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A Primate Model for the Study of Hallucinogens

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SCHLEMMER, R F , JR AND J M DAVIS *A primate model for the study of hallucinogens* PHARMACOL BIOCHEM BEHAV 24(2)381–392, 1986 —An animal model for studying the actions of hallucinogenic drugs using primate social colonies is presented Although hallucinogens induce a number of behavioral changes in this paradigm, one emergent behavior, limb jerks, appears to be selectively induced by three classes of hallucinogens in doses which correlate with those reported to be hallucinogenic in humans Several non-hallucinogenic congeners of hallucinogens failed to significantly elicit this response Other behavioral changes induced by hallucinogens in monkeys such as ptosis and social withdrawl may be useful in studying aspects of hallucinogen intoxication other than hallucinations, or psychosis in general Upon daily administration, tolerance developed to all hallucinogens tested except two, as is seen in humans Moreover, cross-tolerance between hallucinogens could be demonstrated Further experiments with the hallucinogen 5-methoxy N,N-dimethyltryptamine revealed that although certain individual behaviors could be antagonized by serotonin antagonists, dopamine antagonists, and physostigmine, no drug completely reversed the behavioral abnormalities induced by this hallucinogen It is suggested that this paradigm, which offers an hallucinogen-induced behavior which correlates well with the human hallucinogen response and permits observation of a wide variety of other potentially relevant behaviors in primates, may be useful in developing and testing theories of hallucinogenic drug action It may be especially valuable in view of the present difficulties of conducting hallucinogen research in humans

Hallucinogen animal model Primate social behavior Limb jerk response Social withdrawal
Submissive behavior Tolerance Cross-tolerance LSD 5-MeODMT DMT Mescaline
Serotonin antagonists Dopamine antagonist

OVER the past three decades, a number of animal models have been used to study the action of hallucinogenic drugs Hallucinogen models have been recently reviewed in more detail elsewhere [1,7], but many of these models are discussed and used in studies reported in this volume Although a number of models have facilitated the formulation and testing of theories of hallucinogenic drug action, few appear to show specificity for hallucinogens This is not surprising, since some hallucinogen-induced behaviors in humans are also induced by other psychoactive agents, (e g , ptosis, paranoia, affective changes, and even hallucinations) Yet, an animal model which parallels the human hallucinogenic response to hallucinogens is needed to fully evaulate the pharmacology of these drugs Since no animal model has been convincingly proven to measure hallucinations in animals (making the tenuous assumption that animals can hallucinate), investigators have had to rely on correlative models to study this effect in animals For the past ten years, we have studied a primate model of hallucinogenic drug action which permits the observation of multiple behavioral changes induced by hallucinogens where certain behaviors appear to correlate very well with the human hallucinogen response, including hallucinations

In this model, hallucinogens were administered to selected members of non-human primate social colonies to study the effects of these agents in a paradigm where more complex behavior can be evaluated The rationale for this approach was taken from studies in our laboratory and others where the effects of psychomotor stimulants on highly integrative primate behavior have been successfully studied [13, 14, 17, 19] We sought to determine what behavioral changes (if any) induced in monkeys by hallucinogens correlated with the effects of hallucinogens in humans

METHOD

Subjects The subjects for all experiments were adult Stumptail macaque (*Macaca arctoides*) monkeys The majority of animals were feral They were continuously housed in colonies of 4–5 monkeys in large group cages (1 5×2 5×3 5 m) or as dyad groups in smaller cages (0 75×1 00×1 25 m) The monkeys were allowed to form a stable hierarchal structure prior to initiation of any experiment The cages were located in environmentally controlled rooms which were on a 12 hour light-dark cycle Each group received a generous supply of food (Purina Monkey Chow) daily supplemented with fruits and vegetables and had continuous access to water throughout the experiments Veteri-

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TABLE 1

BEHAVIORAL CHANGES INDUCED BY ACUTE ADMINISTRATION OF HALLUCINOGENS TO SELECTED MEMBERS OF PRIMATE SOCIAL COLONIES

Drug (Dose)		LSD (0 01)	DMT (2 00)	5-MeODMT (0 25)	MDA (3 00)
Limb Jerks	Base	0 53 ± 0 17	0 17 ± 0 06	0 11 ± 0 06	0 00 ± 0 00
	Tx	49 00 ± 11 61†	28 40 ± 6 35†	16 00 ± 5 11†	27 75 ± 8 82†
Body Shakes	Base	0 69 ± 0 12	0 98 ± 0 09	0 87 ± 0 16	0 42 ± 0 08
	Tx	7 80 ± 0 86†	6 20 ± 2 35†	8 78 ± 1 13†	0 00 ± 0 00‡
Ptosis	Base	0 00 ± 0 00	0 00 ± 0 00	0 00 ± 0 00	0 00 ± 0 00
	Tx	5 20 ± 2 13†	0 20 ± 0 20	0 00 ± 0 00	0 00 ± 0 00
Distance>3 ft	Base	3 50 ± 0 28	4 22 ± 0 25	4 76 ± 0 36	0 28 ± 0 08
	Tx	4 40 ± 1 44	7 40 ± 0 98†	7 11 ± 1 02*	8 00 ± 1 78†
Submissive Gestures Given	Base	1 70 ± 0 23	1 20 ± 0 15	2 47 ± 0 26	1 09 ± 0 17
	Tx	2 40 ± 2 16	2 40 ± 1 60	3 22 ± 0 46	1 50 ± 0 65
Aggress Gest Received	Base	0 36 ± 0 10	0 11 ± 0 03	0 87 ± 0 31	0 00 ± 0 00
	Tx	0 17 ± 0 17	0 60 ± 0 40	0 89 ± 0 77	0 00 ± 0 00
Social Groom	Base	3 08 ± 0 41	5 63 ± 0 44	4 42 ± 0 64	2 41 ± 0 49
	Tx	0 00 ± 0 00*	0 20 ± 0 20*	1 11 ± 0 56†	0 00 ± 0 00
Self Groom	Base	2 09 ± 0 23	2 79 ± 0 20	2 58 ± 0 32	0 47 ± 0 13
	Tx	0 00 ± 0 00*	0 80 ± 0 37*	0 78 ± 0 22*	0 00 ± 0 00
Locomotion	Base	4 51 ± 0 38	3 19 ± 0 25	4 10 ± 0 46	0 58 ± 0 18
	Tx	4 20 ± 1 36	9 20 ± 3 38†	2 56 ± 0 60	0 75 ± 0 48
Checking	Base	32 68 ± 0 96	30 29 ± 0 76	52 42 ± 1 88	16 45 ± 1 51
	Tx	46 40 ± 3 85	87 40 ± 16 00†	64 33 ± 3 97†	107 25 ± 13 12†
Lying Down	Base	1 26 ± 0 17	1 62 ± 0 21	1 62 ± 0 28	0 38 ± 0 15
	Tx	4 20 ± 1 80†	3 40 ± 1 60	1 89 ± 0 81	0 00 ± 0 00

Each value represents the mean ± SEM for 4–9 monkeys (LSD n=5, DMT n=5, 5-MeODMT n=9, MDA n=4) for each behavior Doses for each drug are expressed as mg/kg

Statistical significance is indicated by *$p<0.05$ when compared with respective baseline (Base), †$p<0.01$ when compared with respective baseline

‡MDA induced a significant increase in body shakes at lower doses (0 3 and 1 0 mg/kg)

narians experienced in treating primates monitored the studies at all times and had the right to intervene or discontinue an experiment when they believed it was necessary

