Differential Tolerance to Biological and Subjective Effects of Four Closely Spaced Doses of N,N-Dimethyltryptamine in Humans

Rick J. Strassman, Clifford R. Qualls, and Laura M. Berg

Tolerance to the behavioral effects of the short-acting, endogenous hallucinogen, N,N-dimethyltryptamine (DMT) is seen inconsistently in animals, and has not been produced in humans. The nature and time course of responses to repetitive, closely spaced administrations of an hallucinogenic dose of DMT were characterized. Thirteen experienced hallucinogen users received intravenous 0.3 mg/kg DMT fumarate, or saline placebo, four times, at 30 min intervals, on 2 separate days, in a randomized, double-blind, design. Tolerance to "psychedelic" subjective effects did not occur according to either clinical interview or Hallucinogen Rating Scale scores. Adrenocorticotropic hormone (ACTH), prolactin, cortisol, and heart rate responses decreased with repeated DMT administration, although blood pressure did not. These data demonstrate the unique properties of DMT relative to other hallucinogens and underscore the differential regulation of the multiple processes mediating the effects of DMT.

Key Words: N,N-dimethyltryptamine, hallucinogens, tolerance, serotonin receptors, schizophrenia, drug abuse

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Introduction

Hallucinogens produce a unique syndrome of psychological effects in humans. Perceptual, cognitive, and affective processes are often profoundly altered, with the maintenance of a relatively clear sensorium (Freedman 1968). The neuropharmacology of "classic" hallucinogens lysergic acid diethylamide (LSD), mescaline, and psilocybin, emphasizes serotonin (5-HT) mechanisms (Glennon et al 1985).

Tolerance to hallucinogens' behavioral effects, by which reduced responses occur with repeated administration, is seen in humans (Isbell et al 1956) and lower animals (Freedman et al 1958). Cross-tolerance, by which drugs of disparate structure, but presumed similar mechanism of action, produce tolerance to each other, also occurs (Balestrieri and Fontanari 1959; Appel and Freedman 1968). Tolerance to the effects of the naturally occurring, short-acting tryptamine hallucinogen, N,N-dimethyltryptamine (DMT) is difficult to elicit in animals (Kovacic and Domino 1976), and was not seen in one previous human report (Gillin et al 1976). In addition,

From the Departments of Psychiatry (RJS, LMB) and Medicine (CRQ), School of Medicine, and the Department of Mathematics and Biostatistics (CRQ), University of New Mexico, Albuquerque, NM.

Address reprint requests to Rick J. Strassman, M.D., 1783 Rockland Avenue, Victoria, BC V851X1, Canada.

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LSD-tolerant individuals showed undiminished responses to DMT (Rosenberg et al 1964).

Whether tolerance to DMT in humans can be demonstrated is important for at least two reasons. Although tolerance to longer-acting hallucinogens occurs readily, the time course of this tolerance makes careful study of this process unwieldy. If tolerance to a shorter-acting drug such as DMT could be demonstrated, it might be possible to study tolerance development to subjective and biological effects of the repeated administration of an hallucinogen within a day.

The inability of LSD to produce cross-tolerance to DMT challenges the assumption that all "classic" hallucinogens produce their effects by similar mechanisms, and emphasizes the importance of detailed psychopharmacological characterization of individual members of this drug class. If tolerance to DMT were impossible to demonstrate, the agent would no longer would be considered a typical hallucinogen.

Methods

Subjects

Experienced hallucinogen users were recruited as described previously (Strassman and Qualls 1994). Witnessed written informed consent was obtained. All volunteers were free of current axis I disorders, determined by a semistructured psychiatric interview (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-IIIR) [SCID-R-OP] [Spitzer et al 1987]), and were medically healthy, determined by physical examination and laboratory screening tests. None was taking any medications regularly. Ages ranged from 22 to 45 years (mean 35.5 years). There were nine men and four women. Women were studied during the early follicular phase of their menstrual cycle.

Studies took place in the inpatient unit of the University of New Mexico Hospital's General Clinical Research Center (GCRC). All subjects received nonblind test doses of intravenous (IV) 0.05 and 0.4 mg/kg DMT fumarate on separate days, as described previously (Strassman et al 1994). Intravenous (IV) DMT fumarate was administered over 30 s through an indwelling forearm venous catheter, and the IV line was flushed with sterile saline for an additional 15 s. Cardiovascular responses were assessed frequently, and the Hallucinogen Rating Scale (HRS [Strassman et al 1994]) was administered after drug effects had resolved. Three subjects were dropped in this phase: one because of a vasovagal reaction to 0.4 mg/kg DMT, one because of a hypertensive response to 0.4 mg/kg DMT, and one because of a dysphoric response to 0.05 mg/kg DMT.

Pilot Studies

In order to determine dose and interval parameters for the tolerance study, we performed pilot work with three volunteers. Previous literature reported that four (daily) doses of long-acting hallucinogens elicit tolerance (Isbell et al 1956). The only published human DMT tolerance protocol demonstrated no tolerance development with twice daily sessions, separated by 5 hours, for 5 consecutive days (Gillin et al 1976). However, "field reports" suggest a "refractory period" of only 15–30 min (Stafford 1992). Since plasma DMT levels are nearly undetectable 30 min after IV administration of "psychedelic" doses of 0.2 or 0.4 mg/kg (Strassman et al 1994), we believed a 30–60 min interval was an appropriate target.

In order to assess tolerability of repeated dosing of IV DMT, and to make certain no sensitization to repeated DMT doses occurred (Gillin et al 1973), we gave a minimal dose, 0.05 mg/kg, every hour, four times. The interval was then shortened to 30 min 1 week later. This process was repeated with 0.1, 0.2, 0.3, and 0.4 mg/kg DMT. One volunteer found 3 hourly injections of 0.4 mg/kg IV DMT too taxing, refusing the fourth dose. Thus, 0.3 mg/kg given at 30 min intervals, four times, was chosen as our tolerance regimen.

