

BEHAVIORAL EFFECTS OF LSD IN THE CAT: PROPOSAL OF AN ANIMAL BEHAVIOR MODEL FOR STUDYING THE ACTIONS OF HALLUCINOGENIC DRUGS*

BARRY L. JACOBS, MICHAEL E. TRULSON and WARREN C. STERN

Department of Psychology, Princeton University, Princeton, N.J. 08540, and Burroughs Wellcome Company, Research Triangle Park, N.C. 27709 (U.S.A.)

(Accepted December 10th, 1976)

SUMMARY

In the course of examining the complete dose-response relationship for the behavioral effects of LSD in the cat, we discovered that, in addition to large increases in investigatory and hallucinatory-like responses, two behaviors, not previously reported, are emitted with a high probability under LSD. Beginning from a baseline of essentially zero in saline-treated animals, limb flicks and abortive grooming increase in frequency in direct relation to the dose of LSD administered (2.5, 10, 25 and 50 $\mu\text{g/kg}$ i.p.) and then decrease at higher doses (100 and 200 $\mu\text{g/kg}$). Limb flicks are a species-specific behavior seen in normal cats almost exclusively in response to the presence of a foreign substance, such as water, on the hindpaw or forepaw. In abortive grooming, the cat orients to the body surface as if to groom but does not emit the consummatory grooming response (bite, lick or scratch), or emits the response in midair. These behaviors can serve as an animal behavior model for the actions of LSD and related hallucinogens in humans. The specificity of these behavioral changes is indicated by the fact that they are never seen in response to other classes of psychoactive drugs such as D-amphetamine, atropine, caffeine and chlorpheniramine. They are, however, elicited by compounds such as psilocybin which are structurally and functionally related to LSD. The validity of the model is based on evidence indicating that it is: specific to hallucinogens, dose dependent, observed in a dose range effective in humans, parallels the major parameters of the actions of LSD in humans (see following paper), sensitive, robust, reliable, quantifiable and easy to score.

* A preliminary report of some of these results has previously been published: B. L. Jacobs, M. E. Trulson and W. C. Stern. An animal behavior model for studying the actions of LSD and related hallucinogens, *Science*, 194 (1976) 741-743.

INTRODUCTION

Lysergic acid diethylamide (LSD) and structurally and/or functionally related hallucinogens such as N,N-dimethyltryptamine (DMT) and psilocybin are of great interest because of the profound psychological effects they produce in humans. In spite of intense public and scientific interest in these drugs, however, many questions concerning the parameters and physiological bases of their actions remain unanswered.

Experiments directed at these issues which employ human subjects are precluded either for moral or ethical reasons, or because they require examination of tissue derived from living organisms. Therefore, we must turn to animal experiments for the answers to most of these questions. However, utilization of animals in experiments dealing primarily with psychological variables, such as hallucinations, raises the unanswerable question of how one discerns whether an animal is experiencing a hallucination. Another approach involves using some aspect of animal behavior (or physiology) as a model of the human variable. In order to qualify as an animal model for the actions of hallucinogenic drugs in humans, a particular behavior would have to: change specifically in response to this class of drugs, and no other; vary in magnitude in a dose-dependent manner; be responsive to a dose range approximately within the human range; and closely parallel the major parameters of the action of the drug in humans, e.g., show a similar time course of action and a similar development of tolerance. More generally, a good model should be sensitive, robust, reliable, quantifiable and easy to score.

We reasoned that the establishment of an animal behavior model for the actions of hallucinogenic drugs could best be accomplished by close observation and analysis of the behavior of animals administered these drugs. Although previous studies have examined the effects of LSD and related hallucinogens on behavior in a variety of species (e.g., rat and mouse^{6-10,12,15-18,23-33,36,39,43-45,49,50}, cat^{2,19,22,25,27,30,38,40,41,48}, and monkey^{20,33,34,42}), few of them have explored a complete dose range or closely examined the behavioral changes. Most importantly, none of them have reported an effect which was demonstrated to be specific to LSD. Accordingly, in our initial study, we administered LSD to cats and attempted to compile a complete and detailed record of all major behavioral changes, with special attention toward those behaviors that might be evoked specifically by LSD. Subsequent experiments described in this paper demonstrate that the observed behavioral effects of LSD are not due to a peripheral action, that these behaviors are also elicited by a related indole nucleus hallucinogen, and that they are never seen in response to a variety of other psychoactive drugs. In the accompanying article, we demonstrate the usefulness of this model by employing it to elucidate some of the parameters of LSD's action.