Behavioral observation On specified days of each experiment, a 60 minute observation of the entire colony or dyad group was conducted by an experienced primate observer who was unaware of the treatment protocol During that time, the observer quantified and recorded the behavior of each monkey in the colony or dyad in rotation for 60 minutes using the focal sampling technique Behavior was recorded in accordance with a checklist of 40 social and solitary behaviors common to this species and several abnormal or emergent behaviors induced by psychotomimetics in this species A detailed description of all checklist behaviors can be found elsewhere [17]

Observations began at a specified time after drug or saline injection, depending on the onset and peak time for the drug under investigation That time remained constant throughout an experiment During the observation session, each monkey was observed in rotation for 30 seconds every five minutes for 60 minutes At the end of the session, scores for the twelve 30 second intervals were summed for each monkey which represented the daily score for that behavior for an individual Since the emergent behavior body shakes occurred at a lower frequency than most other behaviors, a record of the total number of body shakes seen throughout the 60 minute period was recorded regardless if the body shake occurred during one of the 30 second observation intervals or not This is reported as "total body shakes"

Because these studies were conducted over a ten year period, it was impossible to determine correlation coefficients between all observers However, correlation coefficients were determined whenever possible The overall correlation coefficient between observers always exceeded 90% ($r>0.90$)

Drugs Ten hallucinogens were tested either in members of social colonies or dyad groups The drug, dose most frequently used (expressed as mg (base)/kg unless otherwise noted), and time of administration prior to the beginning of behavioral observation were the ergot derivative *d*-lysergic acid diethylamide (*d*-LSD, NIDA, Bethesda, MD), 0 01 mg/kg, 15 min, the phenethylamine derivatives, mescaline (Sigma, St Louis, MO), 17 mg/kg, 60 min, 3,4,5-trimethoxyamphetamine (TMA), 8 mg/kg, 45 min, 4-methyl 2,5-dimethoxyamphetamine (DOM, NIDA), 0 17 mg/kg, 30 min, 3,4-methylenedioxyamphetamine (MDA,NIDA), 3 mg/kg, 15 min,

TABLE 2

BEHAVIORAL CHANGES INDUCED BY ACUTE ADMINISTRATION OF HALLUCINOGENS TO MONKEYS HOUSED IN DYAD GROUPS

		Mescaline (17 00)	DOM (0 17)	TMA (8 00)	Psilocin (0 40)	DET (2 00)
Limb Jerks	Base	4 90 ± 1 18	4 90 ± 1 18	4 90 ± 1 18	4 90 ± 1 18	0 00 ± 0 00
	Tx	43 00 ± 27 65†	119 00 ± 51 29†	183 75 ± 88 35†	46 25 ± 22 41†	84 00 ± 24 81†
Body Shakes	Base	1 05 ± 0 23	1 05 ± 0 23	1 05 ± 0 23	1 05 ± 0 23	0 90 ± 0 23
	Tx	18 75 ± 1 84†	20 25 ± 4 77†	11 25 ± 2 75†	1 00 ± 0 71	2 00 ± 1 08
Ptosis	Base	0 00 ± 0 00	0 00 ± 0 00	0 00 ± 0 00	0 00 ± 0 00	0 00 ± 0 00
	Tx	12 00 ± 3 03†	14 00 ± 1 78†	23 25 ± 5 76†	1 25 ± 1 25	0 00 ± 0 00
Social Groom	Base	10 05 ± 1 80	10 05 ± 1 80	10 05 ± 1 80	10 05 ± 1 80	7 00 ± 1 96
	Tx	3 25 ± 1 89*	2 50 ± 2 50*	0 25 ± 0 25†	0 00 ± 0 00†	0 00 ± 0 00*
Self Groom	Base	7 50 ± 1 52	7 50 ± 1 52	7 50 ± 1 52	7 50 ± 1 52	18 65 ± 1 42
	Tx	1 25 ± 0 48†	0 00 ± 0 00†	0 00 ± 0 00†	0 00 ± 0 00†	0 00 ± 0 00†
Locomotion	Base	13 05 ± 1 75	13 05 ± 1 75	13 05 ± 1 75	13 05 ± 1 75	14 50 ± 2 26
	Tx	10 25 ± 3 22	7 75 ± 1 25	5 50 ± 3 93	6 50 ± 2 72	4 75 ± 3 47
Checking	Base	141 60 ± 5 93	141 60 ± 5 93	141 60 ± 5 93	141 60 ± 5 93	96 70 ± 4 36
	Tx	151 00 ± 9 35	166 50 ± 11 59†	182 50 ± 13 73†	166 50 ± 11 59†	130 50 ± 32 19
Lying Down	Base	1 05 ± 0 48	1 05 ± 0 48	1 05 ± 0 48	1 05 ± 0 48	0 95 ± 0 49
	Tx	0 00 ± 0 00	0 00 ± 0 00	0 00 ± 0 00	1 25 ± 0 75	10 25 ± 5 92*

Each value represents the mean ± SEM for 4 monkeys for each behavior Doses for each drug are expressed as mg/kg
Statistical significance is indicated by *$p<0.05$ when compared with respective baseline (Base), †$p<0.01$ when compared with respective baseline

and the tryptamine derivatives, N,N-dimethyltryptamine (DMT, Sigma), 2 mg/kg, 5 min, 5-methoxy N, N-dimethyltryptamine (5-MeODMT, Sigma), 0 25 mg/kg, 5 min, N,N-diethyltryptamine (DET, Sigma), 2 mg/kg, 5 min, psilocin (NIDA), 0 4 mg/kg, 15 min and psilocybin (NIDA), 0 4 mg/kg, 15 min

Relevant non-hallucinogenic drugs reported here included the LSD congeners, 2-brom-LSD (BOL, NIDA), 0 1 mg/kg, 15 min, and lisuride hydrogen maleate (Schering AG, Berlin, Germany), 0 05 mg (salt)/kg, 15 min, the phenethylamine congener, 3,4-dimethoxyphenethylamine (DMPEA, Sigma), 17 mg/kg, 60 min, and tryptamine (Sigma), 10 mg/kg, 15 min All drugs were administered intramuscularly

Each experiment began with the observation of non-drugged behavior which was considered baseline During that time all monkeys in the group received normal saline or drug vehicle intramuscularly at the designated time prior to observation In addition, monkeys in the colony or dyad not receiving drug injection during the treatment period were given an intramuscular injection of normal saline at the same time the treated animals received the drug injection

Protocol For most drugs, the first experiment was designed to determine an acute dose-response curve For LSD, for example, five doses ranging from 0 0003–0 03 mg/kg were tested in each member of a colony of five monkeys in a Latin-square design Only one monkey received treatment per day and at least 14 days elapsed before another dose of LSD was administered to the same animal Since it was impractical to conduct subsequent studies on all active doses of each hallucinogen, one dose of each drug was selected to be used in the more entailed studies which followed

The effect of repeated administration of hallucinogens was studied for seven substances, LSD, DMT, 5-MeODMT, DET, psilocin, mescaline, and DOM In these experiments, one dose (see above) was administered once daily at the same time each day for 5–12 consecutive days Behavioral observation was conducted on each day of drug administration In social colony experiments, 2–3 monkeys received drug treatment at the same time In the dyads, only one of the two animals received drug throughout the treatment period In each case, there was a cross-over so that each monkey received the same treatment by the completion of the experiment