Tolerance Study

Subjects were admitted to the GCRC in the morning, having been fasting since midnight. One angiocath-style catheter was placed in an antecubital vein for blood drawing and kept open with a sterile saline drip. Another catheter was placed in the other arm for infusions. This arm also had an automatic blood pressure cuff applied to it. A Yellow-Springs Instruments (Yellow Springs, OH) YSI-400 reusable flexible thermistor probe configured to a Vita-Log PMS-8 physiological monitor (CSP, Inc., Palo Alto, CA) was inserted into the rectum for continuous temperature recording. Accuracy was 0.03°C.

Blood samples for ACTH, prolactin, and cortisol were drawn at −30 and −1 min, and samples for DMT were drawn at −1 min. Blood pressure and heart rate measurements, and blood samples, were obtained at +2, 5, 10, 15, and 28 min. Blood was collected for assay of ACTH, prolactin, and DMT for all the time points. Cortisol was drawn only at 28 min after each infusion (2 min before subsequent infusions), to assess the degree of preinjection ("baseline") cortisol negative feedback on ACTH response.

All subjects wore black eyeshades to reduce ambient light, and to provide a more introspective experience. We have found that many subjects will overlook subtle effects if their eyes are open and they are looking about the room. An abbreviated version of the HRS, containing only

questions that showed significant effects of DMT vs. placebo from our initial dose–response study (Strassman et al 1994), was given after the 15 min blood draw. If time remained before the next infusion, discussion focussed on descriptive, rather than psychotherapeutic, topics. However, the rigorousness of the repeated DMT sessions often required psychological support and guidance as the morning progressed.

The next infusion began at approximately +29 min 15 s. Thus, +30 for the first session was equivalent to "0" for the subsequent session. The above process was repeated for the second, third, and fourth sessions, with the final time point for data collection being +30, rather than +28, of the fourth session.

Although the study was "double-blind" in design, it was apparent quickly whether DMT or saline was administered as the first injection of the first study day. Once this was established, volunteers knew that the day's other injections would also be either DMT or saline. They also could assume what the second study day would entail (i.e., repeated administration of the other study drug); however, they did not know what to expect regarding tolerance development.

Assays

Plasma levels of DMT, expressed as the free base, were measured by gas chromatography–mass spectrometry (Walker et al 1979). Limit of detectability was 1 ng/mL. Plasma ACTH was assayed by immunoradiometric assay (Nichols Diagnostic Laboratories, San Juan Capistrano, CA); lower limit of detectability was 0.2 pmol/L. Limits of detectability for cortisol and prolactin radioimmunoassays (Diagnostic Products, Los Angeles, CA) were 6 nmol/L and 1 μg/L respectively. DMT assays were performed in triplicate, and all others were performed in duplicate.

Statistics

All analyses were performed using Statistical Analysis System for the personal computer (PC-SAS), version 6.04 (Cary, NC). Values are given as means (SEM). p Values <0.05 are considered significant.

Our primary statistical analysis was a repeated-measures analysis of variance (ANOVA), with repeated factor *session* (four occurring in one morning), and a grouping factor *dose* (placebo or DMT). Dependent variables were several derived values for blood concentrations of prolactin, ACTH, and DMT; heart rate (HR) and mean arterial pressure (MAP); and rectal temperature. The derived variables were baseline, ΔMax, and Δ area under the curve (AUC).

Baseline values for the first session were means of −30 and −1 min values for all but the temperature data, although the mean values for −5 to −1 min points was used for temperature. For subsequent sessions (2–4), "baseline" values for MAP, HR, and blood levels were those obtained at +28 min, 2 min before the next infusion. For temperature, the "baselines" for sessions 2–4 were the means for the immediately preceding 5 min (+26 to +30). ΔMax was the maximum response above baseline for each session. ΔAUC was the area under the response curve above baseline for each session, calculated by the trapezoidal rule.

For the HRS, mean scores for previously described "clinical clusters" were calculated (Strassman et al 1994). These were somesthesia (visceral/interoceptive, somatic sensations), cognition (thought processes and content), affect, perception, volition (ability to interact willfully with one's mental and physical self, and one's environment), and intensity (a global assessment of robustness of effect). HRS scores also were analyzed by repeated measures ANOVA, with repeated factor session, and grouping factor dose.

The dose factor could have been treated as a repeated factor. However, our analysis indicated that adjusting for session first induced independence between doses.

We defined "tolerance" using either of two methods. First, when the ANOVA demonstrated significant DMT or placebo effects, we performed post hoc comparisons using paired t tests. We compared responses for the first DMT (D) vs. placebo (P) infusions (P_1D_1) and for fourth DMT vs. placebo responses (P_4D_4). If P_1D_1 demonstrated a significant difference, but P_4D_4 did not, tolerance may be said to have occurred, since drug and placebo responses no longer differed by the last session.

Second, we also compared changes in responses from session 1 to 4 for drug (D_4D_1) and placebo (P_4P_1). Another indication of "tolerance" is if responses decreased significantly by session for either drug or placebo. This is a less robust indication, however, if D_4P_4 were still significantly different (i.e., responses to DMT decreased over time but never reached placebo values).

Results

The most important findings of this study were that tolerance to the subjective effects of four closely spaced injections of IV DMT fumarate, assessed by clinical interview, and quantified by Hallucinogen Rating Scale (HRS) subscores, did not occur; ACTH and prolactin blood level and heart rate responses showed tolerance, but mean arterial BP responses did not; and peak DMT levels differed significantly across sessions; however, levels were very low before, and did not differ among, sessions.

