/ml) were within the range of concentrations reported for control subjects in other studies (Post et al. 1980; Hildebrand et al. 1990; Ben Menachem et al. 1989). A one-way ANCOVA using age and height as covariates revealed that MDMA users had significantly lower levels of CSF 5-HIAA than controls (15.2 ± 7.9 ng/ml in controls versus 10.3 ± 3.1 ng/ml in MDMA subjects, $F[1,54] = 11.6$, $p = .001$). Because the raw data suggested a possible effect of gender, the results were further analyzed using a 2 × 2 (groups × gender) ANCOVA, again with age and height as covariates. This analysis also revealed a significant main effect of group ($F[1,52] = 14.9$, $p < .001$), as well as a significant group × gender interaction ($F[1,52] = 5.1$, $p < .03$). Post hoc comparisons indicated that, within the MDMA group, reductions in CSF 5-HIAA were greater in females than in males (46% versus 20%), and that within the control group, males had lower levels of CSF 5-HIAA than females (Table 4). The latter observation is in keeping with previous findings of others (Wode-Helgodt and Sedvall 1978; Post et al. 1980; Roy et al. 1988).

As in other studies (Wode-Helgodt and Sedvall 1978; Stanley et al. 1985), a significant negative correlation was found between height and CSF 5-HIAA in control subjects ($r = -.42$, $p = .03$). In MDMA subjects, this negative correlation was absent ($r = .18$, $p = .34$).

Cerebrospinal fluid 5-HIAA levels were negatively correlated with the number of MDMA exposures ($r = -0.2$), but the correlation was not statistically significant ($p = .33$). Cerebrospinal fluid 5-HIAA levels were not significantly correlated with the duration of MDMA use, frequency of MDMA use, or the time since last MDMA exposure.

A 2 × 4 (group × season) ANCOVA with age and height as covariates did not show a significant effect of season, or a group-by-season interaction on CSF 5-HIAA ($F[3,50] = .89$, $p = .45$). Comparable number of control and MDMA subjects were examined during each season of the year.

HVA. Concentrations of HVA in the CSF of control subjects in this study (27.4 ± 21.3 ng/ml mean ± SD; range 8.1 to 117.9 ng/ml) were also within the range of concentrations reported for control subjects in other studies (Post et al. 1980; Hildebrand et al. 1990; Ben Menachem et al. 1989). A 2 × 2 (group × gender) AN-

Table 4. Monoamine Metabolite Levels in CSF of Control and MDMA Subjects*

		Metabolites		
	n	5-HIAA[||]	HVA	MHPG
Group				
Control	28	15.2 ± 7.9	27.4 ± 21.3	8.5 ± 8.3
MDMA	30	10.3 ± 3.1[†]	19.4 ± 7.8	8.5 ± 6.0
Subgroups				
Control male	17	13.4 ± 5.8	24.6 ± 10.2	9.3 ± 9.6
MDMA male	18	10.8 ± 2.6	22.1 ± 8.5	9.6 ± 6.6
Control female	11	18.7 ± 9.3[‡]	34.8 ± 29.9	7.2 ± 6.1
MDMA female	12	10.1 ± 2.6[§]	18.7 ± 7.0[§]	6.9 ± 4.7

* Values are means (± SD) expressed in ng/ml.
[†] Significant difference compared to control group ($p \leq .05$).
[‡] Significant difference compared to control male group ($p \leq .05$).
[§] Significant difference compared to control female group ($p \leq .05$).
[||] For 5-HIAA, intraassay and interassay coefficients of variation were 2.3% and 4.7%, respectively. For HVA, intraassay and interassay coefficients of variation were 2.9% and 5.6%, respectively. MHPG = 3-methoxy-4-hydroxyphenolglycol.

COVA with age and height as covariates revealed a significant effect of group ($F[1,52] = 6.9$, $p = .01$), as well as a significant group × gender interaction ($F[1,52] = 4.3$, $p = .04$). Post-hoc comparisons indicated that MDMA females had lower levels of CSF HVA than control females but that levels of CSF HVA in control and MDMA males were not significantly different (Table 4).