The two short-acting hallucinogens, DMT and 5-MeODMT were also tested using more frequent administration In these experiments, DMT, 2 mg/kg, and 5-MeODMT, 0 25 mg/kg, were administered IM every 25–35 minutes for 9 hours Behavioral observation was conducted every other hour (0–1 hr, 2–3 hr, 4–5 hr, 6–7 hr, and 8–9 hr after injection) One injection needed to be given during each observation session Observation began 5 minutes after injection (as with previous experiments with these drugs) At 30 minutes into the session there was a 5 minute break to administer the injections The observer was asked to leave the room during this time The observation then continued for the remaining 30 minutes The next injections were administered immediately after the observer finished the observation session and had left the room Data from the two 30-minute segments were combined to give the 60 minute observation scores The hallucinogen was then administered to the same monkeys once again the next day 26 hours after the first injection to determine if the tolerance persisted The experiment was conducted in a social colony of five animals Two to three monkeys received treatment at the same time Those animals not receiving drug were given an equivalent

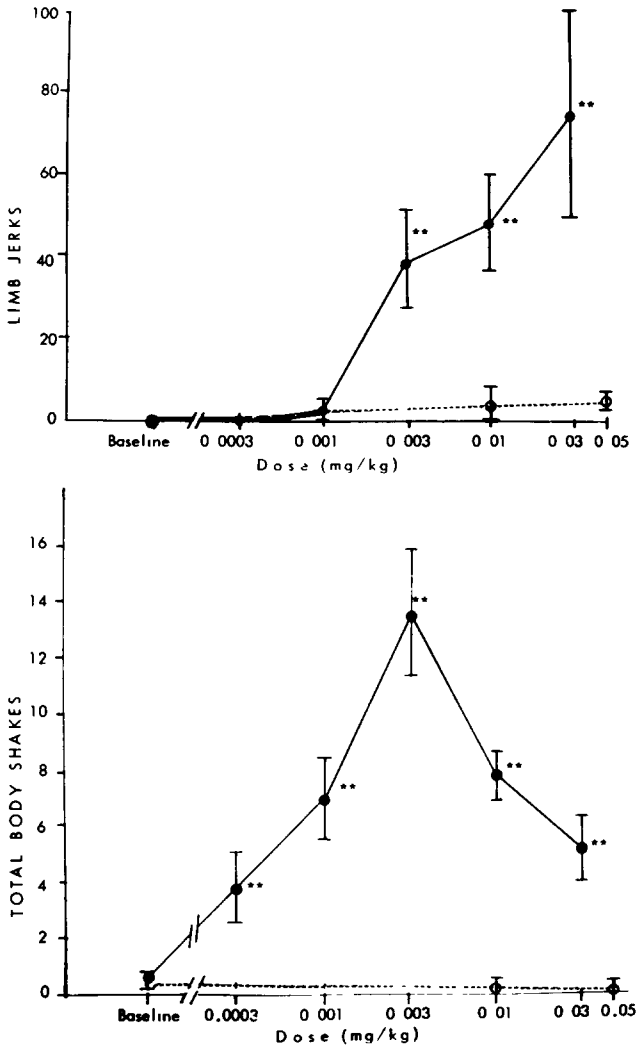

FIG 1 The dose-dependent induction of the emergent behaviors limb jerks and body shakes in monkeys by LSD (solid line) Each point represents the mean±SEM per acute dose for five monkeys The related non-hallucinogen lisuride (dotted line) is shown for comparison purposes Statsitical significance is shown as $^{**}p<0.01$ when compared with respective baseline value Taken from Schlemmer and Davis [17]

volume of normal saline IM each time the treated monkeys received drug injection Each of the experiments was preceded by a one day baseline observation where all monkeys received a 9 hour injection regimen of normal saline identical to that during drug treatment Behavioral observations were conducted every other hour as well

An experiment to determine if cross-tolerance developed between mescaline and LSD was conducted in a colony of four animals Following baseline, two monkeys received one dose of mescaline, 17 mg/kg Two weeks later these monkeys received one injection of LSD, 0 01 mg/kg, for two consecutive days followed by mescaline on the third day The other two monkeys in the colony received LSD for two days and mescaline on day three, then the acute dose of mescaline two weeks later

Several drugs with known action on certain neurotransmitter systems were administered in combination with 5-MeODMT (1) to determine if any of these agents would antagonize the behavioral effects of this hallucinogen and (2) to gain insight into the mechanisms by which this hallucinogen elicits its behavioral effects Experiments were conducted using social colonies of 4–5 monkeys in a cross-over fashion with 2–3 monkeys receiving drug treatment at the same time Each experiment began with a baseline observation period of no less than four days Then 5-MeODMT, 0 25 mg/kg, was given alone once daily for five consecutive days This was followed by administration of the test drug for 14 consecutive days with the exception of pentobarbital During the first 7 days, the test drug was administered alone with observation occurring on days 3–7 Then 5-MeODMT was administered concomitantly with the test drug during the final five days Drugs tested with 5-MeODMT included the serotonin antagonists cinanserin HCl (Squibb, Princeton, NJ), 5 mg/kg, metergoline (Farmitalia, Milan, Italy), 0 3 mg/kg, methysergide maleate (Sandoz, Hanover, NJ), 1 mg/kg, cyproheptadine HCl (Merck, Sharp, and Dohme, West Point, PA), 1 mg/kg, and methiothepin maleate (gift from Dr M Protiva, Prague, Czechoslovakia), 0 15 mg/kg, the dopamine antagonists haloperidol (McNeil, Ft Washington, PA), 0 1 mg/kg, and trifluoperazine HCl (Smith, Kline, and French, Philadelphia, PA), 0 02 mg/kg, the cholinesterase inhibitor, physostigmine (O'Neal, Jones and Feldman, St Louis, MO) 0 04 mg/kg, in combination with peripheral anticholinergic methscopolamine HCl (Upjohn, Kalamazoo, MI), 0 01 mg/kg, the phenothiazine antihistamine promethazine HCl (Wyeth, Philadelphia, PA), 2 mg/kg, and the anxiolytic, diazepam (Roche, Nutley, NJ), 1 mg/kg The hypnotic pentobarbital Na (Abbott, North Chicago, IL), 7 5 mg/kg, was administered acutely alone and two weeks later with 5-MeODMT Cinanserin, metergoline, methysergide, cyproheptadine, and diazepam were given once daily 2–2 5 hours prior to observation Methiothepin was administered once daily 22 hours prior to observation Haloperidol, trifluoperazine, and promethazine were administered twice daily with the last injection given 2 5 hours prior to observation Physostigmine was given 45 minutes and pentobarbital 30 minutes prior to observation

Statistical analysis All data are expressed as the daily mean±SEM score per observation session for each behavior Data were analyzed using a two-way analysis of variance (ANOVA) or a three-way partially-crossed ANOVA The least significant difference method was used to compare means within an analysis

RESULTS

Acute Administration of Hallucinogens and Primate Behavior

Onset and duration of action The hallucinogens with the most rapid onset of action and shortest duration of action were DMT and 5-MeODMT Behavioral changes were noted as quickly as 30 seconds to one minute after IM injection The effect peaked within 20–30 minutes Baseline behavior usually returned within 60 minutes The onset of action of LSD was 10–15 minutes after injection with a peak effect between 40–60 minutes Significant behavioral changes were typically diminished within two hours The hallucinogen with the longest onset of action was mescaline Significant behavioral changes were not noted until 45–60 minutes after injection and lasted up to 4 hours Other hallucinogens tested had an onset of action, peak effect, and duration of action equal to or between that of LSD and mescaline