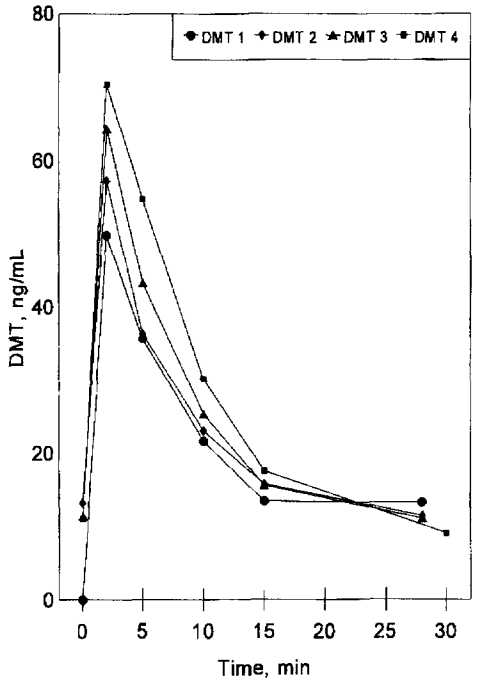

Figure 1. Mean DMT free base levels in 13 volunteers after four doses of 0.3 mg/kg intravenous DMT fumarate, administered at 30 min intervals. The number after "DMT" corresponds to the session (e.g., "DMT 2" refers to the second DMT injection). Time "0" values for sessions 2–4 are +28 min values for sessions 1–3, respectively.

DMT Blood Levels

There was no measurable DMT before any first session (DMT or placebo days), nor at 2 min after any first placebo session. Thus, our assay elicited no "false-positive" readings.

DMT Δmax values differed across sessions ($F = 4.76$; $p = 0.007$), ranging from 44.5 (5.7) ng/mL (session 2) to 62.5 (6.6) ng/mL (session 4). In addition, ΔAUC values differed significantly by session ($F = 4.40$; $p = 0.01$). Residual DMT levels before sessions 2–4, however, did not differ from each other ($F = 0.58$; $p = 0.57$). Figure 1 presents these data graphically.

Subjective Effects

CLINICAL INTERVIEWS. 0.3 mg/kg IV DMT produced a typical spectrum of "psychedelic" effects. Effects developed before the saline flush was completed, peaked at 1–2 min, and were well resolved by 28 min. Residual intoxication at +15 min was not sufficient to prevent any subject from completing the HRS, although many volunteers felt tired and "altered" before the third and fourth doses of DMT.

DMT effects included the nearly instantaneous onset of a physical/somatic "rush," beginning in the head, which quickly led to a dissociated state. Volunteers "braced" for the effects of 0.4 mg/kg DMT, which all had received before, although only two had received 0.3 mg/kg in pilot work. Subsequent sessions were experienced with less *anticipatory* anxiety, although emotional responses to consecutive DMT sessions were similar.

An abstract, geometric, rapidly moving, intensely colored, kaleidoscopic display of visual effects followed the "rush," and would often lead to the perceiving of more representational images, such as people, "creatures," and complex scenes. Auditory effects were less common and were relatively indistinct sounds rather than spoken words. Transient anxiety accompanied the onset of effects, and changed to elation and euphoria in most subjects. The fear of losing control lessened throughout the morning, which is reflected in the "volition" score on the HRS, below. Cognition was relatively unimpaired, although most spoke of a heightening of evaluative processes, or "faster" and "clearer" thinking.

On the saline placebo treatment day, all volunteers experienced a "rush" of varying intensity as the first dose was administered. Once it became clear that no DMT was to be administered that morning, subjects' responses to placebo were negligible for the remaining three sessions.

HALLUCINOGEN RATING SCALE. Mean HRS cluster scores all showed a robust effect of 0.3 mg/kg DMT relative to placebo, consistent with our previous data demonstrating "psychedelic" effects at dosages of 0.2 mg/kg and higher (Strassman et al 1994). Despite isolated session effects, inspection of the means (Table 1, Fig. 1) reveals little if any reduction of DMT effects across sessions. The HRS cluster demonstrating the greatest decrease across DMT sessions was *volition,* although a direct comparison of D_4D_1 revealed only a trend ($p = 0.06$) toward significance. These questions were related to the following effects: "change in effort to breathe"; "ability to follow sequence of events"; "ability to 'let go'"; "ability to focus attention"; "feeling in control"; and "ability to move around if asked to." Every *volition* question demonstrated the same pattern of decreasing response scores across DMT sessions.

Somaesthesia, or interoceptive/visceral/somatic effects, showed a slight decrease across sessions for both drug and placebo conditions, although significant reductions were not seen in individual comparisons (neither D_4D_1 nor P_4P_1).

Of interest was the effect of placebo on *affect* scores. Although a significant P_4P_1 reduction is seen across placebo sessions, the effect primarily is due to changes in scores between P_1 and P_2, suggesting a reduction in anxiety, or sense of relief, as it became clear that the day

