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Persistent Effects of (±)3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") on Human Sleep

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Summary: (±)3,4-methylenedioxymethamphetamine (MDMA) is a recreational drug of abuse which damages serotonin neurons in animals. It is not known whether MDMA is also neurotoxic in humans, and if so, whether there are functional consequences. Given the putative role of serotonin in sleep, it was hypothesized that one manifestation of serotonin neurotoxicity in humans might be disturbances of sleep. To determine whether MDMA use has effects on sleep, all-night polysomnograms of 23 MDMA users were compared to those of 22 age- and sex-matched controls. On average, MDMA users had 19 minutes less total sleep and 23.2 minutes less non-REM (NREM) sleep than controls. These statistically significant differences in NREM sleep were due primarily to an average of 37 minutes less stage 2 sleep, with no significant differences noted in stages 1, 3 or 4. Although it is not known whether the alterations in sleep observed in MDMA users are due to serotonin neurotoxicity, the present findings suggest that MDMA use can lead to persistent changes in CNS structures involved in human sleep generation.
Key Words: MDMA—Serotonin—Neurotoxicity—Amphetamines—Sleep.

Recreational use of (±)3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), a ring-substituted amphetamine derivative that acts indirectly by stimulating the release of brain monoamines (1), has become increasingly popular in the United States and Europe (2,3). In animals, MDMA has been shown to damage brain serotonin neurons (4–9). Because the neurotoxic dose of MDMA in nonhuman primates approximates the typical recreational dose for humans (10), there is concern that humans using MDMA may also incur selective neurotoxic damage to brain serotonergic systems (11). While the specific role of serotonin in human behavior is not known, it has been implicated in the regulation of sleep (12), mood (13), anxiety (14), pain (15), aggression (16), memory (17) and appetite (18).

Although the specific mechanisms by which serotonin influences sleep are not known, one of the more widely held views is that serotonin acts indirectly by modulating the role of other neurotransmitters involved in sleep (19,20). It also has been proposed that serotonin may act indirectly by influencing the accumulation of hypnogenic factors (21,22). Regardless of exactly how serotonin influences sleep, it seems clear that serotonin is involved in normal sleep–wake mechanisms (23). Thus, if individuals previously exposed to significant amounts of MDMA incur serotonergic damage, abnormalities in sleep might be anticipated. Specifically, based on preclinical and clinical data (24–30), we hypothesized that MDMA users would have decreased total sleep time (TST), and that the decrease in TST would be related to reductions in both REM and NREM sleep.

METHODS

Subjects

Fifty-three volunteers participated in the study. Experimental subjects all reported that they had used MDMA on more than 25 separate occasions. Control subjects had no prior history of MDMA use. All sub-

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TABLE 1. *Subject characteristics*

Characteristic	MDMA subjects	Control subjects
Number	23	22
Age (mean ± SD)	26.7 ± 6.0	26.1 ± 4.5
Sex (number of males)	15	17
Time zone of origin		
No. from Eastern	2	17
No. from Central	9	0
No. from Mountain	1	0
No. from Pacific	11	5
SCID-R Dx, no. of subjects		
History of alcohol abuse	1	4
History of alcohol dependence	2	0
Current organic mood disorder	1	0
Current panic disorder	1	0
Current marijuana use	1	0
Total no. of subjects SCID-R Dx	6	4

SCID-R = Scheduled Interview for DSM-III-R. The SCID-R diagnoses above are for those identified as conditions associated with effects on sleep.

jects agreed to refrain from use of any psychoactive substances for at least two weeks before participating in the study, and understood that abstinence would be confirmed by a urine and blood drug screen upon presentation at the clinical research center. Prior to study participation, all subjects were screened by telephone interview, and when appropriate, were invited to the clinical research center for further evaluation. At that time, after giving informed consent, subjects also underwent a physical examination and psychiatric interview using the Scheduled Interview for DSM-III-R (SCID-R). Each experimental subject estimated the number of times s/he had used MDMA. Exclusion criteria for all subjects included past or present major medical illness, history of psychosis, current major depressive illness, current alcohol dependence or history of sleep disorder. Sleep study analyses were limited to subjects between 18 and 40 years of age, because suitable age and sex matched controls were not available for older subjects. Of the 47 subjects who met the above criteria, two control subjects failed to complete the protocol and were excluded from the data analyses, leaving 22 controls and 23 experimental subjects. All subjects entered the clinical research unit 1 day before the sleep study. Diet and activity of the subjects were controlled during the study.