METHOD

Adult female cats weighing 2.0-3.3 kg were used in all experiments. They were individually housed in standard stainless steel cat cages which also served as the

experimental observation chamber. Animals were allowed a 2-3 week period for habituation to their cages and the laboratory setting before experiments were begun. Only animals that were relatively easy to handle were used.

Using a counterbalanced design, each animal received all dose levels of LSD, with at least 8 days intervening between consecutive sessions. Cats were given intraperitoneal injections of either saline or lysergic acid diethylamide tartrate (2.5, 10.0, 25.0, 50.0, 100.0 or 200.0 $\mu\text{g/kg}$). Behavioral observations, by raters who were "blind" to the treatment, were made during the hour immediately following drug administration. The hour was divided into four 15 min segments and the frequency of occurrence of each behavior was tallied on a standard scoring sheet. Many of the behavioral descriptions are self-explanatory, however, a few require further comment. Rubbing the head area with the forepaw, licking, and scratching are all subsumed under grooming. Abortive grooming is scored when the cat orients to the body surface as if to groom but does not emit the consummatory grooming response (bite, lick, or scratch), or emits the response in midair. Limb flicking is a behavior seen in normal cats almost exclusively in response to the presence of a foreign substance on the hindpaw or forepaw. The paw is then lifted and rapidly snapped or flicked outward from the body. Investigatory or play behavior refers to pawing or sniffing at objects or in corners, chasing the tail, or batting at pieces of food, feces, etc. Hallucinatory-like behavior is scored when the cat looks around at the floor, ceiling or walls of the cage and appears to be tracking objects visually, or when the cat either hisses at, bats at, or pounces at "objects" not seen by the observer.

In order to control for the peripheral serotonin antagonist effects of LSD, behavioral observations were made following administration of the potent peripheral serotonin antagonists brom-LSD (25 and 100 $\mu\text{g/kg}$) or methysergide maleate (25, 100, 500 and 2500 $\mu\text{g/kg}$). The specificity of the LSD-induced behavioral changes was examined by observing the behavioral effects of compounds from other major drug classes: D-amphetamine sulfate (0.25, 1.0 and 5.0 mg/kg), atropine sulfate (0.5 and 2.5 mg/kg), caffeine (1, 5 and 20 mg/kg), chlorpheniramine maleate (0.5, 2.5 and 5.0 mg/kg) and tryptamine (50, 500 and 5000 $\mu\text{g/kg}$), a non-hallucinogenic indole nucleus drug. Finally, in order to examine the generality of the behavioral changes seen in response to LSD, animals were observed following administration of psilocybin (25, 100 and 500 $\mu\text{g/kg}$), an indole nucleus hallucinogen structurally related to LSD, or the structurally unrelated hallucinogen, Δ^9 -tetrahydrocannabinol (0.5, 1.0 and 5.0 mg/kg). In all cases drug doses are expressed as the salt, and all drugs were administered via the intraperitoneal route.

RESULTS

LSD

The behavioral effects of LSD can be divided into 3 categories. First, those that did not significantly change in frequency in response to LSD: rubbing, treading or kneading, and vocalization. The second group of behaviors manifested a relatively high frequency of occurrence following saline injection and then showed a significant

dose-dependent increase in response to LSD: staring (other than forward for 5 sec or more), grooming, and head or body shakes. Finally, the third group of behaviors were either non-existent or occurred with a very low frequency in saline-treated animals, but emerged to become the most prominent behaviors of LSD-treated animals. Since the latter group of behaviors will be proposed as an animal model for the actions of LSD, we will begin by discussing them in some detail.