Table 1. Responses to DMT or Saline Placebo

	ANOVA *F(p)*		Mean (SEM)				Contrasts *t(p)*			
	Dose	Session	P_1	P_4	D_1	D_4	P_1D_1	P_4D_4	P_4P_1	D_4D_1
HRS										
Intensity	208.6 (0.001)	0.38 (ns)	0.18 (0.15)	0 (0)	2.47 (0.17)	2.57 (0.24)	10.0 (0.001)	10.8 (0.001)	−1.17 (ns)	0.63 (ns)
Somesth	185.0 (0.001)	3.58 (0.02)	0.36 (0.10)	0.10 (0.05)	2.42 (0.17)	2.05 (0.21)	8.88 (0.001)	9.81 (0.001)	−1.96 (ns)	−1.54 (ns)
Affect	79.5 (0.001)	0.29 (ns)	0.44 (0.07)	0.24 (0.04)	1.72 (0.16)	1.92 (0.21)	7.27 (0.001)	8.23 (0.001)	−3.17 (0.008)	1.21 (ns)
Perception	301.1 (0.001)	1.75 (ns)	0.05 (0.03)	0 (0)	2.36 (0.15)	2.10 (0.23)	14.5 (0.001)	9.30 (0.001)	−1.76 (ns)	−1.18 (ns)
Cognition	120.4 (0.001)	0.54 (ns)	0.08 (0.04)	0.08 (0.06)	1.90 (0.16)	2.07 (0.21)	11.1 (0.001)	10.4 (0.001)	0.09 (ns)	1.06 (ns)
Volition	16.6 (0.001)	3.36 (0.02)	1.09 (0.21)	0.83 (0.16)	1.79 (0.15)	1.31 (0.16)	3.04 (0.01)	2.23 (0.04)	−1.62 (ns)	−2.12 (0.06)
ACTH										
Base	24.7 (0.001)	5.88 (0.001)	7.0 (0.97)	2.99 (0.43)	6.39 (0.73)	6.63 (0.62)	−0.95 (ns)	6.07 (0.001)	−4.18 (0.002)	0.29 (ns)
ΔMax	44.8 (0.001)	12.1 (0.001)	3.17 (2.11)	0.53 (0.11)	14.0 (1.93)	4.58 (1.26)	4.34 (0.001)	3.30 (0.007)	−1.22 (ns)	−4.51 (0.001)
ΔAUC	40.1 (0.001)	6.23 (0.001)	−3.99 (31.9)	1.94 (3.96)	211.0 (40.5)	37.2 (18.7)	4.39 (0.002)	1.89 (ns)	−0.17 (ns)	−3.65 (0.005)
PRL										
Base	2.44 (ns)	1.79 (ns)	8.18 (1.05)	5.11 (0.84)	7.08 (0.55)	8.43 (1.07)	−1.54 (ns)	5.99 (0.001)	−3.29 (0.007)	1.45 (ns)
ΔMax	34.5 (0.001)	2.07 (ns)	0.17 (0.67)	0.43 (0.13)	3.71 (0.66)	1.64 (0.36)	4.41 (0.001)	3.48 (0.005)	0.37 (ns)	−3.39 (0.006)
ΔAUC	23.2 (0.001)	1.09 (ns)	−18.8 (17.5)	−2.36 (4.62)	63.3 (17.8)	17.0 (7.83)	4.38 (0.001)	2.51 (0.03)	0.96 (ns)	−2.71 (0.02)
Heart rate										
Baseline	5.56 (0.03)	2.09 (ns)	68.9 (1.76)	65.2 (2.25)	73.3 (2.86)	78.5 (3.24)	1.87 (ns)	6.67 (0.001)	−2.36 (0.04)	2.12 (0.06)
ΔMax	16.2 (0.001)	6.89 (0.001)	5.2 (1.50)	4.0 (1.17)	25.7 (4.47)	7.53 (3.81)	4.74 (0.001)	0.90 (ns)	−0.68 (ns)	−3.33 (0.006)
ΔAUC	0.08 (ns)	2.01 (ns)	−22.0 (35.4)	13.1 (32.0)	53.0 (39.7)	−107.1 (60.5)	—	—	—	—
MAP										
Baseline	4.87 (0.04)	1.75 (ns)	87.2 (1.72)	88.0 (1.51)	89.7 (1.22)	91.3 (1.39)	1.63 (ns)	1.61 (ns)	0.40 (ns)	1.34 (ns)
ΔMax	22.5 (0.001)	0.82 (ns)	4.8 (1.25)	3.2 (1.36)	15.5 (2.04)	13.9 (2.21)	5.35 (0.002)	3.55 (0.004)	−0.72 (ns)	−0.76 (ns)
ΔAUC	6.41 (0.02)	0.80 (ns)	16.8 (33.6)	−2.5 (36.3)	142.6 (47.2)	90.3 (50.6)	2.82 (0.02)	1.32 (ns)	−0.32 (ns)	−1.09 (ns)
Temp										
Baseline	0.72 (ns)	14.0 (0.001)	37.3 (0.06)	37.26 (0.11)	37.2 (0.07)	37.5 (0.08)	−1.23 (ns)	3.33 (0.01)	−0.10 (ns)	7.05 (0.001)
ΔMax	12.6 (0.002)	3.52 (0.02)	0.08 (0.03)	0.02 (0.01)	0.11 (0.03)	0.06 (0.02)	1.25 (ns)	1.76 (ns)	−2.30 (0.05)	−1.95 (ns)
ΔAUC	11.4 (0.003)	1.20 (ns)	0.66 (0.55)	−0.36 (0.46)	1.06 (0.42)	0.58 (0.72)	0.58 (ns)	1.74 (ns)	−2.07 (ns)	−0.59 (ns)

Hallucinogen Rating Scale (HRS) cluster score, neuroendocrine (ACTH: pmol/L; PRL: prolactin, μg/L), cardiovascular (HR: heart rate; MAP: mean arterial pressure), and core temperature (Temp) responses to four administrations of 0.3 mg/kg IV N,N-dimethyltrytamine (DMT) fumarate or four administrations of saline placebo, given at 30 min intervals. ANOVA refers to a repeated measures analysis of variance with repeated factor session and grouping variable dose, except for temperature, which, because of missing values, used an ANOVA without repeated measures. Overall *F*-values are tabulated in the body of the table, with corresponding *p* values in parentheses. The values in the middle section refer to mean (SEM) values obtained during 0.3 mg/kg IV DMT (D) and saline placebo (P) treatments. The subscript refers to the session number (e.g., P_4 is the value for the fourth session of the placebo treatment). Contrasts are performed by paired *t* tests between two treatment session combinations (e.g., P_4D_4 is the comparison of values between the two treatments for the fourth session). For this section, *t* values are tabulated, with the corresponding *p* values in parentheses. Refer to the text for the calculations involved in derived values (e.g., baseline, Δmax, and ΔAUC).