MHPG. There were no significant effects of group ($F[1,54] = .01$, $p = .9$) or gender ($F[1,54] = .5$, $p = .5$) on CSF MHPG levels (Table 4).

Prolactin: Basal Level and Response to L-Tryptophan

A 2 × 2 (group × gender) ANCOVA with age as the covariate revealed a significant effect of gender on basal prolactin levels ($F[1,46] = 28.5$, $p < .001$). Post-hoc comparisons indicated that females had higher basal prolactin levels than males, and that basal prolactin levels did not differ between control and MDMA subjects (Table 5).

A 2 × 2 (group × gender) ANCOVA with age and basal prolactin level as covariates showed that after L-tryptophan infusion, females had greater peak increases in prolactin levels than males ($F[1,45] = 8.2$, $p = .006$), and that females also had larger areas under the prolactin response curve (AUC) ($F[1,45] = 5.6$, $p = .02$) than males. No significant drug effects were found for either of the prolactin responses (peak prolactin change or prolactin AUC, Table 5).

Determination of plasma tryptophan levels before and after L-tryptophan infusion showed that the peak change in plasma tryptophan level was positively correlated with the peak change in plasma prolactin ($r = .33$, $p = .02$) and the prolactin AUC ($r = .41$, $p = .003$). When the 2 × 2 (group × gender) ANCOVA was repeated including the change in plasma tryptophan level as an additional covariate (other covariates were age and basal prolactin), the gender effects on the prolactin responses to L-tryptophan were still apparent (for peak prolactin change $F[1,44] = 5.9$, $p = .02$ and for prolactin AUC $F[1,44] = 4.1$, $p = .05$), suggesting that the greater prolactin response in women is not solely related to greater peak changes plasma L-tryptophan levels.

Table 5. Prolactin Levels Before and After Infusion of L-Tryptophan in Control and MDMA Subjects*

	n	Before	After[†]	AUC[‡]
Control male	16	6.1 ± 3.8	13.4 ± 6.5	1289 ± 1114
MDMA male	18	5.2 ± 2.5	14.8 ± 8.5	1102 ± 590
Control female	7	14.9 ± 9.3[§]	30.3 ± 10.5[§]	2279 ± 811[§]
MDMA female	10	10.4 ± 4.5[§]	33.8 ± 9.2[§]	2438 ± 1711[§]

* Values are means (± SD) expressed in ng/ml.
[†] Mean ± SD peak prolactin levels after L-tryptophan infusion.
[‡] Mean ± SD area under the curve for the prolactin response.
[§] Significant gender difference.

Pain Measures

Pain Sensitivity (Initial Pain Score). A 2 × 2 (group × gender) ANOVA showed a main effect of gender ($F[1,54] = 5.7$, $p = .02$) on pain sensitivity, with no effect of group, and no group × gender interaction. Post hoc comparisons indicated that females in both the control and MDMA groups had higher initial pain scores (pain sensitivity) than males (Table 6).

Pain Endurance (Length of Time Pain Was Endured or Time Before Subjects Found Pain Unbearable. There were no significant effects of group or gender on pain endurance.

Pain Tolerance (Total Pain Score, See Methods). A 2 × 2 (group × gender) ANOVA also revealed an effect of gender on pain tolerance ($F[1,54] = 4.9$, $p = .03$), with females having lower total pain scores than males (Table 6).

Correlation analysis revealed a negative correlation between pain sensitivity and pain endurance ($r = -0.62$, $p < .001$) and pain tolerance ($r = -0.46$, $p < .001$) in both control and MDMA subjects.