Limb flicking, abortive grooming, investigatory or play behavior, and hallucinatory-like behavior all have a curvilinear relationship to the dose of LSD (Fig. 1). In general, these behaviors have a mean hourly frequency at or near zero in saline-treated animals, increase in frequency in a dose-dependent manner, reaching their peak at 25 or 50 $\mu\text{g/kg}$ LSD, and then decline in response to the administration of 100 and 200 $\mu\text{g/kg}$ doses. Because these behaviors are seen almost exclusively in response to LSD and related hallucinogens, they may be considered emergent characteristics of the effects of these drugs.

Perhaps the most impressive effect of LSD was the elicitation of the limb flicking response. This is a species-specific behavior normally used exclusively for removing foreign substances from the limbs. In saline-treated animals, this response was seen only twice in the 1 h observation period on 12 cats ($\bar{X} = 0.2/\text{h}$). When the same animals were administered LSD, this response significantly increased in frequency in a dose-dependent manner to a peak of 45.9/h at a dose of 50 $\mu\text{g/kg}$ ($P < 0.001$, Anova). After the 200 $\mu\text{g/kg}$ dose, the frequency of flicks significantly declined to a mean of 15/h ($P < 0.001$, *t*-test). Every animal tested responded with at least 1 flick to doses of 25, 50 and 100 $\mu\text{g/kg}$.

The limb flick in LSD-treated cats is a very rapid response, which appears to be reflexive. It occurs most frequently when the animal is sitting or standing quietly. This response may be the most sensitive reflection of the effects of LSD in the cat since it is the only behavior to significantly increase in frequency in response to the lowest dose of 2.5 $\mu\text{g/kg}$ ($P < 0.01$, *t*-test).

Along with limb flick, the other major emergent behavior which had not been described in previous studies was abortive grooming. This response increased in a significant dose-dependent manner up to 100 $\mu\text{g/kg}$ ($P < 0.001$, Anova), and then significantly decreased at 200 $\mu\text{g/kg}$ ($P < 0.01$, *t*-test). Although the mean frequency of 7.9 bouts of abortive grooming/h at the 100 $\mu\text{g/kg}$ dose does not represent a large absolute value, this response was *never* observed in saline-treated animals. In the case of abortive grooming of the body, the animal would assume a typical grooming posture, turn the head toward the body surface, then either lick or bite in midair or simply extend the tongue without contacting the body. Similarly, abortive forelimb grooming occurred when the limb was raised toward the mouth and the consummatory lick or bite response failed to be emitted or was emitted in midair. As with limb flicks, every animal tested showed at least one instance of abortive grooming in response to high doses of LSD. Emergence of abortive grooming may be reflective of the fragmentary or disjunctive nature of all behaviors in LSD-treated animals. These animals would rarely sustain one type of active behavior for more than several seconds.

During a 1 h observation period, very few cats housed for at least 2 or 3 weeks in a standard cat cage spontaneously emit behavior that would be classified as play or investigatory. However, this dramatically changes when they are administered LSD. As shown in Fig. 1, the frequency of these responses significantly increased in a dose-dependent manner, reaching their peak of 10.8/h at 50 $\mu\text{g/kg}$ ($P < 0.01$, Anova). This response markedly decreased in frequency ($\bar{X} = 1.2/\text{h}$), when the dose was increased from 50 to 200 $\mu\text{g/kg}$ ($P < 0.001$, *t*-test). Unlike flicking and abortive grooming, these responses were not observed in every animal tested. Certain animals emitted very high frequencies, while others emitted little or none. These responses most frequently consisted of sniffing or pawing in the corners of the cage, extending the forepaws through bars of the cage and attempting to touch neighboring cats, batting at or pouncing on bits of food or feces, and tail chasing.

The final emergent response, hallucinatory-like behavior, proved to be the least objective and the most difficult to score. In general this response was scored when the