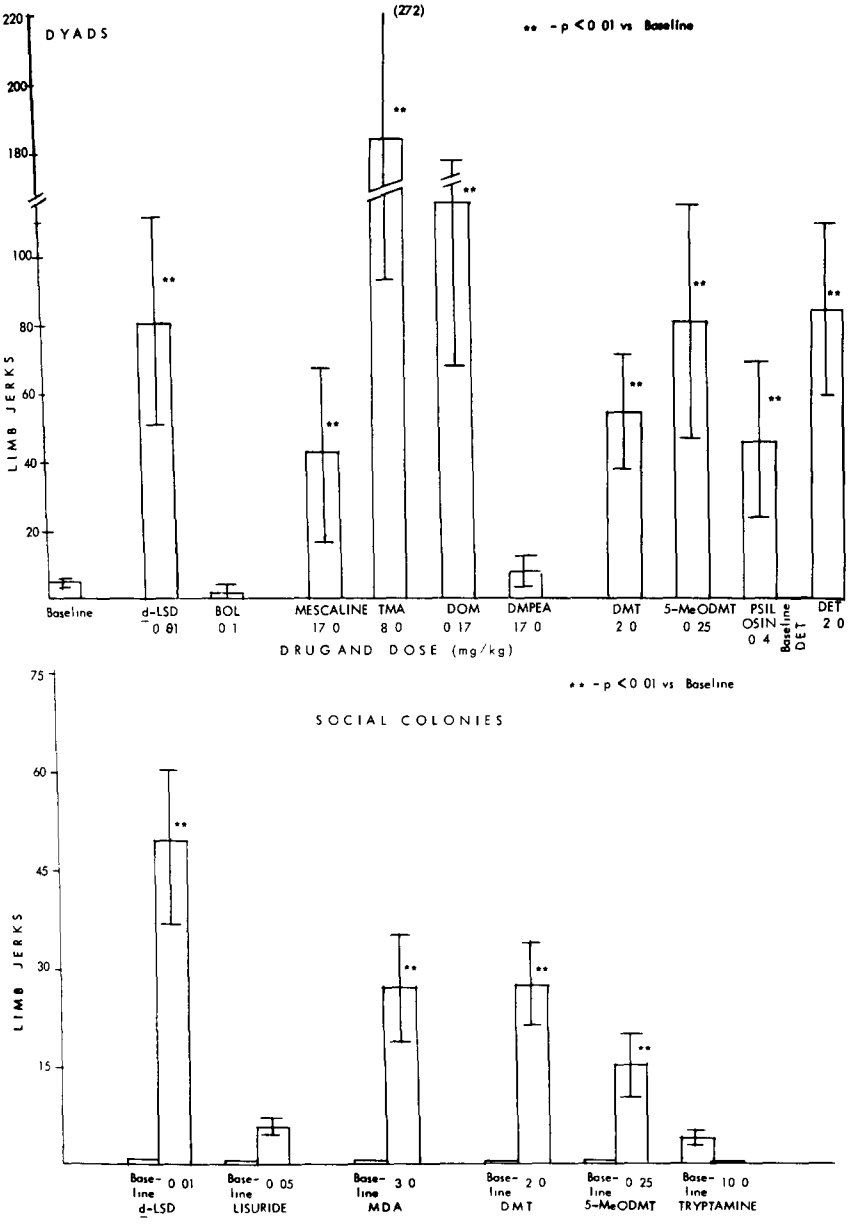

FIG 2 The induction of limb jerks by hallucinogens in monkeys In addition to nine hallucinogens, the effect of four related non-hallucinogens is also shown Each bar represents the mean±SEM for four to five monkeys in social colonies or dyad groups Statistical significance is shown as $**p<0\ 01$ when compared to respective baseline value Taken from Schlemmer and Davis [17]

General effects All hallucinogens tested induced abnormal behavior and disrupted normal behavioral interactions One major distinction could be made between hallucinogens upon gross appearance of the treated monkeys Most monkeys appeared sedated when treated with most hallucinogens (LSD, mescaline, TMA, MDA, psilocin, psilocybin, DET) However, DMT- and 5-MeODMT-treated animals did not appear sedated and at times even appeared hyperactive This can be noted by comparing scores for lying down for LSD, 5-MeODMT, and DMT, and locomotion scores for LSD and DMT (Table 1)

Social behavior All hallucinogens had profound effects on social interactions, usually reducing or eliminating them Affiliative behavior was primarily disrupted For example, initiated social grooming, an important cohesive behavior in this species, was invariably reduced or eliminated by hallucinogenic drugs (Tables 1–2) Distancing scores (time spent away from other monkeys) were usually increased significantly for hallucinogen-treated monkeys (Table 1, distance>3 ft), but rarely to the extent of total isolation Hallucinogens tended to increase the number of submissive gestures given by treated monkeys although this did not always

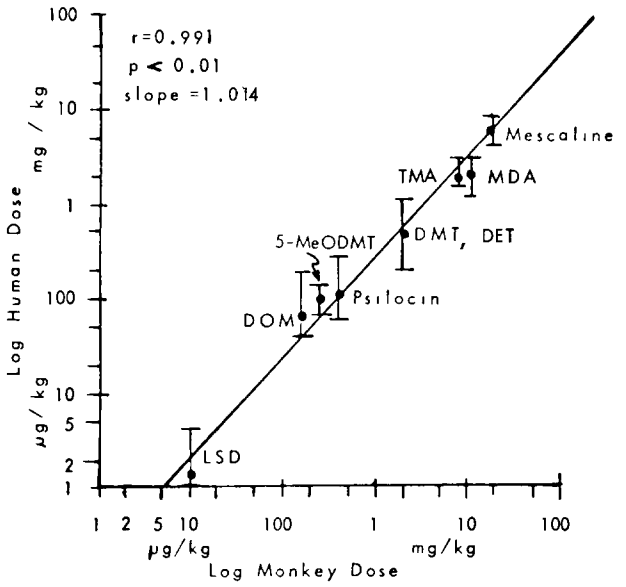

FIG 3 Correlation between the hallucinogen dose which induces limb jerks in monkeys and the hallucinogenic dose reported for humans in log scale The vertical brackets represent the reported human hallucinogenic dose range for each drug Taken from Schlemmer and Davis [17]

reach statistically significant levels (Table 1) Interestingly, this was not due to an increase in aggressive gestures directed to the treated monkeys

Solitary behavior Hallucinogens also induced significant changes in important solitary behaviors as well Monkeys treated with sedative hallucinogens, such as LSD, often sat on a perch or the cage floor, or were lying down with their eyes open, but did not appear to be particularly concerned with most ongoing cage activity Many of these monkeys had ptosis (Tables 1–2) Monkeys treated with DMT or 5-MeODMT, the non-sedative hallucinogens, appeared more alert and restless Locomotion scores were either significantly elevated or unchanged from baseline levels (Table 1) Checking scores (visual scanning) were increased by most hallucinogens (Tables 1–2) On the other hand, self grooming was significantly reduced by most hallucinogens (Tables 1–2)

Emergent behavior Hallucinogens induced two behaviors which were seen infrequently, if at all, during observation of undrugged behavior These were limb jerks and body shakes

