

# Dose-Response Study of N,N-Dimethyltryptamine in Humans

## I. Neuroendocrine, Autonomic, and Cardiovascular Effects

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**Background:** To begin applying basic neuropharmacological hypotheses of hallucinogenic drug actions to humans, we generated dose-response data for intravenously administered dimethyltryptamine fumarate's (DMT) neuroendocrine, cardiovascular, autonomic, and subjective effects in a group of experienced hallucinogen users.

**Methods:** Dimethyltryptamine, an endogenous mammalian hallucinogen and drug of abuse, was administered intravenously at 0.05, 0.1, 0.2, and 0.4 mg/kg to 11 experienced hallucinogen users, in a double-blind, saline placebo-controlled, randomized design. Treatments were separated by at least 1 week.

**Results:** Peak DMT blood levels and subjective effects were seen within 2 minutes after drug administration, and were negligible at 30 minutes. Dimethyltryptamine dose dependently elevated blood pressure, heart rate, pupil diameter, and rectal temperature, in addition to elevating blood concentrations of  $\beta$ -endorphin, cortico-

trocin, cortisol, and prolactin. Growth hormone blood levels rose equally in response to all doses of DMT, and melatonin levels were unaffected. Threshold doses for significant effects relative to placebo were also hallucinogenic (0.2 mg/kg and higher). Subjects with five or more exposures to 3,4-methylenedioxymethamphetamine demonstrated less robust pupil diameter effects than those with two or fewer exposures.

**Conclusions:** Dimethyltryptamine can be administered safely to experienced hallucinogen users and dose-response data generated for several measures hypothesized under serotonergic modulatory control. Additional studies characterizing the specific mechanisms mediating DMT's biological effects may prove useful in psychopharmacological investigations of drug-induced and endogenous alterations in brain function.

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**H**ALLUCINOGENIC drugs reliably induce a unique constellation of subjective effects in humans. They elicit perceptual illusions and hallucinations, primarily visual but often auditory. Mood effects range from euphoria to panic to bland indifference. Somatic effects include dissociation, relaxation, or tension.<sup>1</sup> "Classic" hallucinogens include phenethylamines (eg, mescaline), indolealkylamines (eg, psilocybin and dimethyltryptamine [DMT]), and the lysergamides (eg, lysergic acid diethylamide [LSD]).<sup>2</sup>

These unique compounds were the focus of intensive clinical research in the 1950s and 1960s. The discovery of LSD may arguably have been as important to the development of a "biological" psychiatry as

was the contemporaneous discovery of chlorpromazine. Hallucinogens' use in clinical research was associated with acceptable risks when subjects, both psychiatric patients and normal controls, were carefully screened, prepared, and followed up.<sup>3</sup> Clinical research with hallucinogens, however, became increasingly difficult with their widespread abuse by young adults. Highly publicized "adverse reactions" to hallucinogens, primarily LSD,<sup>4</sup> resulted in their placement into the restrictive schedule I of the Controlled

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See Subjects and Methods  
on next page

## SUBJECTS AND METHODS

The protocol was approved by the Scientific Advisory Committee of the General Clinical Research Center (GCRC) and the Human Research Review Committee of the University of New Mexico School of Medicine, Albuquerque, the New Mexico State Pharmacy Board, the US Drug Enforcement Administration, and the US Food and Drug Administration.<sup>23</sup> Witnessed written informed consent was obtained from all subjects. Confidentiality and anonymity were maintained throughout the study.

### SUBJECTS

We recruited only experienced hallucinogen users. All subjects but one were recruited by word of mouth; this last subject responded to an announcement sent to a graduate student training office at a local university.

Subjects were initially interviewed by one of us (R.J.S.) to screen for medical and/or psychiatric conditions and assess level of experience with, and ability to manage dysphoric reactions to, hallucinogenic drugs. Subjects were dropped from further consideration if they were taking any medications long-term, had a history of psychosis not secondary to drugs or fever, or had a chronic medical disorder.

Prospective subjects then received a Structured Clinical Interview for DSM-III-R (SCID-R), Outpatient Version,<sup>24</sup> administered by a trained psychiatric research nurse. First-degree relatives' psychiatric histories were obtained during the SCID-R. Diagnoses were confirmed by discussion with two research psychiatrists. We then performed a medical history, physical examination, and laboratory screening tests (including a complete blood count with differential cell count, 24-item chemistry panel, thyroid functions [including thyrotropin], urinalysis, and electrocardiogram).

The demographic characteristics of our subjects are given in the **Table**. Subject 11 was dropped after receiving the nonblind (0.04- and 0.4-mg/kg) doses and the 0.05-, 0.1-, and 0.2-mg/kg doses because he had a major depressive episode precipitated by multiple personal stressors that appeared unrelated to his participation in the study. He responded to desipramine hydrochloride. The average ( $\pm$ SEM) age (excluding subject 11) was  $41.5 \pm 1.5$  years. The group was high functioning, with only one subject not being a professional or student in a professional training program. There was a high incidence of prior major depression in the group. Only one subject was suffering any current Axis I disorder; this was an adjustment disorder resulting from an impending divorce. There also was a high incidence of first-degree relatives suffering from depression and/or alcohol abuse. The number of exposures to hallucinogens ranged from six to "hundreds." Two subjects described a history of cocaine dependence/abuse, currently in remission; the remainder had little or no exposure to cocaine or amphetamines. Not all subjects had used marijuana equally, although all had some experience with it.

### METHYLENEDIOXYMETHAMPHETAMINE USE

Of interest was the breakdown of subjects by amount of methylenedioxymethamphetamine (MDMA, "Ecstasy") use. All but two had used MDMA at least once. Six of the 11 subjects had used MDMA five or more times; five had used it twice or less. Methylenedioxymethamphetamine is a mammalian serotonergic neurotoxin<sup>25</sup> with equivocal long-term effects on human neuroendocrine and/or behavioral function.<sup>26</sup> Thus, we were interested in assessing differential effects of the serotonergic agonist, DMT, in these two groups of users. For the sake of approximating equal cell sizes, we described the six former subjects as having had high exposure and the latter five as having had low or no exposure.

### DRUG

Dimethyltryptamine fumarate was prepared by David E. Nichols, PhD, Purdue University, West Lafayette, Ind. Purity, determined by gas chromatography-mass spectrometry and high-performance liquid chromatography, was greater than 99.9%. It was prepared for clinical administration by the Inpatient Pharmacy of the University of New Mexico Hospital in vials containing 40 mg/mL. Sterility and pyrogenicity testing revealed no abnormalities in a representative sample of vials. The dimethyltryptamine fumarate solution was drawn into a sterile tuberculin syringe at the appropriate dose and diluted with sterile saline to 1.0 mL before administration.