Personality Measures

Multidimensional Personality Questionnaire (MPQ). A 2 × 2 (drug condition × gender) multivariate ANCOVA with age as a covariate revealed a main effect of group on the control scale ($F[1,52] = 9.21$; $p = .004$), with MDMA subjects scoring higher (indicating less impulsivity) than controls. Post-hoc comparisons revealed that female MDMA subjects had higher control scores than all other experimental groups. A near significant effect of group was also observed on the harm avoidance scale ($F[1,52] = 3.69$; $p = .060$), with MDMA subjects reporting greater harm avoidance than controls. A main effect of gender was also observed on the harm avoidance scale ($F[1,52] = 5.03$; $p = .029$), with post-hoc testing indicating that female MDMA users had greater harm avoidance than all other experimental groups. Additionally, a gender effect was observed on the higher order scale of constraint ($F[1,52] = 5.0$; $p = .03$), reflecting less impulsive, more conservative, and more harm avoidant personality traits. Post hoc testing revealed that female MDMA subjects had higher scores on this scale than all other subject groups. Group by gender interactions were observed on the alienation scale ($F[1,52] = 4.4$; $p = .004$), the control scale ($F[1,52] = 6.4$; $p = .01$), the harm/avoidance scale ($F[1,52] = 4.2$; $p = .047$), and the constraint scale ($F[1,52] = 4.3$; $p = .043$).

Buss Durkee Hostility Inventory (BDHI). A 2 × 2 (group × gender) multivariate ANCOVA revealed a main effect of group on the indirect hostility scale, with MDMA subjects reporting less hostility than controls ($F[1,52] = 7.4$; $p = .009$). Post-hoc testing revealed that both MDMA groups reported significantly less indirect hostility than control females, but that neither MDMA group was significantly different from male controls. A significant effect of gender was also observed on the indirect hostility scale ($F[1,52] = 6.7$; $p = .013$), reflecting the previously mentioned scores in female MDMA users.

Eysenck Personality Questionnaire (EPQ). No drug or gender effects, or drug × gender interactions were observed on the sociability and impulsivity subscales of this questionnaire.

Correlations Between Biologic and Personality Measures

Correlation analyses between CSF 5-HIAA concentrations and personality scales were performed; analyses were restricted to scales in which significant group or gender effects or group by gender interactions had been observed. Correlations were done for male and female subjects separately because of gender differences in CSF 5-HIAA content.

MPQ. For female subjects, CSF 5-HIAA was positively correlated with alienation ($p < .0001$), with near significant negative correlations on control ($p = .06$). For male subjects, there was a positive correlation between CSF 5-HIAA and harm/avoidance ($p = .02$), and a near significant positive correlation between CSF 5-HIAA and constraint ($p = .07$).

Table 6. Pain Indexes in Control and MDMA Subjects

Group	*n*	Sensitivity*	Endurance†	Tolerance‡
Control male	17	4.3 ± 1.9	12.2 ± 3.2	157 ± 47
MDMA male	18	4.8 ± 0.6	9.9 ± 1.4	114 ± 17
Control female	11	6.1 ± 2.2§	8.9 ± 4.9	95 ± 50§
MDMA female	12	6.1 ± 2.4§	8.2 ± 5.5	100 ± 78

* Mean ± SD pain score recorded at 2 minutes.
† Mean ± SD time pain was endured.
‡ Mean ± SD total pain score.
§ Significant gender difference.

BDHI. Both female and male groups had near significant correlations between CSF 5-HIAA and Indirect Hostility ($p = .09$ and $p = .1$, respectively).

DISCUSSION

The major finding of the present study is that under controlled conditions, MDMA subjects have lower levels of CSF 5-HIAA than control subjects matched for age, height, weight, gender, education, and other drug use. This finding, coupled with the observation that height and CSF 5-HIAA are not negatively correlated in MDMA subjects, as they are in control subjects of this (see Results) and other (Wode-Helgodt and Sedvall 1978; Stanley et al. 1985) studies, suggests that recreational MDMA use is associated with an alteration in central 5-HT metabolism. Although the nature of the MDMA-induced alteration in 5-HT metabolism is difficult to establish on the basis of CSF data alone, the fact that similar CSF 5-HIAA decrements are evident in MDMA-treated monkeys with known serotonergic CNS deficits (Ricaurte et al. 1988c) suggests that CSF 5-HIAA reductions in MDMA users may reflect MDMA neurotoxicity.