Limb jerks are myoclonic spasms of the extremities After injection of a hallucinogen, limb jerks are often frequent and intense, and may involve any extremity, but most often the legs There was great variability in the number of limb jerks induced in treated monkeys However, this response appeared to be consistent across hallucinogens for each monkey In other words, monkeys having a large number of limb jerks with one hallucinogen had a comparatively large number of limb jerks with other hallucinogens Limb jerks were induced in a dose-dependent manner as seen for LSD in Fig 1 All ten hallucinogens tested in these experiments induced limb jerks in all monkeys (Fig 2) On the other hand, 40 psychoactive substances which are known not to be hallucinogenic in humans failed to induce a significant number of limb jerks in this species Of the latter drugs, four are of particular interest Lisuride and BOL, close structural congeners of LSD, DMPEA, a phenethylamine congener, and tryptamine all failed to induce a significant increase in limb jerks from baseline levels (Fig 2) In addition, pilot studies in our laboratory with individually caged Stumptail macaques have revealed that the serotonin uptake inhibitor fluoxetine in acute doses up to 3 mg/kg failed to elicit limb jerks Importantly, the dose necessary to induce limb jerks in monkeys correlates significantly (r=0 99) with the reported human hallucinogenic dose of the ten hallucinogens tested (Fig 3)

Body shakes resemble the response of a dog after emerging from water ("wet dog shakes") The response begins with vigorous, momentary shaking of the head and upper torso which quickly continues down the body Like limb jerks, only hallucinogens induce body shakes in this species, however, not all hallucinogens induced this response LSD, mescaline, DOM, MDA, TMA, DMT, and 5-MeODMT induced a significant number of body shakes, but DET, psilocin, and psilocybin did not (Fig 4) In contrast to the limb jerk response, the threshold dose for the induction of body shakes was usually lower than that for limb jerks and the dose-response curve for body shakes is an "inverted U" type as seen with LSD in Fig 1 Therefore as limb jerks become more intense, body shakes often decreased in intensity Whether there is a direct interaction between these behaviors is unclear at this time, but this is certainly possible

Tolerance

Since tolerance develops to the hallucinogenic effect of most hallucinogens in humans, experiments were conducted to test the effect of repeated administration of several hallucinogens in monkeys Tolerance developed within five days to LSD, mescaline, DOM, DET, and psilocin with once daily administration (Table 3) However, tolerance failed to develop to DMT and 5-MeODMT within 8–12 days using the same treatment schedule This parallels the development of tolerance to these compounds in humans for those hallucinogens that have been tested (Table 3) When tolerance to a specific hallucinogen did occur, it was not noted with every behavioral change induced by that hallucinogen

Tolerance was first evident with the limb jerk response, but also was noted with body shakes, ptosis, and increased checking Conversely, tolerance did not develop to the disruption of either social or self grooming with 5–12 day treatment with any of the five hallucinogens (LSD, mescaline, DOM, psilocin, and DET) where tolerance had developed to limb jerks

Since the only hallucinogens failing to show tolerance also had the shortest duration of action, experiments were conducted where DMT and 5-MeODMT were given more frequently than once a day to determine if frequency of administration is an important determinant of tolerance When both DMT and 5-MeODMT were given at 30 minute intervals over a period of several hours, tolerance developed to both drugs with limb jerks (Fig 5), body shakes, and checking Moreover, as tolerance developed, treated monkeys had a significant increase in resting, heretofore, not seen with either of these agents (Fig 6) Therefore, the non-sedative hallucinogens appeared more like sedative hallucinogens during frequent repeated administration Tolerance still persisted 26 hours after the first injection of 5-MeODMT, but not DMT

An experiment was conducted to determine if cross-tolerance between two hallucinogens could be demonstrated

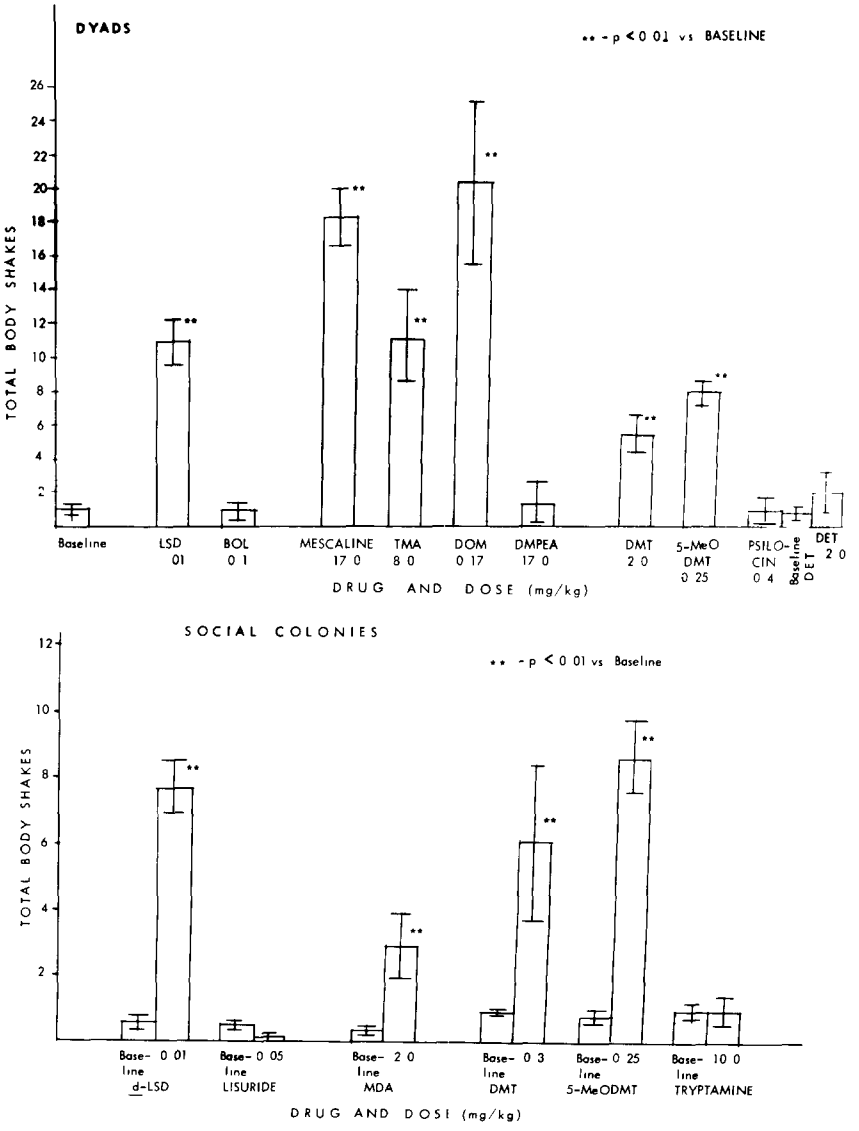

FIG 4 The induction of body shakes by most hallucinogens in monkeys In addition to nine hallucinogens, the effect of four related non-hallucinogens is also shown Each bar represents the mean±SEM for four to five monkeys in social colonies or dyad groups Statistical significance is shown as $^{**}p<0\ 01$ when compared to respective baseline value Taken from Schlemmer and Davis [17]

in this model When mescaline was administered one day following two daily injections of LSD, limb jerks and body shakes were significantly lower than after the first LSD injection and after acute injection of mescaline to the same monkeys at a different time (Table 4) This demonstrates that cross-tolerance does develop between these two hallucinogens