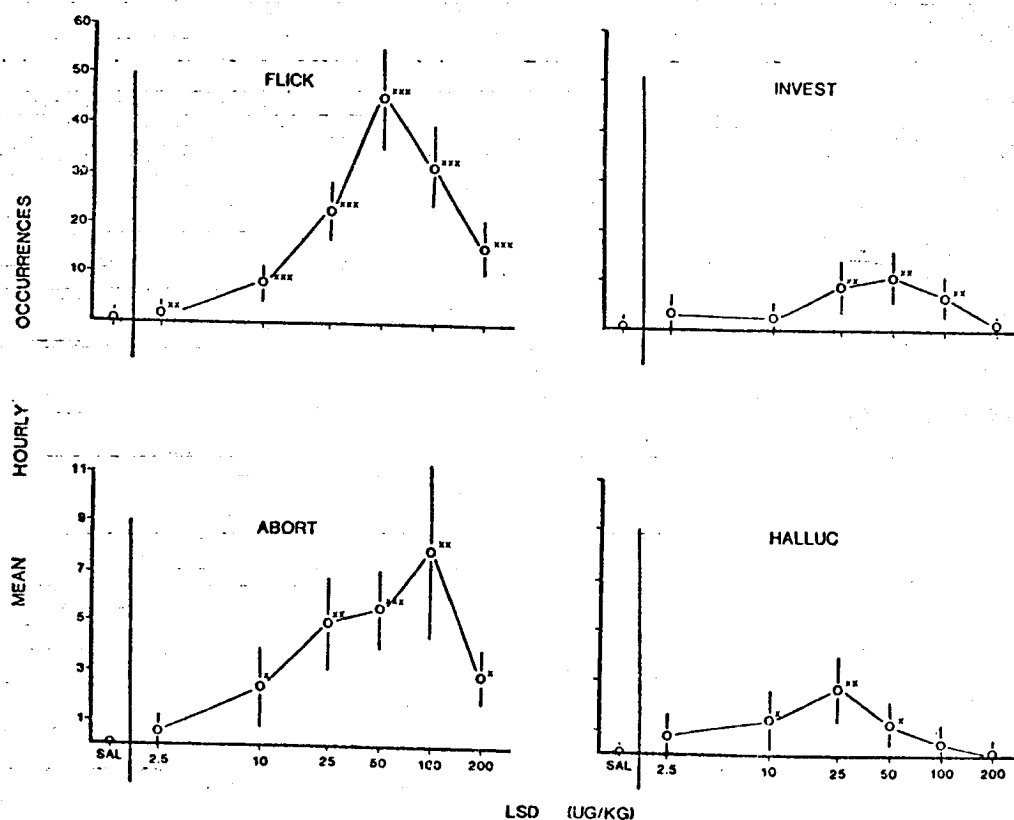


Fig. 1. Behavioral effects of LSD tartrate plotted as mean frequency of occurrence/h ($\pm$ S.E.M.) as a function of increasing dose (plotted on a log scale). Abbreviations: flick, limb flicking; invest, investigatory or play behavior; halluc, hallucinatory-like behavior; abort, abortive grooming. Single factor analyses of variance indicated that varying the dose had a significant effect on the frequency of occurrence of limb flicking and abortive grooming ($P < 0.001$) and on hallucinatory-like and investigatory behavior ($P < 0.01$). Levels of significance of *t*-tests comparing each dose with saline control: $P < 0.05^*$, $P < 0.01^{**}$, $P < 0.001^{***}$.

animal pounced on, batted at, attacked, or seemed to be visually tracking something not apparent to the experimenter. Like play, this behavior is virtually non-existent in well habituated, untreated animals. The mean frequency of occurrence of hallucinatory-like behavior significantly increased as a function of dose ($P < 0.01$, Anova), reached its peak at 25 $\mu\text{g/kg}$, and then declined in response to higher doses, ultimately approaching zero at 200 $\mu\text{g/kg}$. The mean frequency of occurrence was significantly less at 200 than at 50 $\mu\text{g/kg}$ ($P < 0.05$, t -test). This behavior was also emitted with a high frequency in some animals and not at all in others.

Rubbing, treading or kneading, and vocalization do not require much discussion since they did not significantly change frequency in response to increasing doses of LSD (Table I). Treading and kneading seemed to show some increase in response to LSD and thus may reflect a greater degree of relaxation. The lack of distress calls or howling (both subsumed under vocalization), even at the highest doses of LSD may indicate that the animals never felt overly sick, anxious or uncomfortable.