The absence of a negative correlation between height and CSF 5-HIAA in MDMA subjects is noteworthy in one other respect. The inverse relation between height and CSF 5-HIAA is thought to arise, at least in part, from a concentration gradient of 5-HIAA along the craniospinal axis (Sjostrom et al. 1975; Weir et al. 1973; Garelis et al. 1974). Its absence in MDMA users raises the possibility that MDMA perturbs those processes that normally contribute to the CSF 5-HIAA gradient. One way that MDMA could produce this effect is by damaging ascending 5-HT axon projections to a greater extent than descending 5-HT projections. Indeed, recent findings in rodents (Molliver et al. 1990) as well as nonhuman primates (Insel et al. 1989; Ricaurte et al. 1992) suggest that MDMA produces regioselective neurotoxic effects on central 5-HT systems, damaging ascending 5-HT projections more than descending 5-HT projections.

Analysis of the CSF data also revealed that reductions in CSF 5-HIAA were greater in women than in men (46% versus 20%). Although women could be more susceptible than men to MDMA's 5-HT depleting effects (i.e., pharmacodynamic factors could be involved), the larger CSF 5-HIAA deficits in women are more likely to be exposure related, because women in the cohort weighed less than men yet generally reported taking the same dose (one tablet or capsule containing 100 to 150 mg). Moreover, review of the drug history data revealed that, on average, women had used MDMA more than men (115 times as compared to 85). These factors, along with the fact that gender differences in susceptibility to MDMA neurotoxicity have not been noted in preclinical studies, suggest that pharmacokinetic rather than pharmacodynamic factors underlie the greater effect in women. In this regard, it is of note that MDMA-exposed women, in addition to having reduced CSF 5-HIAA, also have reduced CSF HVA (Table 4), a finding that is in keeping with the observation that at high dosage, MDMA can damage dopaminergic as well as serotonergic neurons (Commins et al. 1987).

The prolactin response to L-tryptophan in MDMA users did not differ from that in controls. At first glance, this finding would appear to be at odds with that of a previous report (Price et al. 1988) indicating that recreational MDMA users might have blunted prolactin responses to L-tryptophan. However, as pointed out by the authors of that report, the decrements in prolactin response observed in that study cohort did not achieve statistical significance. Furthermore, recent findings in monkeys indicate that following MDMA injury, 5-HT axons innervating the hypothalamus (i.e., those presumably subserving the prolactin response), unlike those projecting to the neocortex, recover in the months ensuing MDMA treatment (Ricaurte et al. 1992). Given that on average, subjects in this study had last used MDMA 18 weeks prior to study participation, with some subjects abstaining from MDMA for as long as 2 years, it is possible that the lack of neuroendocrine findings is secondary to serotonergic axonal recovery at the level of those brain structures that mediate the prolactin response to L-tryptophan. Alternatively, it is possible that central 5-HT deficits that give rise to CSF 5-HIAA deficits are insufficiently large or perhaps not appropriately located to give rise to a neuroendocrine functional deficit.

Differences between MDMA users and controls were found on measures of several personality traits thought to involve serotonin, including aggression, impulsivity, harm avoidance, and constraint. Further, female MDMA users, the MDMA subgroup with the greatest decrement in CSF 5-HIAA, were found to be the subgroup with the larger differences in personality. Somewhat unexpected was the direction of the personality differences, which indicated that MDMA users had decreased rather than increased impulsivity and hostility, as well as increased harm avoidance and constraint. Although this might seem surprising at first, the present results might be explained if one considers that the underlying basis for decreased CSF 5-HIAA in MDMA users (presumably neurotoxic injury) may be different from that in patients groups exhibiting increased impulsivity and aggression (patients with personality disorders, violent offenders, suicidal individuals). Specifically, it may be that the nature and regional distribution of central 5-HT deficits induced by MDMA are different from those in patients exhibiting impulsive and aggressive behaviors. Furthermore, in certain

patient groups (e.g., patients with obsessive-compulsive disorder), drugs that promote net increases in serotonin activity have been found to decrease harm avoidant behaviors (e.g., compulsive rituals) (Chouinard 1992). Thus, there is precedent for decreased serotonin function being associated with increased constraint and harm avoidance. Moreover, a recent report indicates that humans with inherited monoamine oxidase A (MAO-A) deficiency, and therefore presumably an increase in brain serotonin, have increased, rather than decreased, impulsive aggressive behavior (Brunner et al. 1993). Finally, it should be noted that personality differences are not simply a confound of drug abuse tendencies, because substance abusers, unlike MDMA users in this study, typically have increased rather than decreased scores on measures of impulsivity (Fishbein et al. 1989).

