Human psychopharmacology of N,N-dimethyltryptamine

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Abstract

We generated dose–response data for the endogenous and ultra-short-acting hallucinogen, N,N-dimethyltryptamine (DMT), in a cohort of experienced hallucinogen users, measuring multiple biological and psychological outcome measures. Subjective responses were quantified with a new rating scale, the HRS, which provided better resolution of dose effects than did the biological variables.

A tolerance study then was performed, in which volunteers received four closely spaced hallucinogenic doses of DMT. Subjective responses demonstrated no tolerance, while biological measures were inconsistently reduced over the course of the sessions. Thus, DMT remains unique among classic hallucinogens in its inability to induce tolerance to its psychological effects.

To assess the role of the 5-HT_{1A} site in mediating DMT's effects, a pindolol pre-treatment study was performed. Pindolol significantly increased psychological responses to DMT, suggesting a buffering effect of 5-HT_{1A} agonism on 5-HT_2-mediated psychedelic effects. These data are opposite to those described in lower animal models of hallucinogens' mechanisms of action.

1. Introduction

Human research with hallucinogenic drugs was severely curtailed by the passage of the Controlled Substances Act of 1970 [21]. Nearly a generation elapsed before a renewal of clinical studies occurred in the United States and Europe. These studies have begun to address gaps in basic understanding of effects and mechanisms of action created by this hiatus, during which many of the standard methods of psychopharmacology and psychotherapy research were developed.

There are several reasons why the careful study of hallucinogens has relevance to psychiatric research.

(1) The clinical syndrome elicited by hallucinogens affects all of the mental functions associated with human consciousness, including mood, perception, cognition, self-control and somatic awareness [5]. Generating mechanistic hypotheses based upon systematic data collection will provide insights into many basic brain–mind relationships.

(2) Use and abuse of hallucinogens among young adults is increasing [10,11], with an attendant rise in emergency room and psychiatric clinic utilization for assessment and treatment of adverse effects [7]. There is a need to understand how best to treat hallucinogen-elicited psychiatric disorders quickly, safely, and effec-

tively, in addition to providing accurate information to clinicians regarding effects and sequelae of hallucinogen use and abuse.

(3) The degree of overlap between endogenous psychoses and hallucinogenic drug inebriation has been debated vigorously [8,12]. The appellations 'psychotogen' and 'psychotomimetic' bespeak early efforts to relate the two syndromes. Similarities appear to be greatest during acute phases of schizophrenia [2]. Short-chain tryptamines remain attractive candidates for naturally occurring psychotogens [3]. Current interest in mixed $5\text{-HT}_2/\text{DA}_2$ antagonists as anti-psychotic agents [14] also underscores the importance of studying 5-HT_2-active hallucinogens as models for endogenous psychoses.

(4) The ability of hallucinogens to enhance the psychotherapeutic process was an area of intense interest during the first phase of hallucinogen research [17]. Restrictions on human use of these drugs prevented necessary clarification regarding with whom, and how best to utilize these drugs within a psychotherapeutic context. Recent advances in psychotherapy research [24] suggest models by which a more careful and systematic approach to combining hallucinogen drug administration with well-characterized forms of psychotherapy may proceed.

We have been investigating effects and mechanisms of action of the short-chain tryptamine, ultra-short-acting endogenous hallucinogen, N,N-dimethyltrypta-

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mine (DMT), in a cohort of experienced hallucinogen users since November, 1990. Three reasons prompted choosing DMT as the compound with which to renew clinical research with hallucinogens. First, it is extremely short-acting [18], and adverse effects which might occur in a busy clinical research unit would be easier to manage. Second, it is a naturally occurring hallucinogen [1], whose role in normal and abnormal mental processes has yet to be explicated adequately. Third, its relative obscurity would not draw undue attention to our work in the early delicate stages of resuming this research, relative to the certain flurry of interest that a better known hallucinogen, such as LSD, might.

We chose to study experienced hallucinogen users for the following reasons: experienced users would be less likely to panic during the powerful hallucinogenic effects expected from DMT; they would be able to provide more detailed accounts of DMT effects, particularly relative to other better known compounds, such as LSD and psilocybin, than naive subjects; finally, liability for development of subsequent 'drug abuse' would be less likely to be sustained in previous or current users.

2. Summary of experiments and results

Each of the three studies to be described utilized male and female experienced hallucinogen users who were otherwise medically and psychiatrically healthy. Screening was rigorous, and included a medical history, physical examination, electrocardiogram, urinalysis, complete blood count, 24-item chemistry panel, and thyroid functions. Subjects were excluded who were taking any medication regularly, or who had a history of high blood pressure. Psychiatric screening included a semi-structured psychiatric interview, the Structured Clinical Interview for DSM-III-R, Outpatient [20], and a survey of drug use history. Those with current drug abuse problems or history of psychosis were excluded. If volunteers had a history of a major depressive episode, they were included if the depression had resolved at least two years before beginning the study, and they were not in stressful life circumstances conducive to a relapse. In addition, if volunteers had not had what the research team considered 'full-blown' experiences on hallucinogenic drugs, they were not enrolled, as we wanted to ensure that volunteers could manage the highly intoxicated state of a high-dose DMT session.

Studies all took place in the inpatient unit of the University of New Mexico Hospital Clinical Research Center. Prospective volunteers first received low (0.05 mg/kg) and high (0.4 mg/kg) screening doses of intravenous (i.v.) DMT fumarate, non-blind, to familiarize themselves with the research setting, provide an opportunity to drop out before extensive data were collected, and for idiosyncratic hypertensive responses

to the low dose to be noted and exclude further participation.