Staring, grooming, and head or body shakes showed significant dose-dependent increases in frequency which peaked at 25–100 $\mu\text{g/kg}$ ($P < 0.01$ or 0.001, Anova). The frequency of all of them declined significantly at the highest dose ($P < 0.01$ or 0.001, t -test) (Table I). Saline-treated animals spent most of their time either with their eyes closed or staring out the front of their cages, whereas, LSD-treated animals frequently stared (a 5 sec fixation) at the top, bottom and sides of their cages. LSD-treated animals engaged in an inordinately large number of grooming bouts. Head or whole body shakes increased in a dose-dependent manner up to 50 $\mu\text{g/kg}$ where its frequency was approximately 5 times that of the saline-injected controls. Occurrences of these responses were often temporally related to occurrences of limb flicking and/or abortive

TABLE I

Dose-response relationships for LSD in the cat

Mean frequency/h $\pm$ S.E.M.; N = 12.

Behavior	LSD tartrate ($\mu\text{g/kg}$)						
	0.0	2.5	10.0	25.0	50.0	100.0	200.0
Rubbing	1.9 $\pm$ 1.3	1.5 $\pm$ 0.8	1.1 $\pm$ 1.0	2.6 $\pm$ 2.0	2.1 $\pm$ 1.6	1.7 $\pm$ 1.5	0.1 $\pm$ 0.1
Treading or kneading	0.0 $\pm$ 0.0	1.1 $\pm$ 0.4	0.4 $\pm$ 0.3	1.2 $\pm$ 0.3	0.7 $\pm$ 0.3	0.4 $\pm$ 0.2	0.7 $\pm$ 0.3
Vocalization	1.2 $\pm$ 0.8	1.3 $\pm$ 1.1	1.3 $\pm$ 0.9	0.6 $\pm$ 0.3	0.5 $\pm$ 0.5	0.6 $\pm$ 0.5	0.7 $\pm$ 0.7
Staring**	5.1 $\pm$ 1.4	3.2 $\pm$ 1.4	8.8 $\pm$ 2.3†	15.4 $\pm$ 2.7††	18.2 $\pm$ 3.2†††	24.4 $\pm$ 5.2†††	4.5 $\pm$ 2.1
Grooming*	7.4 $\pm$ 2.4	8.4 $\pm$ 2.5	18.0 $\pm$ 4.2†	22.6 $\pm$ 6.3††	16.3 $\pm$ 2.8†	11.2 $\pm$ 2.5	7.2 $\pm$ 2.5
Head or body shake**	6.4 $\pm$ 1.1	9.3 $\pm$ 2.2	10.8 $\pm$ 2.7†	13.2 $\pm$ 3.1†	30.3 $\pm$ 6.9†††	13.5 $\pm$ 3.4†	6.7 $\pm$ 2.2

Levels of significance for single factor analysis of variance examining the effect of dose on the frequency of each behavior: * $P < 0.01$; ** $P < 0.001$.

Levels of significance of t -tests comparing each dose with saline control (0.0 $\mu\text{g/kg}$ LSD): † $P < 0.05$; †† $P < 0.01$; ††† $P < 0.001$.

grooming. They were often concatenated with these other behaviors to form rapidly occurring sequences.

Finally, many cats emitted the following general behaviors in response to LSD: yawning; and licking chops; standing or sitting in bizarre positions, e.g., with hindleg extended in space; kitten-like behavior, e.g., chasing their tails and pawing the air while lying on their sides or backs; leaping about the cage (often falling off their perch); sitting on the perch and staring down and back (they also frequently appeared to be responding to their own reflection in the stainless steel walls of their cages); continual scanning of environment by moving the head about; compulsive scratching in litter pan; biting wood perch or metal of cage; pawing in water.

We never observed howling, spitting, rage or marked fear following LSD. Nor did we observe obvious salivation or lacrimation. The animals rarely ate lab chow or drank water following LSD. The drug did, however, induce frequent defecation and occasional emesis.