### PROCEDURES

#### Nonblind Drug Administration

First, all subjects received nonblind administrations of 0.04 and 0.4 mg/kg of intravenous (IV) dimethyltryptamine fumarate in the GCRC, usually on consecutive days. Previous work<sup>22</sup> had demonstrated no tolerance to the cardiovascular and subjective effects of a full IM dose of DMT given twice daily for 5 consecutive days. Thus, we did not believe tolerance to DMT's effects would occur at this interval. We decided to administer the drug IV rather than IM as had been reported previously.<sup>16</sup> This was because of our initial dose-finding studies using a subject with experience smoking DMT free base, the usual form and route of administration by recreational users.<sup>27</sup> The onset and intensity of effect of 1.0 mg/kg of IM dimethyltryptamine fumarate was described by this subject as significantly less rapidly developing and hallucinogenic than his previous experience with the smoked drug. Further dose-finding studies with him and another experienced DMT smoker established that 0.4 mg/kg of IV dimethyltryptamine fumarate produced a "rush" and hallucinogenic effect comparable with those seen with a "full dose" of smoked free base.

The nonblind days served several purposes. They allowed us to assess the cardiovascular and subjective

effects of a subclinical and fully hallucinogenic dose of dimethyltryptamine in a novel and potentially anxiety-provoking setting. These days also provided the research team and subjects an opportunity to become acquainted and familiar with each other in the research center setting without the extensive blood drawing and use of the rectal thermistor that could exaggerate any potentially paranoid reactions. Subjects also were able to "calibrate" themselves to what to expect regarding minimal and maximal effects of the drug, one of the purposes of the double-blind study being whether they could distinguish among incremental doses of DMT. Finally, these nonblind days provided subjects with the opportunity to drop out of the study before we had collected extensive data on them.

Subjects were admitted to the GCRC by 9 AM after having fasted since midnight. An IV line was inserted into a forearm vein and kept patent with heparinized saline. Subjects were allowed to relax for 30 minutes before the drug was given. Dimethyltryptamine was infused over 30 seconds and flushed with 5 mL of sterile saline over the next 15 seconds. Blood pressure and heart rate (HR) were taken with an automatic cuff several times before and frequently during the 30 minutes following drug administration. The research team (a registered nurse and psychiatrist) sat quietly on either side of the subject, attentive to verbal and nonverbal cues, but did not offer any direction or advice unless absolutely necessary during the first several minutes, the time of the peak effect of the drug. Sublingual nitroglycerin, and IV diphenhydramine and diazepam, were available at the bedside for sustained hypertension, allergic reactions, or excessive anxiety, respectively. As drug effects resolved, discussion focused on the nature of the subject's experiences. After subjects ate a snack or meal, they were discharged home.

No subject withdrew voluntarily after the nonblind days. One subject was withdrawn because of a marked diastolic blood pressure response (to  $>105$  mm Hg) to the 0.04-mg/kg dose.

#### Double-blind, Placebo-Controlled, Randomized Drug Administration

A computer-generated randomization sequence was coded and kept by the Inpatient Pharmacy of the University of New Mexico Hospital. Subjects were admitted by 9 AM to a dimly lit ( $<100$  lux) room on the GCRC. Two IV lines were started: a small-gauge metal needle in one arm for drug administration, and a large-gauge, three-holed plastic angiocatheter for blood withdrawal. A reusable rectal thermistor probe (YS-400, Yellow Springs Instruments, Yellow Springs, Ohio), configured to a physiological monitor (Vita-Log PMS-8, CPS Inc, Palo Alto, Calif), was inserted. The monitor sampled rectal temperature every minute, and the thermistor probe has an accuracy of  $\pm 0.03^{\circ}\text{C}$ . Blood pressure and HR (vital signs), and pupil diameter (measured by placing a card with black circles differing by 1-mm increments juxtaposed 10 to 15 cm from the subject's eyes), were taken at 30, 15, and

2 minutes before drug administration. Blood samples for corticotropin,  $\beta$ -endorphin, prolactin, GH, cortisol, and melatonin levels were drawn 30 and 2 minutes before drug administration. Drug and saline flush were administered over 45 seconds, and time 0 was when the saline flush was completed. Doses were 0.05, 0.1, 0.2, and 0.4 mg/kg of dimethyltryptamine fumarate and sterile saline placebo. Blood samples were drawn, and pupil diameter and vital signs measured 2, 5, 10, 15, 30, and 60 minutes after drug administration. Study sessions occurred at an interval of at least 1 week and took place from January to September 1991. The one woman subject was studied during the early follicular phase of her cycle. A negative serum pregnancy test drawn the night before her study days was always available before drug administration.

#### ASSAYS

Dimethyltryptamine (free base) blood levels were assayed using the gas chromatography-mass spectrometry technique of Walker et al.<sup>28</sup> Limit of detectability was 1 ng/mL. Corticotropin and  $\beta$ -endorphin levels were assayed by immunoradiometric assays (Nichols Diagnostic Laboratories, San Juan Capistrano, Calif), and lower limits of detectability were 0.2 and 2.2 pmol/L, respectively. Limits of detectability for cortisol, GH, and prolactin radioimmunoassays (all from Diagnostic Products, Los Angeles, Calif) were 6 nmol/L, 1  $\mu\text{g/L}$ , and 1  $\mu\text{g/L}$ , respectively. Growth hormone and prolactin values below 1  $\mu\text{g/L}$  were entered as 0.9  $\mu\text{g/L}$ . The melatonin radioimmunoassay<sup>29</sup> limit of detectability was 5 pmol/L. All assays were performed in duplicate.

#### STATISTICS

Variable values are given as mean  $\pm$  SEM. All analyses were performed using PC SAS Version 6.03 (Cary, NC). Several derived variables were computed for analyses. Baseline values for blood pressure, HR, and pupil diameter were derived by averaging the three values obtained before drug administration (ie, -30, -15, and -2 minutes). Baseline temperature was computed by averaging values for 5 minutes immediately preceding drug administration. Hormone baseline values were computed by averaging results from the -30- and -2-minute samples. Maximum rise above baseline is indicated  $\Delta\text{Max}$ ;  $\Delta\text{AUC}$  represents the area under the curve above baseline, calculated by the trapezoidal rule.

Our primary statistical tool was the univariate analysis of variance (ANOVA) with repeated measures, with dose as the repeated factor. Pairwise comparisons, when the overall F value generated a  $P < .05$ , were performed using the "contrast" statement in the general linear models procedure in SAS. To assess a possible modulatory role of methylenedioxymethamphetamine exposure on dimethyltryptamine's effects on a particular variable, we performed a two-way univariate repeated-measures ANOVA using MDMA history as the independent variable.

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## MISSING DATA

We did not analyze blood hormone level results for the one female subject in the group because her veins collapsed at some point for almost every session, and her blood data were incomplete. However, we did analyze her autonomic and cardiovascular responses.