Our first dose–response study utilized 0.05, 0.1, 0.2 and 0.4 mg/kg i.v. DMT fumarate, and saline placebo, in a double-blind, randomized design, using 12 volunteers. These results have been published [22,23]. A new rating scale for hallucinogen effects, the Hallucinogen Rating Scale (HRS), was developed, which clustered responses into six clinical categories: Affect, Volition, Somatic Effects ('Somaesthesia'), Perception, Cognition, and Intensity. Biological measures included: heart rate (HR), mean arterial blood pressure (MAP), pupil diameter, core temperature; and adrenocorticotropin (ACTH), β-endorphin (βE), prolactin (PRL), growth hormone (GH), melatonin, cortisol and DMT-free base blood levels. The 'psychedelic' threshold for DMT was at 0.2 mg/kg, at which most biological effects also demonstrated statistically significant differences from saline placebo. Only melatonin showed no stimulation by DMT, while GH levels, although stimulated, could not be differentiated by dose. Pupil diameter, HR, MAP, ACTH, βE, DMT, and subjective responses all peaked within 2 min; PRL and cortisol responses lagged by 5–15 min, while temperature and growth hormone elevations did not begin until psychological effects had resolved, by 15–20 min.

Psychological effects began nearly immediately during the DMT infusion, peaked within 2 min, and usually were completely resolved within 30 min. The higher doses of DMT produced a rapidly moving, multi-dimensional, kaleidoscopic display of intensely colored abstract and representational images. Auditory effects were less common, and were not frank hallucinations. Transient anxiety was common, but usually quickly became replaced by euphoria. Dissociation of awareness from the physical body was common, as were later feelings of alternating heat and cold. The higher dose effects completely replaced ongoing mental experience, and usually was described as more compelling and convincing than 'ordinary' reality or dreams. Lower doses (0.1 and 0.05 mg/kg) primarily affected physical and affective functions, with little perceptual disturbances. HRS data were more capable of distinguishing between dose levels (e.g., between 0.1 and 0.05 mg/kg) than were biological data. These data were interpreted in the light of 5-HT mechanisms, especially $5\text{-}HT_2$ and $5\text{-}HT_{1A}$ site activation.

More experimental studies were then designed, the first being an assessment of DMT's ability to induce tolerance to its biological and psychological effects. Previous attempts in humans had failed to elicit tolerance [6], while heroic efforts in lower animals were required to do so [13].

A fully hallucinogenic dose, 0.3 mg/kg, of i.v. DMT fumarate, or saline placebo, was administered at half-hour intervals, 4 times in a morning, to 13 experienced

hallucinogen-using volunteers. Neither clinical interviews nor HRS results demonstrated development of psychological tolerance. HR decreased from the first to second session, and did not change thereafter, suggesting 'reduction of anticipatory anxiety,' rather than 'tolerance;' while no reduction in MAP was seen. ACTH and PRL responses did decrease over the course of the morning, suggesting tolerance development. This differential tolerance development was interpreted as being mediated by independently regulated desensitization of relevant 5-HT receptor mechanisms. Thus, DMT remains unique in its inability to develop tolerance to its psychological effects.

Our last study completed assessed the role of the 5-HT_{1A} site in mediating DMT effects. This was performed because DMT has nearly equal affinity for the 5-HT_{1A} and 5-HT_2 sites [4], and the behavioral effects of the hallucinogen 5-methoxy-DMT are blocked by pindolol [19], a potent 5-HT_{1A} antagonist [16].

Twelve volunteers received a sub-hallucinogenic dose, 0.1 mg/kg, i.v. DMT, or saline placebo, in combination with 30 mg oral racemic pindolol, or placebo-pindolol, in a four-cell double-blind, randomized design. Volunteers found that pindolol pre-treatment enhanced DMT effects by two to three times, which was substantiated by scores on the HRS, in which four to six clinical clusters demonstrated a significant enhancement by pindolol. PRL responses were reduced, while those of ACTH were unaffected. HR responses were blunted, probably due to pindolol's anti-sympathetic effects, while MAP effects were enhanced. These behavioral data, opposite to those noted in the animal literature, suggest an inhibitory effect of 5-HT_{1A} agonism in tryptamine-induced hallucinogenesis. Pindolol blockade allowed unopposed 5-HT_2 agonism, which we believe also mediated the enhanced MAP responses to DMT. The reduced PRL response supports a stimulatory role for the 5-HT_{1A} site in human PRL secretion, while the lack of effect on ACTH suggests a minimal role for this site in the DMT response. These data also are important because they demonstrate differential (and at times, opposite) regulation of neuroendocrine, cardiovascular, and subjective effects of hallucinogens in humans.

3. Conclusions and future directions

DMT can be safely administered to experienced hallucinogen users in fully 'psychedelic' doses. By so doing, earlier clinical research findings can be extended to include contemporary psychopharmacological methodologies, and basic hypotheses tested. In the case of DMT, a battery of neuroendocrine data have been generated, and a new rating scale developed. The lack of tolerance to DMT's psychological effects has been established more rigorously, which strengthens its role as a putative

endogenous 'psychotogen' [9]. Our study of the role of the 5-HT_{1A} site in mediating DMT effects in humans has yielded results opposite to those expected from animal data.

Current studies include a pre-treatment protocol using the only currently available 5-HT_2 antagonist, cyproheptadine, which will expand previous human work with this combination [15]. In addition, we are beginning to develop comprehensive dose–response data for the longer-acting, and more widely abused hallucinogen, psilocybin (4-phosphoryloxy-N,N-DMT).

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