Polysomnogram recordings and scoring

Subjects came to the sleep center for 2 consecutive nights of polysomnographic recordings (PSGs). On both nights, routine sleep EEG recordings were obtained using two channels for eye movements, two EEG channels (C3A1, C4A2), and one submental EMG channel. On the first night EMG was recorded from the left and right anterior tibialis muscles. Respiratory activity was recorded using oximetry, airflow from the mouth and nose, and respiratory effort was measured by abdominal and thoracic strain gauges. Sleep time was from 11:00 p.m. to spontaneous awakening after 6:00 a.m. with a maximum of 8 hours permitted before ending sleep. The PSGs from the first night were scored for apnea and periodic limb movements in sleep. EEG data from the first night were considered "adaptation sleep", and were not used for experimental analyses. Polysomnograms from the second night were visually scored by two independent raters for all sleep stages following the standard Rechtschaffen and Kales procedures (31). When significant differences were noted in a particular stage (e.g. stage 2), sleep records were further analyzed for differences within that stage (e.g. spindle or K-complex density). Technicians responsible for recording and scoring polysomnograms were unaware whether subjects had been exposed to MDMA or were controls.

Statistics

Minutes of TST (all sleep stages other than wake), stages 2, 3 and 4 sleep, and REM sleep were compared between the groups using a standard analysis of variance (ANOVA). Independent factors in the ANOVA in addition to MDMA use were time zone of origin (ordered from east to west), age and presence or absence of DSM-III-R diagnoses which might affect sleep structure (current alcohol abuse or dependence, mood or anxiety disorder).

RESULTS

Subjects

The 23 subjects with significant histories of MDMA use and 22 control subjects completing the protocol were fairly well matched for sex (65% and 77% males, respectively) and for age (averages of 26.7 and 26.1 years, respectively) (Table 1). More MDMA subjects were from the Mountain and Pacific time zones (47.8% MDMA subjects versus 22.7% control subjects). There were no major differences between groups in the number of DSM-III-R diagnoses which might affect sleep (six MDMA subjects versus four control subjects). The MDMA subjects reported using MDMA on average 79.4 times (range of 25 to 300 times).

Polysomnogram data for primary hypotheses

MDMA subjects had significantly less TST than control subjects (mean ± SEM of 384.4 ± 8.7 and 403.8 ± 6.1 minutes, respectively; $p = 0.038$), and signifi-

TABLE 2. *Polysomnographic measurements of sleep*

Sleep measurement	Mean ± standard error		ANOVA	
	MDMA	Control	*F* value[f]	p value
For testing primary hypotheses				
TST[a] (minutes)	384.4 ± 8.7	403.8 ± 6.1	4.60	0.038
NREM (minutes)	301.4 ± 7.4	324.6 ± 6.0	8.45	0.006
REM (minutes)	83.0 ± 4.7	79.1 ± 4.5	0.44	0.507
Lighter sleep (stage 1)				
Stage 1 sleep	29.8 ± 2.8	29.6 ± 3.6	0.01	0.92
Deeper sleep (stages 2–4)				
Stage 2	185.1 ± 8.3	222.4 ± 6.5	11.4	0.002
SWS (stages 3, 4)	86.5 ± 7.2	72.6 ± 8.0	0.58	0.45
For descriptive purposes				
Sleep latency[b] (minutes)				
To 1.5 minutes of sleep	15.2 ± 1.9	13.9 ± 2.5	0.348	0.56
To stage 2 sleep	20.3 ± 2.8	16.4 ± 2.6	0.675	0.42
Wake after sleep onset (minutes)	33.2 ± 7.7	25.1 ± 4.9	0.726	0.40
Final wake time (minutes)	3.8 ± 2.2	1.52 ± 1.0	1.665	0.20
Sleep efficiency[c] (%)	89.0 ± 1.7	91.4 ± 1.0	1.492	0.23
REM latency (minutes)	60.3 ± 6.3	75.2 ± 5.7	2.317	0.14
Wake from sleep onset to REM	3.7 ± 1.8	3.9 ± 1.3	1.063	0.31
Number of REM periods[d]	4.4 ± 0.1	4.1 ± 0.1	0.197	0.66
MA/hours of total sleep time[e]	12.7 ± 1.3	13.0 ± 0.9	0.084	0.77

df = 1,40.