Pupil diameter was difficult to measure consistently, as subjects varied widely in their ability and/or desire to open their eyes during acute drug intoxication. Thus, these measurements were obtained at the subjects' discretion. Additionally, several subjects had technically poor rectal temperature tracings because of difficulties with probe placement, and these data could not be used. Two subjects had unsatisfactory temperature data for the 0.05- and 0.2-mg/kg sessions; one had no 0.1-mg/kg session data; and one had no temperature data from his placebo session. Finally, one subject refused the rectal thermistor probe, and no temperature data were collected from him. As SAS cannot perform repeated-measures ANOVA on subjects with missing data, we used a less robust one-way ANOVA for the temperature and pupil diameter data, with dose as the independent variable. Fisher's Least Significant Difference Test for pairwise comparisons was performed if the overall F value generated a significance of  $P < .05$ . To assess the effect of DMT exposure on MDMA's effects on pupil diameter and rectal temperature, we performed a two-way ANOVA with dose and MDMA history as independent factors.

Substances Act. Human studies with these drugs effectively ended in the mid-1970s. Despite legal restrictions and severe penalties for manufacture, possession, and distribution of hallucinogens, their use among college students has held relatively steady over the past 20 years.<sup>5</sup>

Basic research into the mechanisms of action of hallucinogens continued, however, and contributed to recent advances in serotonin (5-HT) receptor pharmacology.<sup>6</sup> Recent behavioral, in vivo, and ligand binding data suggest agonist or partial agonist effects at the 5-HT<sub>2</sub>, 5-HT<sub>1A</sub>, and 5-HT<sub>1C</sub> receptors.<sup>7-10</sup> Dopaminergic<sup>11</sup> and noradrenergic<sup>12</sup> effects have been described but not studied recently.

Hallucinogenic drugs have diffuse and relatively well-documented biological effects, presumably related to their serotonergic properties. Growth hormone (GH), prolactin,  $\beta$ -endorphin, corticotropin, and cortisol levels are all affected by serotonergic stimuli.<sup>13</sup> Consistent with the presumed serotonergic properties of the classic hallucinogens, levels of several of these hormones increase with their administration. For example, human prolactin blood levels rise in response to dimethyltryptamine,<sup>14</sup> and rat plasma corticoid levels are stimulated by LSD.<sup>15</sup> Cardio-

vascular variables, core temperature, and pupillary diameter also are affected by serotonergic hallucinogens. Examples of these effects include DMT's hypertensive and mydriatic,<sup>16</sup> LSD's pyretogenic and mydriatic,<sup>17,18</sup> and psilocybin's hypertensive and tachycardic<sup>19</sup> properties.

Dimethyltryptamine is a short-acting hallucinogen, first discovered in hallucinogenic Amazonian snuffs.<sup>20</sup> It was later synthesized and determined to be active by parenteral (intramuscular [IM]) administration only.<sup>16</sup> Its discovery in human body fluids prompted a flurry of investigations into its possible biosynthesis in man and its role as a putative endogenous psychotogen.<sup>21</sup> Difficulties distinguishing peripheral levels of DMT between normal controls and patients with endogenous psychoses led to a loss of interest in the function of this hallucinogenic tryptamine.<sup>22</sup>

It has been impossible to test in humans hypotheses of hallucinogen mechanisms of action developed from basic research. Systematic psychopharmacological investigations are the necessary interface bridging recent neuropharmacological findings to human effects. Dose-response investigations applying current psychiatric research methods to assess hallucinogens' effects can generate data providing the bases for more experimental studies, such as selective blockade with receptor subtype antagonists.

Several properties recommend DMT as an appropriate drug with which to renew such investigations. Its short duration minimizes prolonged dysphoric reactions in the potentially stressful environment of a modern clinical research center. The lack of a widespread "folklore" concerning its effects provides less bias and expectations from subjects. Finally, DMT's role in human brain function has yet to be explicated in normal and pathological states. That is, understanding effects and mechanisms of action of DMT may shed light on the etiology and treatment of endogenous hallucinatory conditions.

We have performed a dose-response study of the neuroendocrine, cardiovascular, autonomic, and subjective effects of dimethyltryptamine fumarate using a double-blind, placebo-controlled, randomized design. This article focuses on biological data generated by this study.

## RESULTS

The major findings of this study are the following: (1) Intravenous dimethyltryptamine fumarate was fully hallucinogenic in doses of 0.2 and 0.4 mg/kg. Effects were felt nearly instantaneously, peaked within 2 minutes after injection, and resolved within 20 to 30 minutes. The time course of DMT blood levels matched the march of subjective effects. (2) Multiple biological variables rose dose dependently in response to DMT. The time course of elevations in blood levels of pro-opiomelanocortin

## Demographic Characteristics of Subjects\*

Subject No./ Age, y/Sex	Occupation	Axis I Diagnoses	Marital Status	Family Psychiatric History	Times Used			
					Marijuana	Cocaine, Amphetamines	Hallucinogens	Methylene dioxymethamphetamine
1/45/M	Construction worker	None	Divorced ×2, married	None	10-20	0	10-20	10
2/39/F	Psychologist	None	Divorced ×2, married	Father, depression, chronic; eating disorder?; mother, "hysterical"	100s	50-100	>50	75-100
3/38/M	Physician	Major depression, resolved; cannabis dependence, partial remission	Divorced ×1	Father, depression (taking amitriptyline hydrochloride)	1000s	3	50	1
4/45/M	Psychologist	Adjustment disorder, depressed	Divorced ×3	Brother, adjustment disorder, mixed	>400	15	30	10-15
5/34/M	Graduate student	Alcohol dependence, in remission; cannabis abuse, in remission	Never married	Brother, major depression	1000s	20-25	20-30	1
6/37/M	Resident physician	Major depression, resolved	Never married	None	1000s	15-20	50-60	0
7/42/M	City administrator	None	Divorced ×1, married	None	100s	<10	>100	5-10
8/36/M	Drug dealer	Cannabis dependence, in remission; cocaine dependence, in remission; stimulant abuse, in remission	Divorced ×1, married	Father, alcohol abuse	1000s	100s	>200	5-10
9/46/M	Owner of large business	Adjustment disorder, depressed, resolved; alcohol abuse, in remission	Divorced ×1	Mother, alcohol abuse; father, alcohol abuse	100s	50-100	6	0
10/45/M	Restaurant manager, writer	Cocaine dependence, in remission; alcohol abuse, in remission; major depression, resolved; depressive disorder, NOS, resolved	Divorced ×3	Father, alcohol abuse	100s	100	>100	10-12
11/38/M	Physician	Prolonged (18-mo) grief reaction vs major depression, resolved	Divorced ×2	Mother, major depression; father, alcohol abuse	50	3	75-100	8
12/50/M	Counselor	None	Divorced ×2, married	Alcohol abuse	100s	15-20	10	2

\*NOS indicates not otherwise specified. Subject 11 suffered a major depression during the study and was withdrawn before completing it. His data are included for illustrative purposes.