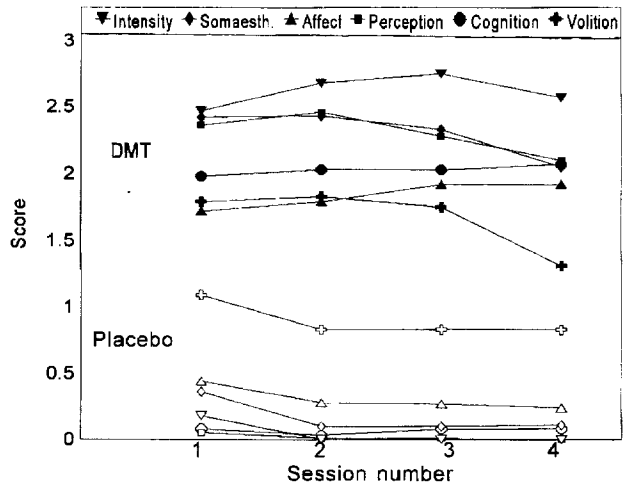

Figure 2. Mean HRS scores in 13 volunteers after four injections of 0.3 mg/kg intravenous DMT fumarate or four injections of saline placebo, administered at 30 min intervals.

would involve only repeated placebo injections. Figure 2 and Table 1 display these data.

Neuroendocrine Effects

ACTH. These data are displayed in Table 1 and graphically in Figure 3. Baseline values showed significant dose and session effects. For session 1, baseline values did not differ (P_1D_1), but did so by session 4 (P_4D_4). Baseline values for the DMT treatment remained stable over session (D_4D_1), yet those for placebo fell significantly (P_4P_1). Since there were significant baseline effects, but no apparent ceiling effects, the adjustment for baseline differences here is justified.

ΔMax and ΔAUC ACTH demonstrated significant dose and session effects. Placebo responses were not significantly different across sessions (P_4P_1). For Δmax and ΔAUC, DMT-induced responses were initially significantly greater than placebo (D_1P_1), and decreased across session (D_4D_1). ΔMax values remained significantly greater than placebo by session 4 (P_4D_4), but were not significantly different for ΔAUC. Thus, tolerance appears more robust using ΔAUC for ACTH.

Of note is the apparent conditioned response of ACTH after the first placebo dose, similar to that seen in response to placebo in our initial dose–response study (Strassman et al 1994). Although D_4 and P_1 were not compared directly here, response patterns seen in Figure 3 suggest that by the fourth dose of DMT, the development of tolerance had reduced ACTH responses nearly to the level of the conditioned response to initial placebo administration.

CORTISOL. As can be seen in Figure 4, cortisol baseline values did not differ before the first dose of either DMT or placebo. Cortisol blood levels taken at 28 min after each injection (i.e., *baseline,* and not maximum response values before each DMT injection) followed different patterns for DMT and placebo, and showed dose and session effects, whether or not the 28 min sample from the fourth session was included in the ANOVA. Levels rose significantly in the DMT condition, and then returned to initial baseline values after the fourth injection. In the placebo condition, they fell gradually and significantly after every session.

PROLACTIN. Table 1 and Figure 5 demonstrate the gradual decrease of values for placebo across session (P_4P_1), and values after DMT sessions were unchanged (D_4D_1). Thus, although initial baseline values were similar (P_1D_1), by session four, they differed significantly (P_4D_4). As for ACTH, baseline adjustments (i.e., calculation of "Δ values") are relevant for prolactin responses.

ΔMax and ΔAUC prolactin values for DMT fell significantly over session (D_4D_1), suggesting some degree of tolerance, although placebo responses were similar across

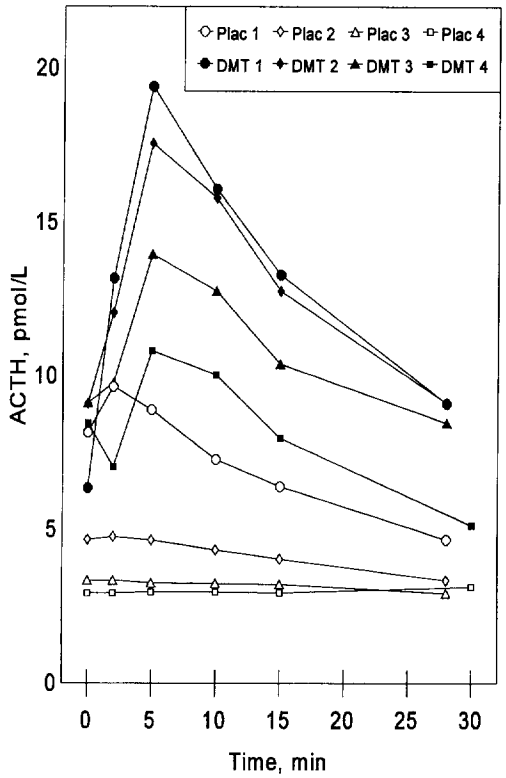

Figure 3. Mean ACTH plasma values in 13 volunteers after four injections of 0.3 mg/kg intravenous DMT fumarate or four injections of saline placebo, administered at 30 min intervals. Plac, saline placebo; number after Plac or DMT corresponds to the sessions. Time "0" values for sessions 2–4 are +28 min values for sessions 1–3, respectively.