[a] Total sleep time is all sleep time (excluding wake time) from sleep onset (defined by 1.5 minutes of sleep) to final awakening.

[b] Sleep latency measurements are from lights out to either the start of the first 1.5 minutes of consecutive sleep epochs or to the first 30-second epoch of stage 2 sleep.

[c] Sleep efficiency is the percentage of time asleep while in bed.

[d] REM period starts with an REM epoch and ends after 15 minutes of NREM or wake.

[e] MA = movement arousals.

[f] *F* values from the ANOVA given for comparison of MDMA and controls. The values in the top part of the table provide the statistical tests for the basic hypotheses. Other values are listed for descriptive purposes only.

cantly less NREM time (mean ± SEM of 301.4 ± 7.4 and 324.6 ± 6.0 minutes, respectively; p = 0.006) (Table 2). There was no significant differences between MDMA and control subjects for the amount of REM sleep (mean ± SEM of 82.4 ± 4.7 and 79.1 ± 4.5 minutes, respectively; p < 0.10) (Table 2).

Within NREM sleep, MDMA subjects had significantly less stage 2 sleep (mean ± SEM of 185.1 ± 8.3 minutes for MDMA subjects versus 222.4 ± 6.5 minutes for controls, p = 0.002). There were no differences between the two groups for slow-wave sleep (SWS) [(stages 3 + 4) mean ± SEM of 86.5 ± 7.2 minutes for MDMA subjects versus 72.6 ± 8.0 minutes for controls, p > 0.1] (Table 2). No differences between groups were noted for total duration of stage 1 (mean ± SEM of 29.8 ± 2.8 minutes for MDMA subjects versus 29.6 ± 3.6 minutes for control subjects, p > 0.1) (Table 2).

Increased age was associated with a decline in SWS (stage 3 + 4) time (df = 1,40, $F = 4.99$, p = 0.03), with no apparent effects on stages 2 or 1. Psychiatric diagnoses or time zone of origin were not associated with changes in SWS (3 + 4), stage 2 or stage 1 sleep. When data were analyzed after removing the 11 subjects with one of the DSM-III-R diagnoses identified as possibly altering sleep, the same statistically significant results were observed (i.e. MDMA subjects had less TST, NREM sleep and stage 2 sleep than control subjects, with no differences between groups for the amount of time spent in REM sleep, stage 1 sleep or SWS). These same results were obtained when the analysis was performed for these directional hypotheses with the limited subset of data for the 28 subjects from only the Eastern and Central time zones.

Other polysomnographic variables

The descriptive comparison of other usual sleep measurements is presented in Table 2 and includes: sleep latency, minutes of stage 3 (S3), minutes of stage 4 (S4), wake minutes after sleep onset, minutes of final awakening before leaving bed, minutes from sleep onset to the first REM, wake minutes after sleep onset to the first REM, number of REM periods, movement arousals per hour of sleep and sleep efficiency. Advanced age was found to be associated with decreased stage 4 (df = 1,41, $F = 12.98$, p < 0.01). There were marginally significant differences (p < 0.10) for the two treatment groups for any of these measurements (Table 2). The pattern of occurrence of SWS in relation to REM periods was reviewed for each patient, and all showed the usual pattern with most of the SWS occurring before the second REM period with relatively increasing amounts of stage 2 and stage 1 sleep occur-

ring later. No differences between the two groups were noted for the pattern of sleep during the night.

Patients with one of the psychiatric diagnoses that might alter sleep had significantly greater number of movement arousals per hour than those without such a diagnosis ($df = 1,40$, $F = 4.84$, $p = 0.03$). There was a significant age effect for minutes of stage 4 sleep. There were no other significant effects for age, time zone of origin or psychiatric diagnoses.

Relationship between extent of MDMA use and sleep abnormalities

The correlation between sleep abnormalities and the number of times individuals had used MDMA did not achieve statistical significance ($p > 0.50$).