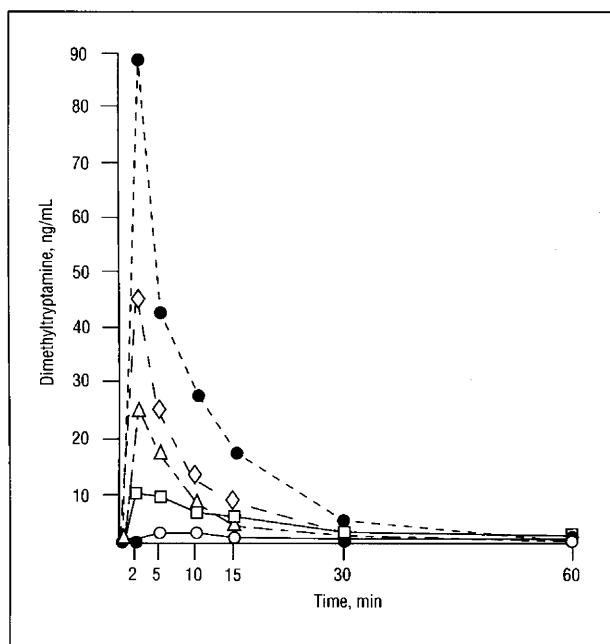
(POMC) peptides (corticotropin and  $\beta$ -endorphin), HR, blood pressure, and pupil diameter paralleled subjective effects and DMT blood concentrations. Elevations of prolactin and cortisol blood levels lagged 5 to 10 minutes behind these changes. Core temperature and GH effects did not begin until the first set of perturbations had almost resolved (15 to 30 minutes) and may not have peaked by 60 minutes after DMT administration.

### DMT BLOOD LEVELS

There was no measurable DMT in blood samples before drug administration or after saline placebo administra-

tion for any subject except for subject 4. He had measurable DMT levels at one point before active drug administration and twice after placebo injection. His low levels in these circumstances are consistent with endogenous levels in a study of normal volunteers using a similar assay.<sup>30</sup> However, he regularly took "Chinese herbs" and "homeopathic tinctures" as tonics, unlike any of our other subjects.

Plasma levels of DMT peaked at the first blood draw, 2 minutes after the injection was completed, closely corresponding to peak psychological effects. Generally, a doubling of dose resulted in a doubling of  $\Delta$ Max values. These data are displayed in **Figure 1**. As previously de-



**Figure 1.** Mean dimethyltryptamine (free base) values in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

scribed,<sup>31</sup> DMT levels varied widely among subjects, peak values ranging from 32 to 204 ng/mL after the 0.4-mg/kg injection.

## BASELINE EFFECTS

There were no differences among baseline values for any biological variable among the five treatment conditions.

## NEUROENDOCRINE EFFECTS POMC PEPTIDES

The  $\Delta$ AUC and  $\Delta$ Max for both corticotropin and  $\beta$ -endorphin rose dose dependently in response to dimethyltryptamine fumarate, with the 0.4-mg/kg dose's effects being statistically greater than all other doses for both of these variables. The effects of placebo and the 0.05- and 0.1-mg/kg doses could not be separated statistically. Of interest was the stimulation of corticotropin and  $\beta$ -endorphin levels by saline placebo. This has the appearance of a conditioned response to placebo injection in all these subjects who had previously received the somewhat anxiety-provoking 0.4-mg/kg dose nonblind. These data are displayed graphically in **Figure 2** (corticotropin) and **Figure 3** ( $\beta$ -endorphin).

## Prolactin

The  $\Delta$ Max and  $\Delta$ AUC for prolactin demonstrated a significant dose-dependent stimulatory effect of dimethyltryptamine fumarate. The 0.4-mg/kg dose raised both of

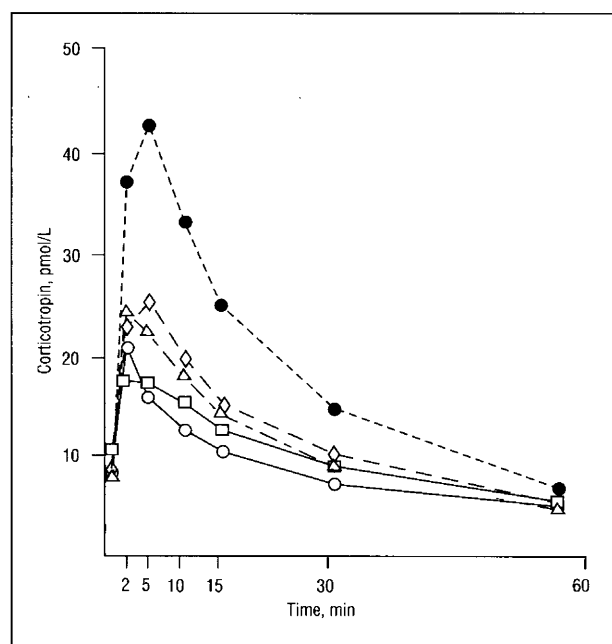
these variables significantly more than placebo and the 0.05- and 0.1-mg/kg doses. The effects of 0.4 and 0.2 mg/kg on  $\Delta$ Max prolactin could not be distinguished from each other, although the 0.4-mg/kg dose's effects on  $\Delta$ AUC were significantly greater than those of 0.2 mg/kg. The effects of 0.2, 0.1, and 0.05 mg/kg of dimethyltryptamine fumarate and of placebo on  $\Delta$ AUC were not statistically separable. These data are graphically presented in **Figure 4**. Note that prolactin effects were slightly delayed relative to the POMC peptides.

## Cortisol

The  $\Delta$ AUC and  $\Delta$ Max for cortisol both demonstrated dose-dependent stimulatory effects of dimethyltryptamine fumarate. The 0.4-mg/kg dose raised these two variables more than all other doses. The effects of 0.4 mg/kg on  $\Delta$ AUC for cortisol could not be statistically distinguished from the effects of 0.2 mg/kg, however. Neither could the 0.4-mg/kg dose's effects on  $\Delta$ Max for cortisol be separated statistically from 0.2 and 0.05 mg/kg. Effects of the 0.05-, 0.1-, and 0.2-mg/kg doses on  $\Delta$ AUC and  $\Delta$ Max were not statistically different, although their effects were numerically greater than those of saline. These data are graphically presented in **Figure 5**.

## Growth Hormone

There was a trend for DMT to produce a rise in  $\Delta$ AUC for GH. The  $\Delta$ Max for GH rose in response to DMT administration. Although all doses of DMT raised GH lev-



**Figure 2.** Mean blood corticotropin values in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

els relative to saline placebo, effects of different doses could not be distinguished from each other. These data are graphically displayed in **Figure 6**. Note the delay in GH effects relative to the other neuroendocrine results.