TABLE II

Effect of various psychoactive drugs on the frequency of selected behaviors (mean/h)

Drug	Dose (mg/kg)	N	Behaviors			
			Flick	Abort	Invest	Halluc
Saline	—	6	0.0	0.0	0.5	0.2
Brom-LSD	0.025	5	0.0	0.6	1.0	0.2
	0.100	5	1.6*	0.0	0.0	0.0
Methysergide maleate	0.025	5	0.2	0.0	0.8	0.6
	0.100	5	3.8**	1.8**	1.0	0.0
	0.500	5	4.0**	0.7	3.3	0.0
	2.500	4	2.7	2.7	4.7	0.0
D-Amphetamine sulfate	0.250	5	0.0	0.0	0.6	0.0
	1.000	5	0.0	0.2	0.2	0.0
	5.000	5	0.0	0.0	0.0	0.0
	0.500	5	0.0	0.0	0.4	0.0
Atropine sulfate	2.500	5	0.0	0.6	0.8	0.0
	1.000	4	0.0	0.0	0.0	0.25
Caffeine	5.000	4	0.25	0.0	2.0	0.0
	20.000	4	0.0	0.0	3.25	0.0
	0.500	4	0.0	0.0	0.0	0.0
Chlorpheniramine maleate	2.500	4	0.0	0.0	0.0	0.0
	5.000	4	0.0	0.0	0.0	0.0
	0.025	6	1.2**	0.5	1.7	0.0
Psilocybin	0.100	6	6.3**	2.7*	4.2	0.5
	0.500	6	5.8*	0.8	0.7	0.0
	0.500	4	0.0	0.0	0.0	0.0
Δ^9 -tetrahydrocannabinol	1.000	4	0.0	0.0	0.0	0.0
	5.000	4	0.25	0.0	0.0	0.0
	0.050	4	0.0	0.0	1.25	1.25
Tryptamine	0.500	4	0.0	0.0	0.0	0.0
	5.000	4	0.0	0.0	0.0	0.0

Levels of significance of *t*-tests comparing each behavior under a drug condition with that behavior following saline: **P* < 0.05; ***P* < 0.025.

Peripheral serotonin blockers

Since LSD is known to be a potent serotonin antagonist in the periphery^{14,51}, we examined the effect of its non-hallucinogenic congener brom-LSD, which has the same potency peripherally¹³, and methysergide, which is more potent than LSD in blocking the action of serotonin in the periphery²¹. Brom-LSD in doses of 25 and 100 $\mu\text{g/kg}$ produced very little behavioral change except for a mean rate of 1.6 flicks/h at the higher dose (Table II). Three out of the 5 animals tested responded with at least one flick in the hour observation period ($P < 0.05$, t -test). Methysergide maleate in doses of 100 $\mu\text{g/kg}$ and higher produced effects similar to a low dose of LSD, e.g., the 100 $\mu\text{g/kg}$ dose elicited 3.8 flicks/h ($P < 0.025$) and 1.8 episodes of abortive grooming/h ($P < 0.025$, t -test). In general, the animals appeared attentive and playful. At the highest dose, 2.5 mg/kg, there was considerable emesis, ataxia, head bobbing or weaving, and dramatic pinna twitching.

Drugs from other classes

In an attempt to explore the specificity of the behavioral response to LSD, we examined the effects of psychoactive drugs from various drug classes. These data are summarized in Table II. In general, none of these compounds produced any effects similar to that produced by LSD.

D-Amphetamine sulfate in low doses (0.25 mg/kg) produced very little behavioral effect. In higher doses (1.0 and 5.0 mg/kg) it produced immobility except for stereotyped head and eye movements. Atropine sulfate had virtually no effect at 0.5 mg/kg, and produced ataxia, restlessness and plaintive meowing at 2.5 mg/kg. Caffeine was almost without effect except at the highest dose (20 mg/kg) where it seems to activate or arouse the animals. Chlorpheniramine appeared to have no effect other than mild sedation in any dose.

Other hallucinogens

The generality and importance of the behavioral changes observed in response to LSD could best be demonstrated by testing a structurally and functionally related indole nucleus hallucinogen, psilocybin. For comparison, we examined the effect of a non-indole nucleus hallucinogen, Δ^9 -tetrahydrocannabinol (THC). These data are summarized in Table II.