DISCUSSION

The results of the present study indicate that individuals with significant prior exposure to MDMA have less TST than age and sex matched controls. Analysis of REM and NREM sleep shows that this difference is due to decreased NREM sleep, with no differences between groups for REM sleep. Within NREM sleep, comparison of MDMA-exposed and control subjects reveals that MDMA subjects have less stage 2 sleep, with no apparent differences in stage 1 sleep or SWS (stage 3 + 4) (Table 2).

The finding that the primary difference between MDMA subjects and controls is the amount of stage 2 sleep is somewhat surprising. Preclinical studies involving pharmacological depletion or anatomic lesions of serotonin neurons generally have shown changes in REM and all of deeper NREM sleep (stages 2, 3 and 4) (24,25). Although studies involving serotonin depletion in humans are few, humans who have been treated with the serotonin synthesis inhibitor p-chlorophenylalanine (PCPA) have been found to have decreased REM sleep, with no changes reported in stage 2 (26). However, most of these preclinical studies involved massive depletions of serotonin with sleep studies generally performed shortly after lesioning. Also, sleep in PCPA-treated humans was evaluated while individuals were still taking PCPA. In contrast, individuals in the present study had taken varying amounts of MDMA in the remote past; the persisting effects may differ from acute effects. It is possible that if studies were performed acutely following MDMA exposure, changes in REM and SWS would be observed.

It should be noted that changes in stage 2 sleep were not due to structural changes in stage 2 itself. Specifically, when individual records were examined in greater detail, no changes in spindle number or density, or differences in K-complexes were detected. Indeed, no gross abnormalities in the sleep records of MDMA-exposed individuals were apparent, suggesting that sleep-generating mechanisms remained largely intact. Even the occurrence of stage 3 and 4 predominantly in the first two NREM cycles showed the same normal pattern for both study groups.

Two factors should be addressed when considering these data. First, because some of the subjects lived in different time zones, polysomnographic recordings might have been affected by recent trans-meridian jet travel. However, 3 days of adjustment generally is adequate for individuals in the age range evaluated in this study. Further, because the expected effects of a west to east time zone change (i.e. increased wake time and longer sleep latency) (32) were not the observed differences between experimental groups, this possibility is less concerning. Time zone of origin also was included in the basic statistical analysis as an independent variable, and no effects were found for any of the sleep variables. As a final check, an analysis of the subset of data from only the Eastern and Central time zones showed essentially the same results as the total sample. A time zone shift of only 1 hour would not be expected to produce the significant effects noted in this study, especially after 3 days of accommodation to the new time zone. A second potential complication of the present findings is the presence of psychiatric disorders in some of the control and MDMA subjects. Again, presence of relevant psychiatric diagnoses was included as an independent variable in the basic statistical analysis and no significant effects were found. Indeed, even when data from these 10 subjects were removed from the analyses, the same statistically significant effects on TST and stage 2 were observed.

It deserves note that despite the heterogeneity of the study population (with some subjects abstaining from MDMA for more than a year), the observed effects on total and stage 2 sleep times are robust. Although the clinical significance of the sleep loss remains unclear, chronic loss of sleep, even in small amounts, might lead to decreased alertness and difficulty with tasks requiring vigilance. Further, individuals with a chronic sleep debt would be expected to be more susceptible to the detrimental effects of sleep deprivation in job-related or social situations. Problems that might be anticipated include errors of omission, diminished ability to retain new information and increased risk for accidents while performing tasks requiring sustained alertness.

In summary, the present results are consistent with the view that serotonin is a modulator of sleep, although the specific mechanism by which serotonin influences sleep remains to be elucidated. The present findings are also consistent with the view that recreational use of MDMA in substantial cumulative doses

may induce lasting CNS serotonergic damage. It may be that by challenging MDMA-exposed individuals with sleep deprivation or with drugs that interfere with serotonin neurotransmission, serotonin dependent functional deficits may become apparent. Such studies hold promise for helping delineate the functional role of serotonin in human behavior. Finally, given the relative paucity of known functional consequences of MDMA use, sleep changes may provide a sensitive measure for detecting subclinical CNS damage secondary to MDMA and related synthetic amphetamine analogs.

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