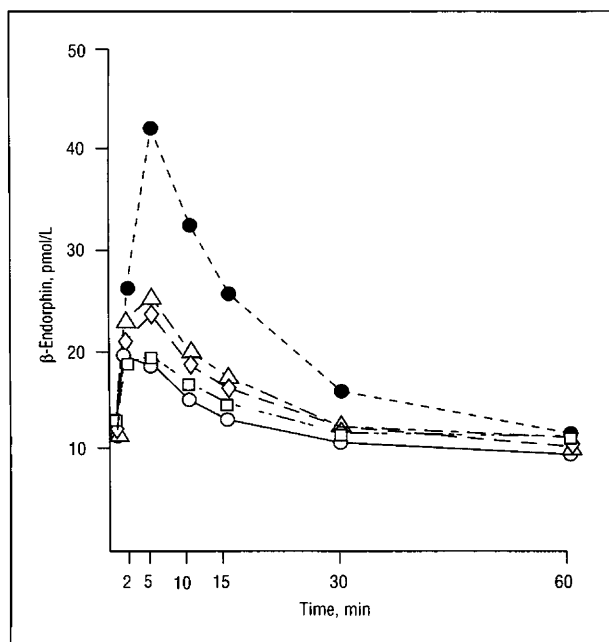
### Melatonin

We only assayed six subjects' blood samples for melatonin from their 0.4-mg/kg sessions. Utilizing one-sample *t* tests, there was no effect of 0.4 mg/kg of dimethyltryptamine fumarate on either  $\Delta\text{Max}$  or  $\Delta\text{AUC}$  for melatonin (data not given), so the remaining samples were not assayed.

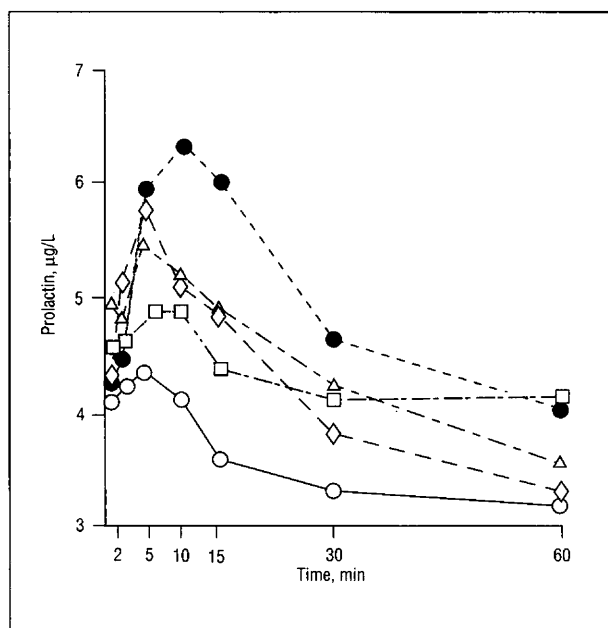
## AUTONOMIC EFFECTS

### Rectal Temperature

The  $\Delta\text{Max}$  and  $\Delta\text{AUC}$  for temperature demonstrated a significant effect of dimethyltryptamine fumarate. For  $\Delta\text{AUC}$ , the 0.4-mg/kg dose's effects were greater than those of 0.1 and 0.05 mg/kg and saline, but could not be distinguished from those of 0.2 mg/kg. The effects of 0.2, 0.1, and 0.05 mg/kg of drug and of saline could not be statistically separated. For  $\Delta\text{Max}$  in temperature, the 0.4- and 0.2-mg/kg doses' effects were greater than those produced by 0.1 or 0.05 mg/kg or placebo. The  $\Delta\text{Max}$  effects of 0.4 and 0.2 mg/kg could not be statistically separated from each other; neither could the effects of the three latter treatments be separated. These data are graphically displayed in **Figure 7**, where the delayed effect relative to other variables can be seen.



**Figure 3.** Mean blood  $\beta$ -endorphin values in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).



**Figure 4.** Mean blood prolactin values in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

### Pupil Diameter

As discussed in the "Procedures" section, our data for pupil diameter contained the most missing points and should be interpreted cautiously. Missing values made a calculation of  $\Delta\text{AUC}$  pupil diameter impossible for the more disruptive 0.2- and 0.4-mg/kg doses. Furthermore, these data were analyzed using ANOVA without repeated measures, a less robust analytic tool.

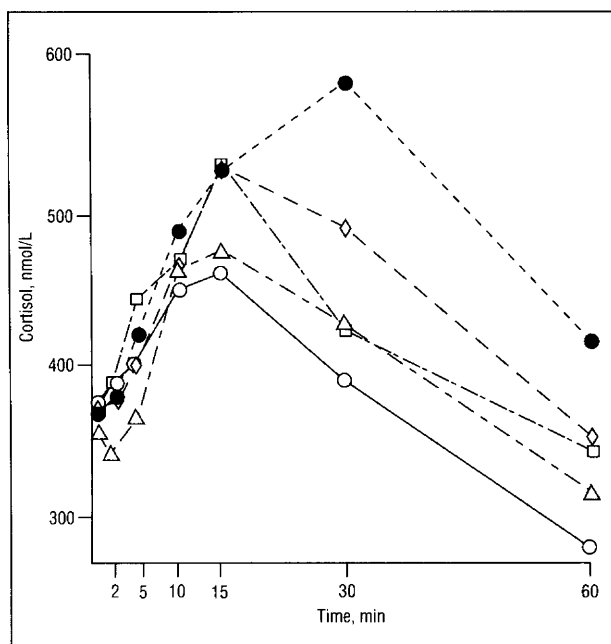
The  $\Delta\text{Max}$  pupil diameter demonstrated significant effects of DMT. The 0.4-mg/kg dose increased pupil diameter more than all other treatments. Effects of placebo and 0.05, 0.1, and 0.2 mg/kg could not be distinguished from each other. These data are displayed graphically in **Figure 8**.

## CARDIOVASCULAR EFFECTS

Dimethyltryptamine dose dependently elevated  $\Delta\text{Max}$  and  $\Delta\text{AUC}$  values for both HR and mean arterial blood pressure (MAP). For  $\Delta\text{Max}$  HR, effects of 0.4 and 0.2 mg/kg were significantly greater than those of 0.1 and 0.05 mg/kg and saline; these latter three treatments' effects were not distinguishable from each other. Neither were the effects of 0.4 and 0.2 mg/kg separable from each other. Effects on  $\Delta\text{AUC}$  HR were less clearly separable by dose but followed the same pattern.

The 0.4-mg/kg dimethyltryptamine fumarate dose raised  $\Delta\text{AUC}$  MAP significantly more than 0.1 and 0.05 mg/kg and saline. These latter three treatments' effects could not be distinguished from each other. Neither were the





**Figure 5.** Mean blood cortisol values in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

effects of 0.2 and 0.4 mg/kg statistically separable. The 0.4- and 0.2-mg/kg doses caused significantly greater elevations of  $\Delta$ Max MAP than 0.1 and 0.05 mg/kg and saline; the two former doses' effects could not be distinguished from each other. These data are graphically displayed in **Figure 9** (HR) and **Figure 10** (MAP).

### MDMA EFFECTS

For all of the biological variables under investigation, only  $\Delta$ Max pupil diameter values were smaller across all doses of DMT in the high-exposure compared with the low- or no-exposure MDMA group (high exposure,  $0.6 \pm 0.2$  mm; low or no exposure,  $1.5 \pm 0.2$  mm;  $F=11.3$ ,  $P=.002$ ).