Several factors should be considered when interpreting these data. First, it is possible that the reduction in CSF 5-HIAA observed in MDMA users is related to a premorbid condition that antedated the use of MDMA. This possibility seems unlikely, however, because care was taken to screen out individuals with past or present psychiatric disorders in which 5-HT dysfunction has been implicated (including depression, anxiety, personality disorders, and alcoholism), and because no significant differences were found between controls and MDMA subjects on standardized psychiatric measures. Second, it could be argued that although MDMA was the drug of choice in most MDMA users, it was not the only drug used, and that other drugs are responsible for the observed changes. Because control subjects, like MDMA subjects, by design had exposure to other recreational drugs (albeit, to a lesser extent), and since few, if any, recreational drugs outside of the amphetamine class produce selective neurotoxic effects of the type produced by MDMA, this possibility also seems unlikely. Third, it could be that decreases in CSF 5-HIAA reflect a decrease in the synthesis, storage, release, or degradation of brain 5-HT, or an increase in the removal of 5-HIAA from the CSF compartment that is unrelated to MDMA neurotoxicity. Although this is possible, as noted above, the fact that MDMA-treated monkeys with documented CNS 5-HT neurotoxicity (Insel et al. 1989; Ricaurte et al. 1988c) show similar CSF 5-HIAA deficits to those here documented in MDMA users mitigates against this possibility.

With regard to the finding that MDMA users have lower scores on scales of impulsivity and control, it is also important to consider the possibility that these differences were secondary to factors unrelated to MDMA use. For example, it is possible that MDMA subjects, who were often strong advocates for its beneficial effects, were biased in their responses on personality questionnaires in order to highlight positive aspects of their drug experience. Although possible, it would be difficult to explain why MDMA users independently and selectively chose to respond in a biased manner on scales relating to impulsivity and hostility (since similar "positive" answers could be given on scales reflecting confidence, positive affect, alienation, and social potency). The negative correlation between CSF 5-HIAA and measures of control would also be somewhat curious if personality differences were due to subject bias, given that subjects were not privy to CSF monoamine levels at the time questionnaires were completed. An alternate explanation for personality differences is that "control" subjects were unusually impulsive, and that differences in MDMA subjects are actually a reflection of abnormalities in the control group. This possibility seems less than likely however, when one considers that impulsivity scores in the control group fall into the range previously reported in "normal" populations.

Predictions regarding the amount of MDMA required to induce 5-HT neural damage in humans are difficult to make based on the present study, because the dose and duration of MDMA use differed among subjects, and because estimates of MDMA exposure are based on self-reports. Additional studies are needed to establish whether individuals who have taken smaller amounts of MDMA also show evidence of altered 5-HT metabolism and to determine why women are more affected than men. Controlled clinical studies are also indicated to ascertain whether dexfenfluramine, a clinically prescribed appetite suppressant, produces similar changes, since dexfenfluramine is taken by more people, and more frequently than MDMA, and is highly toxic to 5-HT neurons in nonhuman primates (Ricaurte et al. 1991).

In summary, the present results indicate that MDMA neurotoxicity, heretofore only documented in animals, may generalize to humans. When evaluated under controlled conditions, recreational MDMA users have reduced CSF 5-HIAA levels compared to matched controls. In addition, when compared to controls, MDMA subjects are less impulsive, more harm-avoidant, and have decreased indirect hostility, supporting the notion that these personality characteristics are modulated by serotonin. Further studies are needed to confirm and extend these observations. In particular, specific pharmacologic or physiologic challenge of central 5-HT systems in MDMA-exposed individuals may provide insight into the role of 5-HT in normal human brain function and may shed light on the involvement of 5-HT in neuropsychiatric disease states.

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