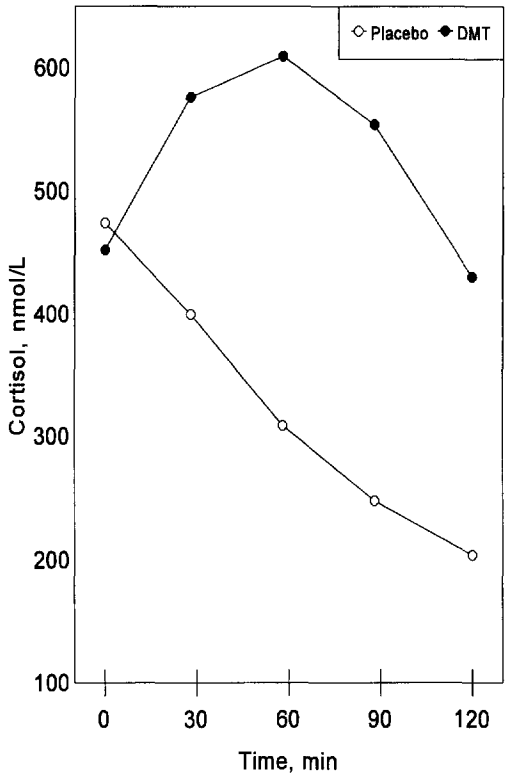

Figure 4. Mean cortisol plasma values in 13 volunteers after four injections of 0.3 mg/kg intravenous DMT fumarate or four injections of saline placebo, administered at 30 min intervals.

session (P_4P_1). However, values by the fourth session still differed by treatment (P_4D_4).

Cardiovascular Effects

HEART RATE. Figure 6 and Table 1 demonstrate that baseline HR values were significantly different for DMT and placebo conditions. Before the first session, there was no effect of dose; however, as the sessions progressed, there was a gradual increase of baseline values for DMT and a decrease for placebo.

In a repeated measures ANOVA, Δmax HR demonstrated significant dose and session effects. Placebo response values were unchanged across session (P_4P_1). DMT response values decreased significantly across session (D_4D_1), and did not differ from placebo values by the fourth session (D_4P_4). It is, however, apparent in Figure 6 that D_1 is the only curve that differs, and this could be due to anxiety when the subjects realize that they are receiving DMT for the first time, and experience some fear with respect to the intensity of drug effect. This anxiety-producing factor would be gone in subsequent sessions, and the reduction in HR after that may have little to do with "tolerance."

There were no significant drug or session effects on ΔAUC HR.

MEAN ARTERIAL PRESSURE. Figure 7 and Table 1 demonstrate no dose or session effects on baseline MAP. ΔMax and ΔAUC MAP responses differed by dose but not by session. The responses were essentially parallel across sessions, with DMT responses being consistently higher than those of placebo. Responses for the fourth DMT session did not differ significantly from the first (D_4D_1), suggesting no tolerance to MAP responses.

TEMPERATURE. Interpretation of these data is confounded by the slow time course for this response to DMT. Our previous study demonstrated that temperature did not begin to rise until 15 min after administration of either 0.2 or 0.4 mg/kg DMT, and had not begun falling by 60 min postinjection (Strassman et al 1994). Thus, the current data are more likely due to cumulative effects of repeated DMT administration (Fig. 8, Table 1). It is clear that baseline and physiologically mandated ceiling effects (e.g., sweating) must be taken into consideration.

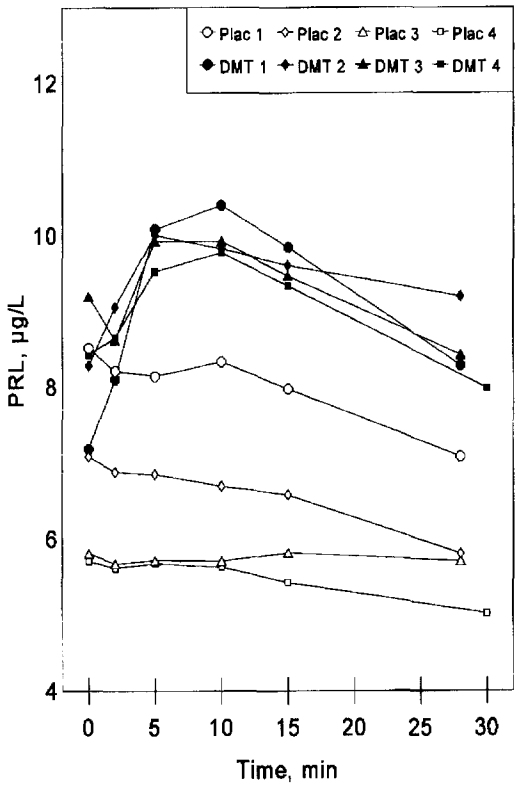

Figure 5. Mean prolactin plasma values in 13 volunteers after four injections of 0.3 mg/kg intravenous DMT fumarate or four injections of saline placebo, administered at 30 min intervals. Refer to Figure 3 for an explanation of the legend. Time "0" values for sessions 2–4 are +28 min values for sessions 1–3, respectively.

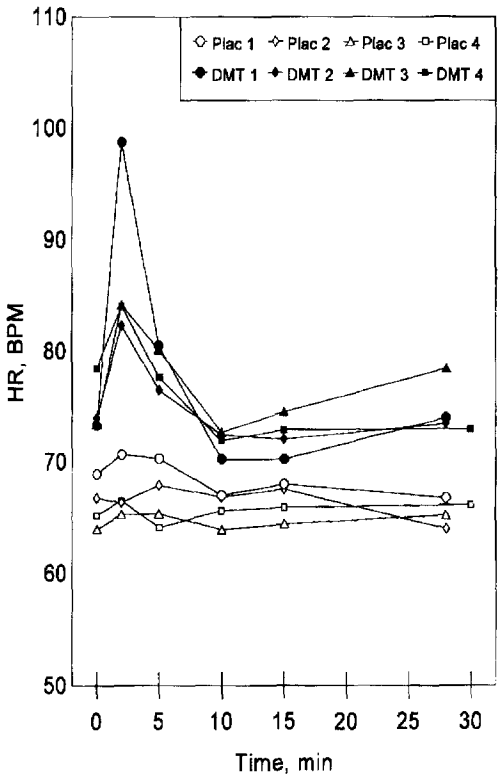

Figure 6. Mean heart rate (beats per minute [BPM]) values in 13 volunteers after four injections of 0.3 mg/kg intravenous DMT fumarate or four injections of saline placebo, administered at 30 min intervals. Refer to Figure 3 for an explanation of the legend. Time "0" values for sessions 2–4 are +28 min values for sessions 1–3, respectively.