### SUBJECTIVE EFFECTS

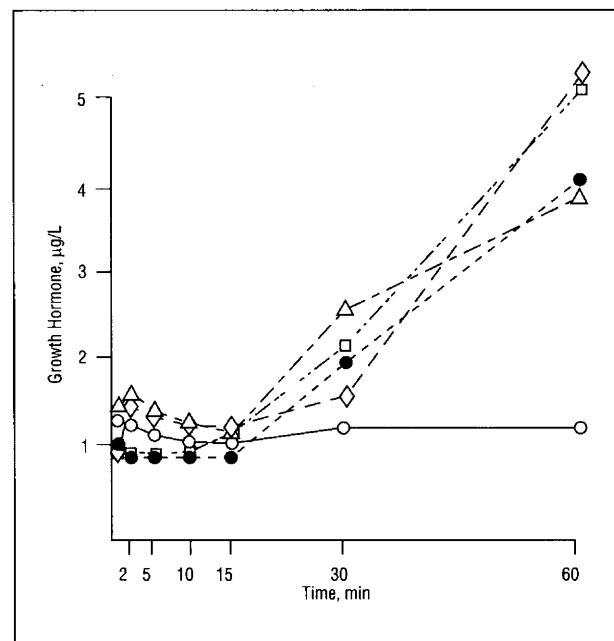
A detailed description of subjective effects, and the development of and preliminary data generated by our new rating scale, the Hallucinogen Rating Scale (HRS), are presented in a companion article.<sup>32</sup> Briefly, subjects felt the onset of effects before the 45-second infusion was completed. Peak hallucinogenic effects (with 0.2 and 0.4 mg/kg) occurred usually by the first blood draw and vital signs check, at 2 minutes after injection, a useful temporal reference point for subjects. Subjects remained moderately intoxicated for another 10 to 20 minutes. They felt relatively normal at 20 to 30 minutes after injection. Several described a relaxed, "at ease" feeling for an additional 30 minutes.

All subjects but one experienced visual hallucinatory phenomena at 0.2 and 0.4 mg/kg of dimethyltryptamine fu-

marate. Brief, poorly formed auditory hallucinations were experienced by most subjects. Somatic effects consisted of an intense rush, felt throughout the body or specifically in the head, and bodily dissociation, usually associated with a transient anxious or fearful emotional reaction. Cognitive effects were not particularly profound; rather, an "observing ego" was maintained, alert and attentive to the perceptual and somatic effects of the drug. The 0.2-mg/kg dose's perceptual perturbations, rush, and disorganizing effects were less intense than for 0.4 mg/kg, and 0.2 mg/kg was the dose preferred by many subjects. The 0.1-mg/kg dose of dimethyltryptamine fumarate produced hallucinatory phenomena in only one subject (the woman in the study). Somatic effects predominated, and many subjects disliked this dose the most. The 0.05-mg/kg dose was mistaken for placebo by several subjects. If effects were noted, they were usually somatic, with a warm, relaxed, and "floating" bodily sensation.

### COMMENT

We safely administered graded doses of IV DMT, an endogenous hallucinogen and schedule I drug of abuse, to a group of experienced hallucinogen users. Dose-dependent responses were observed for several neuroendocrine, cardiovascular, and autonomic variables in a randomized, double-blind, saline placebo-controlled design. Peak psychological effects paralleled the time course of DMT blood levels, which appeared, peaked, and fell rapidly. Blood levels of the POMC peptides, corticotropin and  $\beta$ -endorphin, closely followed the course of DMT



**Figure 6.** Mean blood growth hormone values in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

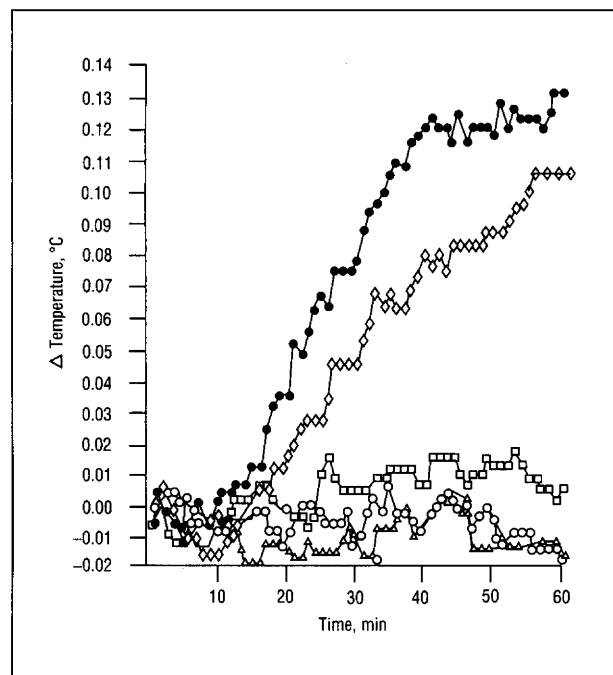


levels and hallucinogenic effects, as did pupil diameter and cardiovascular responses. Cortisol and prolactin levels rose in a dose-dependent fashion and followed the first group of variables' course by 5 to 10 minutes. Core temperature and GH stimulation were most delayed, although GH effects were not separable by dose. Stimulation of daytime melatonin levels was not seen.

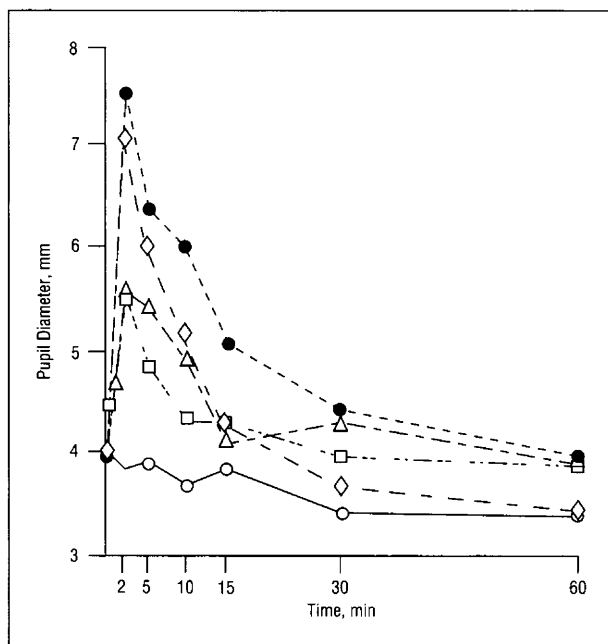
The threshold for significant biological effects of dimethyltryptamine relative to placebo was also that for its hallucinogenic properties: 0.2 mg/kg and higher. The 0.4-mg/kg dose of IV dimethyltryptamine fumarate produced blood levels and psychological effects comparable with those seen with administration of more than twice higher doses of IM dimethyltryptamine hydrochloride or creatine sulfate.<sup>31</sup> However, the IV route generated a more rapid onset (nearly instantaneous) and offset for these effects than the IM route.