Antagonism of Hallucinogen-Induced Behavior in Primates

The hallucinogen 5-MeODMT induced six major behavioral changes in monkeys—the induction of (1) limb jerks and (2) body shakes, (3) a reduction in initiated social grooming, (4) an increase in distancing from other monkeys, (5) an increase in submissive gestures given by treated monkeys, and (6) an increase in checking The best antagonism was seen with 5-MeODMT-induced emergent behaviors The serotonin receptor antagonists metergoline, methysergide, cyproheptadine, cinanserin, and methiothepin all prevented limb jerks and body shakes from rising above the residual baseline levels when 5-MeODMT was given (Fig 7) The dopamine antagonists (and anti-psychotics) haloperidol and trifluoperazine also significantly antagonized 5-MeODMT-induced limb jerks and body shakes, but failed to return them to baseline levels The cholinesterase inhibitor, physostigmine, was surprisingly effective in antagonizing these behaviors However, the non-antipsychotic phenothiazine antihistamine, promethazine, and the anxiolytic-hypnotics, diazepam and pentobarbital failed to reduce limb jerks and body shakes to or near baseline levels

TABLE 3

COMPARISON OF TOLERANCE TO HALLUCINOGENS IN MONKEYS AND HUMANS

Drug (Dose)	Tx Day	n	Limb Jerks	Body Shakes	Tolerance in Humans
d-LSD	Base	5	0 32 ± 0 14	0 77 ± 0 11	yes
(0 01)	Day 1		57 00 ± 16 49†	9 75 ± 2 78†	
	Day 2		17 50 ± 10 24†§	4 75 ± 1 31†§	
DMT	Base	5	0 17 ± 0 06	0 98 ± 0 09	no
(2 00)	Day 1		28 40 ± 6 35†	6 20 ± 2 35†	
	Day 8		30 60 ± 5 60†	6 00 ± 2 74†	
5-MeODMT	Base	9	0 11 ± 0 06	0 87 ± 0 16	unknown
(0 25)	Day 1		16 00 ± 5 11†	8 78 ± 1 13†	
	Day 5		18 78 ± 6 60†	8 11 ± 1 01†	
DET	Base	4	0 00 ± 0 00	0 90 ± 0 23	unknown
(2 00)	Day 1		84 00 ± 24 81†	2 00 ± 1 00	
	Day 4		41 50 ± 18 30†§	1 50 ± 0 50	
Psilocin	Base	4	4 90 ± 1 18	1 05 ± 0 23	yes
(0 40)	Day 1		46 25 ± 22 41†	1 00 ± 0 71	
	Day 5		24 25 ± 13 14†‡	0 00 ± 0 00	
Mescaline	Base	4	4 90 ± 1 18	1 05 ± 0 23	yes
(17 00)	Day 1		43 00 ± 27 65†	18 75 ± 1 84†	
	Day 4		26 25 ± 14 90†	11 00 ± 2 45†§	
DOM	Base	4	4 90 ± 1 18	1 05 ± 0 23	yes
(0 17)	Day 1		119 00 ± 51 29†	20 25 ± 4 77†	
	Day 4		31 75 ± 25 85†§	8 75 ± 2 87†§	

All monkeys received drug treatment once a day All doses are listed as the mg (base)/kg

Statistical significance is indicated by $*p<0.05$ when compared to respective baseline, $\dagger p<0.01$ when compared to respective baseline, $\ddagger p<0.05$ when compared to Day 1 of treatment, $\S p<0.01$ when compared to Day 1 of treatment

Experiments with LSD, DMT, and 5-MeODMT were conducted in social colonies Experiments with DET, Psilocin, Mescaline, and DOM were conducted in dyads

Additional studies in our laboratory have demonstrated that cinanserin, methiothepin, and haloperidol have a similar profile of antagonism of limb jerks and body shakes induced by an acute dose of LSD with haloperidol being slightly less effective than the serotonin antagonists

On the other hand, no drug tested antagonized all behavioral changes induced by 5-MeODMT This was most evident with the disruption of affiliative behavior None of the agents tested restored initiated social grooming or distancing scores to baseline levels when given with 5-MeODMT (Fig 7) Only metergoline was partially effective in reversing the reduction in social grooming and the increase in distancing Cinanserin and pentobarbital were the only other drugs that partially antagonized the increase in distancing, but neither significantly altered the reduction in social groom seen with 5-MeODMT

The increase in submissive gestures induced by 5-MeODMT showed still another antagonism profile Haloperidol, trifluoperazine, and methiothepin all antagonized the increase in submissive gestures given by treated monkeys (Fig 6) The first two are potent dopamine receptor antagonists while methiothepin blocks both serotonin and dopamine receptors Conversely, the serotonin antagonists metergoline, methysergide, cyproheptadine, and cinanserin caused a significant increase in submissive gestures above 5-MeODMT treatment levels when each was administered

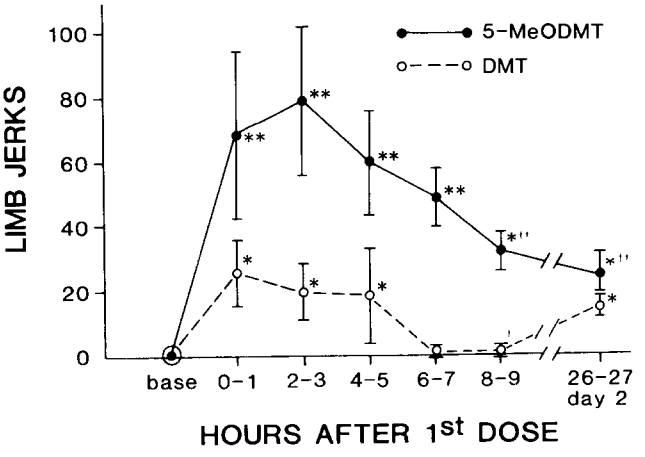

FIG 5 The development of tolerance to the hallucinogens 5-MeODMT and DMT in monkeys with frequent administration as seen with the limb jerk response Each point represents the mean±SEM limb jerks for four monkeys per 60 minute observation session Each drug was administered every 25–35 minutes for 9 hours, then re-administered 26 hours after the initial treatment Statistical significance is shown as $*p<0.05$ or $**p<0.01$ when compared to respective baseline $\dagger p<0.05$ or $\dagger\dagger p<0.01$ when compared to value for first hour of observation (0–1 hr)

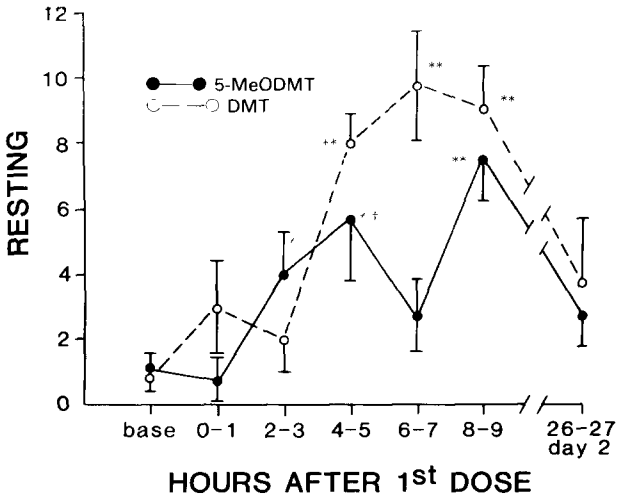

FIG 6 Increase in resting with frequent administration of 5-MeODMT and DMT in monkeys Each point represents the mean±SEM for four monkeys per 60 minute observation session Each drug was administered every 25–35 minutes for 9 hours, then re-administered 26 hours after initial treatment Statistical significance is shown as $*p<0.05$ or $**p<0.01$ when compared to respective baseline $\dagger p<0.05$ or $\dagger\dagger p<0.01$ when compared to value for first hour of observation (0–1 hr)