Baseline values rose for drug treatment (D_4D_1) and remained stable for placebo (P_4P_1). The Δmax and ΔAUC values, therefore, were smaller than baseline value changes and the ANOVA results are of questionable value. In addition, because of missing values, a nonrepeated measures ANOVA was used, and results of these analyses are not strictly comparable to those of the other variables.

Discussion

Four closely spaced hallucinogenic doses of N,N-dimethyltryptamine (DMT) fumarate did not produce tolerance to psychological effects of this short-acting compound. Neuroendocrine effects and heart rate responses diminished to varying degrees with repeated dosing, suggesting tolerance development. Blood pressure effects were unchanged, and temperature data were uninterpretable because of their slow response time. We interpret these data as supporting the unique pharmacological properties of DMT relative to other "classic" hallucinogens, and the differential regulation of mechanisms mediating subjective and biological responses to DMT.

Unique Properties of DMT Relative to Other "Classic" Compounds

Tolerance has been demonstrated for neuropharmacological (McKenna et al 1989), electroencephalographic (Wallach et al 1972), and whole animal behavioral (Freedman et al 1958) assays of hallucinogen effects. However, DMT effects are not typical in this regard (Cole and Pieper 1973), probably due to DMT's unique pharmacodynamic properties.

Current research implicates the 5-HT_2 receptor family in mediating behavioral responses to hallucinogens in lower animals (Glennon et al 1985; Titeler et al 1988). Downregulation of the 5-HT_2 receptor occurs within 2–3 days after treatment with phenethylamine hallucinogens (Leysen et al 1989; McKenna et al 1989), in a time domain comparable to human studies demonstrating tolerance to hallucinogens.

Even more rapid changes occur with short-term exposure to nonhallucinogenic agonists, similar to the time parameters of this study (Trulson and Keltch 1985; Andorn 1986). Hallucinogens, via 5-HT_2 sites (Conn and

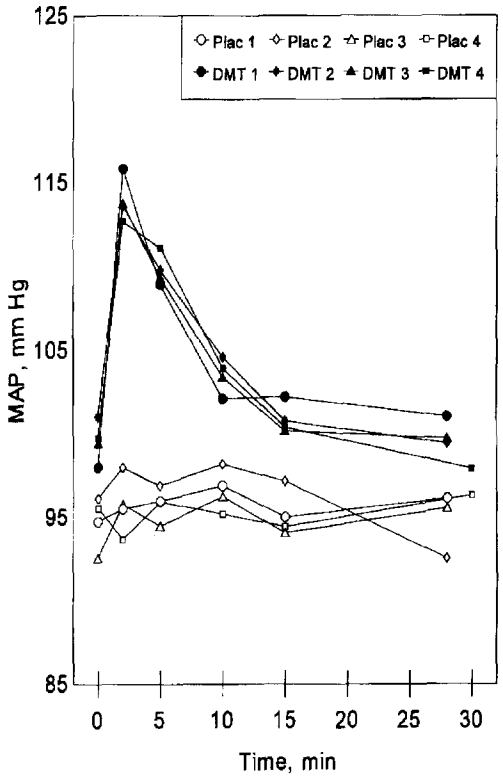

Figure 7. Mean arterial blood pressure (MAP, in mmHg) values in 13 volunteers after four injections of 0.3 mg/kg intravenous DMT fumarate or four injections of saline placebo, administered at 30 min intervals. Refer to Figure 3 for an explanation of the legend. Time "0" values for sessions 2–4 are +28 min values for sessions 1–3, respectively.

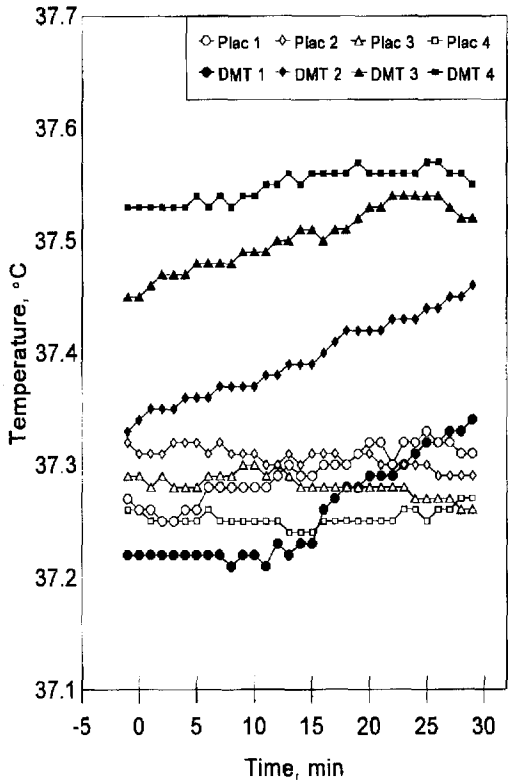

Figure 8. Mean core (rectal) temperature values in 13 volunteers after four injections of 0.3 mg/kg intravenous DMT fumarate or four injections of saline placebo, administered at 30 min intervals. Refer to Figure 3 for an explanation of the legend. Time "0" values for sessions 2–4 are means of +26–30 min values for sessions 1–3, respectively.

Sanders-Bush 1986), likewise increase phosphoinositide turnover (Sanders-Bush et al 1988), which, via receptor phosphorylation, desensitizes the site for agonists. Desensitization of 5-HT_2 responses mediating PI hydrolysis is seen in 20 min, and downregulation of receptor number occurs within 1 hour (Ivins and Molinoff 1991). The rapidity of desensitization may relate to phosphorylation of protein kinase C (PKC), which can occur within 10 min of phorbol ester application (Sibley et al 1987). Because this rapid desensitization can be prevented by PKC inhibitors (Aghajanian 1994), it would be of interest to determine the effects of DMT on PKC function.