Dimethyltryptamine, found in Amazonian hallucinogenic plant mixtures and human body fluids, meets electrophysiological,<sup>33</sup> pharmacological,<sup>34</sup> and behavioral<sup>35</sup> criteria for hallucinogenicity in lower animals. It had been used safely in humans in this country and Europe.<sup>14,16,31</sup> Its short duration of action was believed capable of providing a discrete, more manageable hallucinogenic state in a clinical research setting than might the 8- to 12-hour effects of lysergic acid diethylamide.

Hallucinogenic drugs are serotonergic agonists or partial agonists, in addition to having adrenergic and dopaminergic properties. The 5-HT receptor subtypes of inter-



**Figure 7.** Mean rectal temperature values relative to baseline temperature in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles). Baseline temperature values were calculated by averaging the values of the 5 minutes immediately preceding dimethyltryptamine administration.



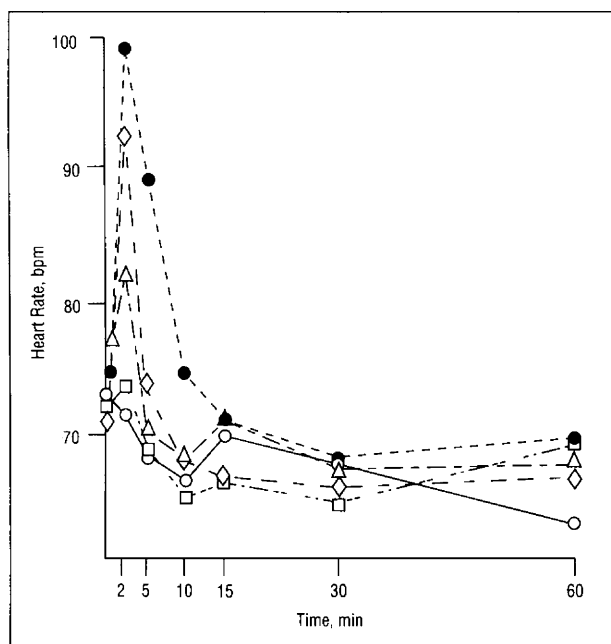
**Figure 8.** Mean pupil diameter values in 11 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

est include the 5-HT<sub>2/1C</sub> and 5-HT<sub>1A</sub>.<sup>36,37</sup> We therefore chose our measured variables because they are believed regulated or modulated to a significant degree by serotonergic neurotransmission. These variables included multiple neuroendocrine markers, blood pressure, HR, rectal temperature, and pupil diameter. As DMT has nearly equal affinities for both the 5-HT<sub>2</sub> and 5-HT<sub>1A</sub> subtypes,<sup>34</sup> many of the effects to be discussed may devolve from activation of either; however, functional interactions in humans also have been described<sup>38</sup> and may be important.

Levels of the POMC peptide hormones, corticotropin and  $\beta$ -endorphin, both rose dose dependently in our subjects. They rose quite quickly, peak values being seen at 5 minutes after injection. With doses of 0.1 mg/kg and higher,  $\Delta$ AUC and  $\Delta$ Max values for these two hormones were nearly identical, confirming their corelease.<sup>39</sup> These rises in  $\beta$ -endorphin and corticotropin extend human<sup>40,41</sup> data demonstrating serotonergic stimulatory effects. Either 5-HT<sub>1A</sub><sup>42</sup> or 5-HT<sub>2</sub><sup>43</sup> subtypes may be involved.

Prolactin levels rose in our subjects in a dose-dependent manner, confirming and extending the data of Meltzer et al.<sup>14</sup> wherein cyproheptadine inconsistently blocked DMT's stimulatory effect. Multiple experimental procedures<sup>44-47</sup> have suggested a stimulatory effect of serotonergic neurotransmission on prolactin levels. Subtype delineation is not clearly understood, but both 5-HT<sub>1A</sub><sup>48</sup> and 5-HT<sub>2</sub><sup>49</sup> receptors appear involved.

Cortisol levels rose dose dependently in our subjects, consistent with the robust elevation of corticotropin described above, and with earlier human data.<sup>14</sup> Se-



**Figure 9.** Mean heart rate values (in beats per minute [bpm]) in 11 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

rotonin receptor activation stimulates peripheral cortisol levels, most likely via corticotropin release,<sup>50</sup> with relevant subtypes having been discussed previously. The cortisol effects in our subjects did not provide as useful a differentiation among doses as the POMC hormones.

Hallucinogen-induced hyperthermia in humans<sup>51</sup> may occur by means of central<sup>52</sup> and/or peripheral<sup>53</sup> 5-HT<sub>2</sub> activation. Dimethyltryptamine's hyperthermic effects are probably mediated by the 5-HT<sub>2</sub> subtype, as 5-HT<sub>1A</sub> agonists are hypothermic in man.<sup>42</sup> The delayed time course of the temperature rise seen with DMT is of interest and may reflect more complex homeostatic mechanisms controlling this variable than those with a more rapid time course.

Previous human studies have described variable effects of longer-acting hallucinogenic drugs on cardiovascular variables, including hypotension and hypertension, and tachycardia and bradycardia.<sup>54</sup> Dimethyltryptamine's excitatory cardiovascular properties confirm and extend previous human data<sup>55</sup> and suggest 5-HT<sub>2</sub> agonism. The 5-HT<sub>2</sub> agonists usually elicit a rise in blood pressure, without reliable increases in HR.<sup>56,57</sup> In contrast, 5-HT<sub>1A</sub> agonists generally produce a drop in blood pressure, again without consistent HR effects.<sup>58</sup>

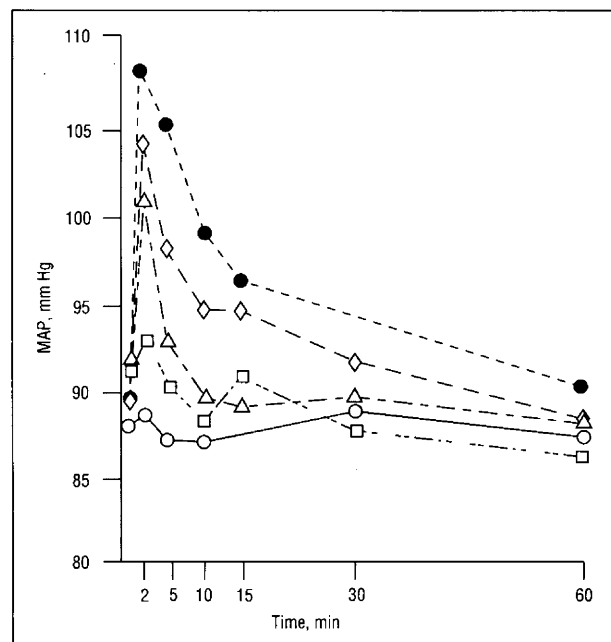
Dimethyltryptamine resembles other classic hallucinogens in its mydriatic properties<sup>59</sup>; this pupillary dilatation may be 5-HT<sub>2</sub> mediated.<sup>60</sup> As the pupillary diameter data were both the least reliably measured (ie, we did not use automated equipment, which also could have measured more dynamic features of pupillary function)

and contained the most missing values, they must be considered preliminary.