TABLE 4

CROSS TOLERANCE BETWEEN MESCALINE AND LSD IN MONKEYS

Drug	Behavior	
	Limb Jerks	Body Shakes
Baseline	0 00 ± 0 00	1 00 ± 0 22
Acute Mescaline	10 00 ± 4 43*	11 50 ± 2 10*
LSD Day 1	19 00 ± 3 72*	10 50 ± 1 94*
LSD Day 2	9 00 ± 1 78*	9 25 ± 1 89*
Mescaline Day 3	1 00 ± 0 71†	7 25 ± 1 03*†

Doses Mescaline 17 mg/kg, LSD 0 01 mg/kg

Statistical significance is indicated by $*p<0.01$ when compared to Baseline, $\dagger p<0.01$ when compared to Acute Mescaline

with the hallucinogen Submissive gesture scores were also increased when promethazine, diazepam, and pentobarbital were administered with 5-MeODMT

5-MeODMT-induced an increase in checking, a behavioral change seen with many psychotomimetic agents The increased checking was antagonized to varying extents by each of the drugs tested except promethazine (Fig 7)

DISCUSSION

Hallucinogens have been administered to a large number of species ranging from spiders to primates From these reports it is apparent that hallucinogens induce a wide variety of behavioral and physiological changes in animals A major problem facing hallucinogen researchers is discerning which changes are relevant to the effects of hallucinogens in humans or useful in determining the mechanisms by which these substances elicit their psychotomimetic effect In view of the present difficulties in conducting hallucinogen research in humans, it is imperative that reliable animal models be developed These data suggest that the primate social colony paradigm may be a very useful animal model for studying the action of hallucinogenic drugs

Over the past three decades, there have been but a few reports of the effects of hallucinogens on unconditioned behavior in primates Unfortunately, some of these studies have used very large doses of hallucinogens to elicit behavioral effects [6,10], making the interpretation of these results difficult In the present study, all hallucinogens were studied within or near the reported human dose range for each drug Importantly, there is an excellent correlation between the active doses of hallucinogens in monkeys and humans in this model

Some behavioral changes (ptosis, appearance of sedation, apparent lack of interest in the activity of others) induced in this study are similar to those seen in humans during hallucinogen intoxication Unfortunately, none of the hallucinogens consistently induced any behavioral change suggestive of hallucinations Although other investigators have reported tracking, grabbing in the air (presumably at imaginary objects), and unexpected startle in monkeys treated with hallucinogens [2, 11, 18], these events occurred only very rarely throughout our studies even at higher doses that bordered toxicity Therefore, this model must primarily be considered a correlative model of hallucinogen activity

The behavioral change induced by hallucinogens which best correlates with the human hallucinogenic response is limb jerks It differs from the "limb flick" response induced by hallucinogens in cats [19a,20] in appearance (M E Trulson, personal communication, F J White, personal communication) The limb jerk in monkeys is a sudden myoclonic spasm of the entire limb, whereas the limb flick in cats resembles the response of a cat attempting to "flick" a foreign substance (e g , water) off its paw Whether or not the limb flick is an involuntary response is open to question However, the limb jerk response appears to be involuntary since hallucinogen-treated monkeys will sometimes sit with their arms folded tightly around their legs in an apparent attempt to prevent limb jerks This response is seen infrequently in drug-free monkeys and appears to be selectively induced by substances that are known to be hallucinogenic in humans Relevant psychoactive compounds that did not induce a significant number of limb jerks upon acute administration include BOL, lisuride, *d* -or *l*-amphetamine, apomorphine, phencyclidine (PCP), and fluoxetine Lisuride is of particular interest since it has produced false positives other animal models of hallucinogen activity [12, 15, 21a, 22] A difference between LSD and lisuride in inducing limb jerks has also been noted in African green vervet monkeys (*Cercopithecus aethiops*) (E B Nielsen, personal communication) Furthermore, in the present study, LSD induced other behavioral changes in addition to limb jerks that were not seen with lisuride [17]

One drug that deserves mention at this point is the serotonin agonist quipazine Acute administration of quipazine, 1 and 3 mg/kg, induces limb jerks (and body shakes) in all monkeys tested [16a] Despite the abundance of animal studies with quipazine, few clinical studies with this drug have been conducted Of those in the literature, none have reported the induction of hallucinations (or many other behavioral effects) by quipazine This has been taken