Behavioral tolerance to closely spaced, repetitive injections of DMT is seen inconsistently in lower animals, including cat (Gillin et al 1973), rat (Rech et al 1975), mice (Cooper et al 1981), and primates (Cole and Pieper 1973; Schlemmer and Davis 1986). Even injections of DMT every 2 hours for 21 days in rat failed to produce complete tolerance (Kovacic and Domino 1976).

Cross-tolerance for hallucinogens occurs when different drugs produce tolerance to each other, and supports a similar mechanism of action (Balestrieri and Fontanari 1959; Appel and Freedman 1968). DMT resistance is not, however, seen in LSD- or DOM-tolerant animals (Rech et al 1975).

In humans, tolerance develops after three or four daily exposures to psychoactive doses of LSD (Isbell et al 1956), DOM (Angrist et al 1974), psilocybin (Hollister 1961), and mescaline (Wolbach et al 1962). LSD sensitivity returns to naive values just as quickly, even after high-dose treatment for over 2 months (Isbell et al 1956).

Consistent with animal data, human DMT tolerance is difficult to demonstrate. A fully hallucinogenic dose of DMT twice a day for 5 days did not evoke tolerance in humans (Gillin et al 1976), and "field reports" of closely spaced, repetitive smoking of DMT free base are conflicting regarding tolerance development (Stafford 1992).

Human studies have shown that both LSD and mescaline (Balestrieri and Fontanari 1959; Wolbach et al 1962), as well and LSD and psilocybin (Abramson et al 1960; Isbell et al 1961), demonstrate cross-tolerance to each other, supporting a similar mechanism of action. However, humans highly tolerant to LSD show no cross-tolerance to a fully hallucinogenic dose of DMT (Rosenberg et al 1964).

We believe that these chronic administration and cross-tolerance data in both humans and other animals support unique pharmacodynamic, rather than pharmacokinetic, properties of DMT relative to other classic hallucinogens, as mediating its inability to elicit tolerance. The recent description of the equipotency of DMT to that of 5-HT in decreasing resting potassium conductance (Aghajanian 1994), compared to low intrinsic activity seen with other hallucinogens (Garratt et al 1993) may contribute to understanding these differences.

Differential Development of Tolerance to DMT

Tolerance development to some, but not all, of the acute effects of DMT suggests that the mechanisms mediating these response are differentially regulated.

DMT has nearly equal affinities for the 5-HT_{1A} and 5-HT_2 sites (Deliganis et al 1991). Complex functional interactions between these two subtypes have been described in single-cell (Araneda and Andrade 1991) to behavioral (Arnt and Hyttel 1989) systems. The effect of 5-HT_{1A} agonism on 5-HT_2 desensitization processes also may contribute to differential tolerance development to DMT. For example, tolerance to the 5-HT_{1A} agonist 8-OH-DPAT produced cross-tolerance to LSD (with nearly equal 5-HT_{1A} and 5-HT_2 affinities [Pierce and Peroutka 1989]), although LSD-tolerant animals were not tolerant to DOI, a relatively pure 5-HT_2 compound (Krebs and Geyer 1994).

The affinity of DMT for the 5-HT_{2C} subtype is not known. If, however, it were significant, the differential acute (Sheldon and Aghajanian 1991) and compensatory (Berendsen and Brockkamp 1991) interactions of this and the 5-HT_{2A} subtypes would contribute to unequal tolerance phenomena seen in this study.

Direct DMT-induced desensitization of 5-HT sites mediating its acute effects on heart rate responses (McCall et al 1987) may underlie the tolerance seen here. Differential responsiveness of cardiovascular effects to peripheral catecholamines (Bagdy et al 1989) relative to direct brainstem activation (Clement and McCall 1990) may contribute to the dissociation of blood pressure and heart rate responses.

In addition to directing affecting 5-HT sites responsible for cortisol (Calogero et al 1990) and prolactin responses (Di Renzo et al 1989), DMT may elicit neuroendocrine tolerance because of negative feedback inhibition. Hypotheses regarding prolactin negative inhibitor feedback are limited by the early stages of characterization of central prolactin receptors (Mucciloi et al 1991).

Hypothalamic–pituitary–adrenal (HPA) fast and intermediate feedback can occur during the time domain of this study (Whitnall 1993). Repetitive, closely spaced injections of CRH to humans, however, did not produce tolerance to ACTH or cortisol responses, although cortisol levels remained elevated during a continuous CRH infusion (Schopohl et al 1986). We interpret our HPA data as supporting a direct effect of DMT on 5-HT receptor function, because ACTH responses fell in the face of relatively stable cortisol levels.

It should be emphasized that although DMT levels differed significantly among sessions, these differences were relatively small. It seems unlikely that the biological and subjective effects noted, either tolerance or lack thereof, are the result of these differences in DMT levels.

HRS clinical clusters are more sensitive to dose effects than the biological variables (Strassman et al 1994), and it is possible that the lack of tolerance to the psychological effects of DMT may be due to the slightly higher levels of DMT seen in subsequent sessions. Separating sessions by 60 or 90 min in future studies may help to clarify this issue.

Conclusion

These data support the uniqueness of DMT among classic hallucinogens. Whether this is based upon pharmacodynamic or pharmacokinetic differences remains to be determined. Tolerance to some, but not all, of the effects of DMT suggest differential regulation of mechanisms involved in tolerance to neuroendocrine, cardiovascular, and subjective effects of hallucinogenic drugs. Future studies attempting to develop tolerance to DMT may use either a continuous infusion of DMT or a greater number of injections.

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