We found no dose dependency of DMT's stimulation of blood GH levels. Meltzer et al<sup>14</sup> demonstrated a cyproheptadine-sensitive stimulatory effect of one DMT dose on peripheral GH levels in humans. Perhaps if we had continued drawing samples for 2 hours, as did Meltzer et al, we might have found better separation of effects by dose.

Subjective effects of IV dimethyltryptamine were consistent with previous reports of parenterally administered DMT<sup>16,31,61</sup> and were marked by perceptual, dissociative, affective, and cognitive alterations typical of the classic hallucinogens. Onset from the IV route was nearly instantaneous, rather than taking several minutes to develop, and effects were shorter than previously published IM data. However, this time course is quite similar to reports of DMT smoked free base.<sup>27</sup> The three subjects in the group with experience smoking DMT free base all volunteered that the IV route was somewhat more rapid and intense in onset and effects than smoking the compound. In this regard, DMT is actively transported across the blood-brain barrier in the rat.<sup>62</sup> A more detailed account of these effects and their quantification by a new rating scale are described in a companion article.<sup>32</sup>

Dimethyltryptamine, as a putative directly acting 5-HT agonist in humans, can be most appropriately compared with 6-chloro-2-(1-piperazinyl) pyrazine (MK-212) and *m*-chlorophenylpiperazine (*m*-CPP), although only *m*-CPP has been given intravenously to humans. Neither drug produces the typical hallucinogenic syndrome in normal sub-



**Figure 10.** Mean arterial blood pressure (MAP) values in 11 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).

jects; however, behavioral effects may be more disruptive in psychiatric samples.<sup>63,64</sup> Both *m*-CPP and MK-212 have complex effects at multiple 5-HT receptor subtypes, in addition to effects on other neurotransmitters.<sup>65</sup>

Intravenous *m*-CPP's biological effects are similar to those of DMT. Cortisol and GH stimulation is comparable in magnitude to DMT's, but the prolactin response to DMT is smaller.<sup>66</sup> Similarly, GH responses are delayed relative to those of prolactin and cortisol. Hyperthermic effects of IV *m*-CPP also are relatively delayed and are greater than those seen with DMT.<sup>67</sup> However, temperature data were collected longer for IV *m*-CPP than for DMT, and we may have missed a rise of similar magnitude. Behaviorally, IV *m*-CPP's peak effects occur somewhat later than those of DMT,<sup>67</sup> perhaps related to DMT's previously mentioned active transport into the brain.

Orally administered MK-212 elevates prolactin and cortisol (but not GH) blood levels,<sup>64</sup> blood pressure, and body temperature.<sup>68</sup> As MK-212 has never been given intravenously to humans, a comparison of the temporal sequence of its effects with IV DMT or *m*-CPP is not possible.

The only biological effect demonstrated in subjects with a greater cumulative exposure to the serotonergic neurotoxin MDMA relative to the group with less exposure was a decreased pupillary response to all doses of DMT. This is opposite to what might be expected based on augmented behavioral effects of hallucinogens in amine-depleted<sup>69</sup> or denervated<sup>70</sup> animals. We are unable to explain this finding, except to note that our pupil diameter data were the least complete and objectively measured, and were analyzed by ANOVA without repeated measures.

We erroneously hypothesized that daytime melatonin levels might be elevated secondary to DMT administration, based on the presence of 5-HT<sub>2</sub> receptors on pineal tissue<sup>71</sup> and stimulation by DMT of a requisite enzyme for melatonin synthesis.<sup>72</sup> However, the lack of a stimulatory effect of DMT on melatonin is relevant regarding the specificity of our neuroendocrine results. Previous work<sup>73</sup> showed that melatonin levels doubled after a "stressful" long-distance race, although  $\beta$ -endorphin levels rose to only half those noted in the present DMT study. These two sets of data make it unlikely that a "stress" effect (ie, purely sympathetic activation) drove our neuroendocrine variables; if so, either melatonin levels would have risen or  $\beta$ -endorphin effects would have been much greater.

### CAVEATS

Our sample of subjects had a heavy loading of personal (50%) and family (67%) histories of affective disorder and/or alcohol abuse, both of which may be associated with abnormalities in serotonergic responsivity.<sup>74,75</sup> Thus, the data generated from this study may not be generalizable to strictly "normal" subjects. In addition, nine of 11 subjects had been divorced, there being a total of 17 divorces in this group. Although not specifically as-

sessed, this high rate of divorce may imply a certain degree of impulsivity within our subjects, another condition in which serotonergic abnormalities have been described.<sup>76</sup>

One subject's blood pressure response to a screening, nonblind dose of 0.04 mg/kg caused him to be withdrawn from further participation. After completing this study, while screening additional subjects for subsequent protocols, another subject with a history of borderline essential hypertension (currently asymptomatic) also had a robust diastolic response to 0.05 mg/kg of dimethyltryptamine fumarate and was withdrawn from further sessions. Thus, we recommend that subjects with a history of hypertension, even though currently asymptomatic, not be considered for IV DMT studies. In addition, all prospective subjects must first be screened with the low, minimally psychoactive 0.05-mg/kg dose; diastolic blood pressure responses to more than 100 mm Hg contraindicate exposure to higher doses of DMT.

### CONCLUSION

Human data are necessary to begin bridging basic neuropharmacological and clinical psychopharmacological concepts of hallucinogenic drugs' effects and mechanisms of action.<sup>77</sup> Using careful screening and preparation of subjects, attentive yet unobtrusive supervision of the acute drug intoxication, and follow-up, DMT was safely administered to a group of experienced hallucinogen users and normative dose-response data generated. The most salient biological variables, based on our data, seem to be corticotropin, prolactin, core temperature, blood pressure, HR, and pupil diameter. Pupil diameter studies, if performed, would benefit from the use of automated equipment.

We believe the importance of these data derive from at least two perspectives. The first is that of understanding effects and mechanisms of action of these intriguing drugs. Many of DMT's biological effects in psychiatrically healthy hallucinogen users are now much better characterized. The properties of other classic and nonclassic hallucinogens (such as 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) now can be assessed for their degree(s) of similarity. In addition, although serotonergic mechanisms are believed primary in mediating hallucinogens' effects, these data can help validate this hypothesis by performing human studies using selective 5-HT receptor subtype antagonists. Experiments also can be designed to assess the relative contributions of noradrenergic and dopaminergic neurotransmission.

Second, DMT might be considered an additional serotonergic probe of neuroendocrine and behavioral variables in research attempting to characterize neurotransmission in normal volunteers and psychiatrically ill subjects with presumed serotonergic abnormalities. Although the hallucinogenic effects of DMT are not sepa-

rable from its threshold effects (relative to placebo) on the multiple biological factors presented herein, these effects, if judiciously managed, should not present insurmountable difficulties. mCPP, for example, increases several patient populations' symptoms but remains a valuable tool for human serotonergic studies. However, it must be emphasized that until DMT's effects are mechanistically characterized in normal subjects, there would not be sufficient data to conclude that altered responses to DMT necessarily implicated altered 5-HT function.

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