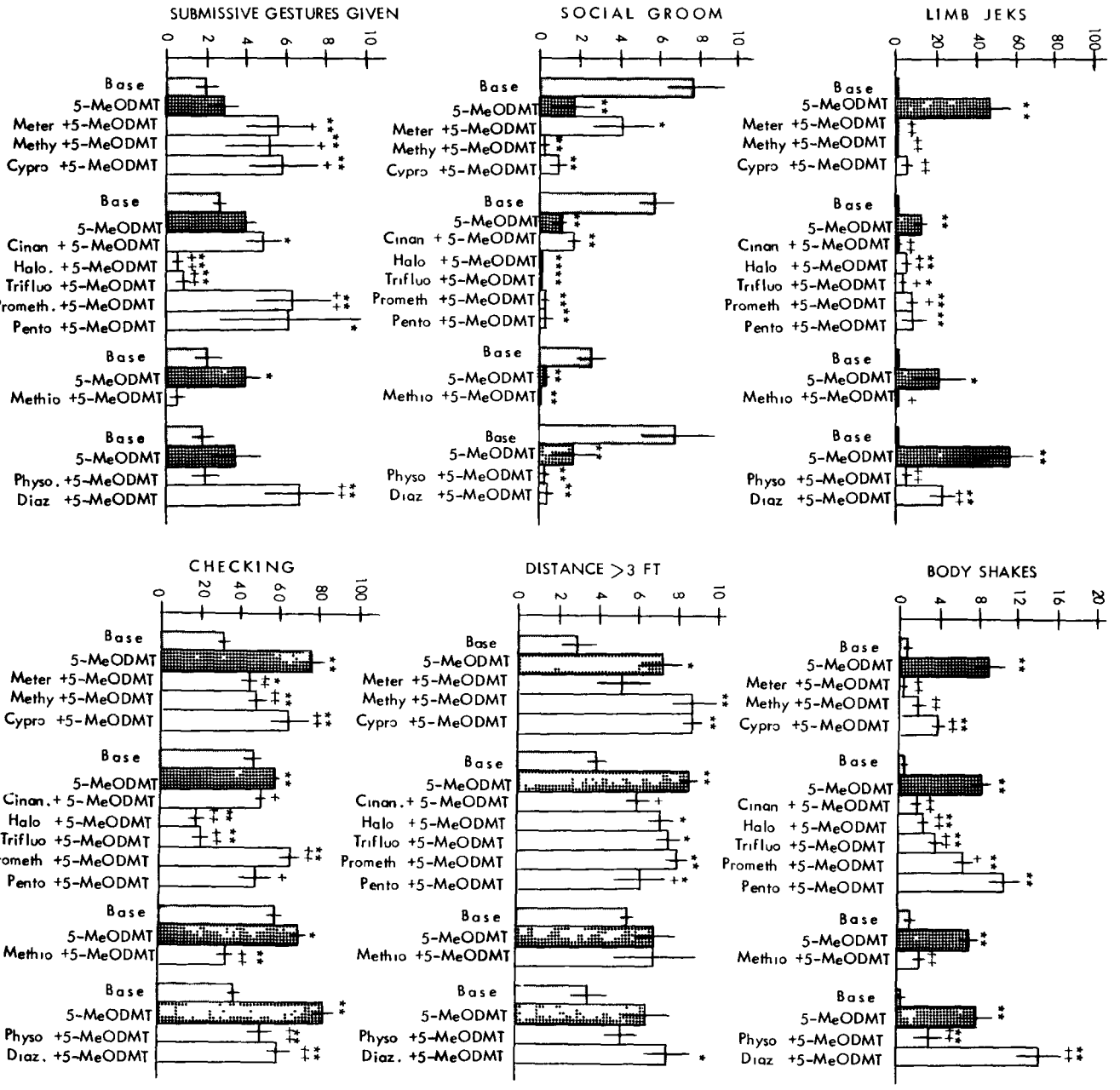

FIG 7 The effect of several psychotropic drugs on 5-MeODMT-induced behavioral changes in monkeys Each bar represents the mean±SEM for each behavior for four to five monkeys Baseline (Base) is shown as stripped bars, 5-MeODMT treatment alone in solid bars, and concomitant 5-MeODMT-antagonist treatment in open bars Drugs tested with 5-MeODMT include metergoline (Meter), methysergide (Methy), cyproheptadine (Cypro), cinanserin (Cinan), haloperidol (Halo), trifluoperazine (Trifluo), promethazine (Prometh), pentobarbital (Pento), methiothepin (Methio), physostigmine methscopolamine (Physo), and diazepam (Diaz) Statistical significance is shown as $*p<0.05$ or $**p<0.01$ when compared with respective baseline value $+p<0.05$ or $++p<0.01$ when compared respective with 5-MeODMT alone value

as evidence that quipazine is not hallucinogenic [22], but it is our opinion that caution should be exercised until a full report of the behavioral responses to quipazine in humans over a reasonable dose range is available Nevertheless, quipazine may produce a false positive response in this model A final judgement awaits hopefully forthcoming clinical reports

Tolerance developed to the limb jerk response which parallelled that seen in humans with each hallucinogen Rapid tolerance developed to LSD, mescaline, DOM, and psilocin, but not to DMT when the drugs were administered once a day Although there are no reports of repeated administration of 5-MeODMT in humans, tolerance also failed to develop to 5-MeODMT when it was administered once a day for up to 12 days However, upon more frequent administration of DMT and 5-MeODMT, a tolerance qualitatively similar to LSD did develop to both of these short-acting hallucinogens This finding is in agreement with those of

Domino with DMT in rats [8] and Trulson and co-workers with 5-MeODMT in rats [21] These results emphasize the importance of time course in the study of hallucinogens Finally, in past clinical studies, cross-tolerance was demonstrated between some hallucinogens including mescaline and LSD [2,23] In agreement with those findings, cross-tolerance between mescaline and LSD was demonstrated in this model as well

Therefore, four requirements for a good model of hallucinogen activity [9] have been demonstrated for the limb jerk response (1) apparent specificity, (2) correlation with human dose, (3) tolerance, and (4) cross-tolerance between hallucinogens

An important feature of the model is that behavioral changes other than the limb jerk response can be evaluated simultaneously For example, monkeys treated with most hallucinogens appeared sedated, but not when treated with DMT and 5-MeODMT Therefore, comparative studies of closely related hallucinogens which differ slightly, such as DMT (non-sedative) and DET (sedative) may be useful in delineating the mediation of hallucinogenic and non-hallucinogenic properties of these agents Other behavioral changes induced in monkeys by hallucinogens may have relevance to the study of psychotic processes The increase in distancing from other animals and the reduction in initiated social grooming indicate the social withdrawal often seen in treated monkeys Withdrawal is considered one of the primary symptoms of schizophrenia [4] We have previously argued that the increase in submissive gestures given by monkeys treated with psychotomimetics in the absence of an increase in aggressive gestures directed toward that animal may model human paranoia [16] Briefly, this suggestion is supported by three pieces of evidence (1) Since the increased submissiveness appears to be unprovoked, the treated monkey apparently considers a non-threatening situation as being threatening which bears similarity to human fear or paranoia (2) Only psychotomimetics known to cause paranoid states in humans induce this combination of responses in monkeys (3) Only drugs (anti-psychotics) which antagonize endogenous or drug induced paranoia in humans effectively block this response in monkeys Therefore, behavioral changes induced by hallucinogens in the clinical situation other than hallucinations (e g , withdrawal, paranoia) may be studied in this model as well This is important since these often neglected symptoms frequently may be more detrimental than the hallucinations *per se* and do not necessarily follow the severity and time course of the hallucinations

Interestingly, several of the behavioral changes induced by hallucinogens in monkeys are also induced in this species by chronic *d*-amphetamine treatment [17] This is particularly true of DMT and 5-MeODMT Behavioral changes common to both classes of psychotomimetics include increased distancing, decreased social grooming, an increase in submissive gestures, and increased checking On the other hand, limb jerks and body shakes have only been noted at low intensity in a few amphetamine-treated monkeys later (3–8 days) in chronic treatment

Additional studies with 5-MeODMT as the hallucinogen further demonstrate the utility of this model as a paradigm to screen for potential hallucinogen antagonists and for gaining insights into the mechanisms mediating the behavioral changes induced by hallucinogens in primates Although individual behavioral changes were antagonized by selective agents, no drug completely reversed the behavioral abnormalities induced by 5-MeODMT Serotonin antagonists and physostigmine were most effective in antagonizing the emergent behaviors limb jerks and body shakes Since all drugs which induce this behavior have serotonin agonist properties while centrally-active anticholinergics such as atropine do not, the results suggest that serotonin systems play an important role in the mediation of these responses Cholinergic and probably dopamine systems also appear to be involved On the other hand, dopamine systems appear to have a primary role in mediating the increased submissiveness induced by 5-MeODMT This is consistent with a report that 5-MeODMT acts as an indirect dopamine agonist as well as having serotonin agonist properties [3] The fact that none of the agents tested reversed the disruption of affiliative behavior induced by 5-MeODMT suggests that the action of this hallucinogen may be mediated by other systems as well Similar studies with other hallucinogens are needed to see if these findings hold true across hallucinogen classes

In summary, a primate model has been presented which represents a unique approach to the study of hallucinogenic drugs in a social situation The model offers a paradigm where a large number of potentially relevant behaviors can be observed simultaneously One emergent behavior, limb jerks, appears to be selectively induced by hallucinogens Although it is unlikely that the limb jerk response is the non-human primate equivalent of hallucinations, it may have heuristic value in the study of hallucinogenic drugs This model lends itself well for studies looking to screen for potential hallucinogen antagonists A good antagonist should return normal behavior as well as reverse abnormal behavior such as limb jerks The model is also well suited for studying the role of various neurotransmitter systems in the mediation of hallucinogen-induced behavior in primates Documentation of hallucinogen-induced behavioral responses in primates combined with the predictive value of the limb jerk response makes this model particularly attractive for hallucinogen research at a time when controlled human studies have been severely restricted

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