Psilocybin closely mimicked the effects of low doses of LSD. A dose of 100 $\mu\text{g/kg}$ elicited larger behavioral effects than either a lower dose (25 $\mu\text{g/kg}$) or a higher dose (500 $\mu\text{g/kg}$), which is similar to the curvilinear relation seen in response to LSD. The 100 $\mu\text{g/kg}$ dose produced 6.3 flicks/h ($P < 0.025$, t -test) and 2.7 episodes of abortive grooming/h ($P < 0.05$, t -test). In addition, there was a fair amount of play behavior, but little or no hallucinatory-like behavior. By contrast, THC in doses ranging from 0.5 to 5.0 mg/kg produced little more than emesis and ataxia at the high doses. There was no similarity to any aspect of the LSD effect. As a final control, we examined the effect of a non-hallucinogenic indole nucleus compound, tryptamine. In doses ranging from 50 $\mu\text{g/kg}$ to 5 mg/kg, no behavioral change was observed, except emesis at the highest dose (Table II).

DISCUSSION

LSD produced a significant dose-dependent increase in 7 of 10 behaviors measured in this study (see Fig. 1 and Table I). A dose of 50 $\mu\text{g/kg}$ appears to be the maximally effective dose in the cat, as measured by change in frequency of the various behaviors. This parallels the dose-dependent (1–16 $\mu\text{g/kg}$) increases in the psychological and perceptual effects observed in human studies³⁵. It is not known what dose of LSD produces the peak effect in humans. A dose of 2.5 $\mu\text{g/kg}$ of LSD appears to be the minimally effective dose in the cat since it produced a change in behavior of some animals, but not others, and because it produced a significant overall increase in limb flicks. This is within an order of magnitude of the range of doses, 0.5–1.0 $\mu\text{g/kg}$, that are minimally effective in humans^{1,31}.

Validity of the model

Because limb flicking, abortive grooming, investigatory or play behavior and hallucinatory-like behavior are emitted at a high rate in response to the hallucinogens LSD and psilocybin, and because they are never seen in response to a variety of other psychoactive compounds, we propose that they may be used as an animal behavior model for the actions of this class of drug. Furthermore, observation and measurement of the first two of these behaviors, limb flicking and abortive grooming, may be sufficient for utilization as an animal model because: (1) they are the easiest behaviors to score, in the sense that their occurrence is relatively unambiguous; (2) they are the most reliable measures (see following paper); (3) they occur at a high frequency, especially in the case of limb flicking; and (4) they are observed in all animals tested.

Previous studies of the effects of indole nucleus hallucinogens in cats failed to report either limb flicking or abortive grooming, and failed to delineate any behavioral changes that might be specific to these compounds^{2,19,22,25,27,30,38,40,48}. A recent study of the effects of LSD in the monkey reported an increase in spasms, but this was also increased by amphetamine⁴². Studies of hallucinogens in rats and mice typically have utilized experimental paradigms, such as startle, or the disruption of a conditioned response, effects which are obviously not specific to hallucinogenic drugs^{9,10,16,17,23–25,36,39,43,45,49,50}. By contrast, the present behavioral measures appear to be specific to hallucinogenic drugs and are essentially non-existent in control animals.

The specificity of these emergent behaviors is indicated by the fact that they were never seen in response to other classes of major psychoactive drugs, such as those affecting the catecholamines (amphetamine), acetylcholine (atropine), or histamine (chlorpheniramine). Caffeine, a phosphodiesterase inhibitor, was also ineffective. These behavioral effects of LSD are not attributable to the inactivation of serotonin in the periphery since methysergide did not elicit any of these emergent behaviors at 25 $\mu\text{g/kg}$, a dose of LSD that produced potent behavioral changes. However, when the dose was increased to 0.1 and 0.5 mg/kg, several flicks and episodes of abortive grooming were observed. This correlates well with the fact that high doses of methysergide have been reported to be moderately hallucinogenic in humans^{11,29}. Further support that the

behavioral effects are not due to a peripheral action of LSD comes from the fact that its non-hallucinogenic congener, brom-LSD, was ineffective in eliciting the emergent behaviors in a dose of 25 $\mu\text{g/kg}$. However, a dose of 100 $\mu\text{g/kg}$ produced 1.6 flicks/h which might be related to the observation that high doses of brom-LSD are mildly hallucinogenic³².

Mechanism of action of LSD

Systemic administration of low doses of LSD selectively depresses the activity of serotonin-containing raphe neurons³, and because of serotonin's exclusively inhibitory synaptic action this results in an increase in the activity of neurons postsynaptic to raphe cells²⁸. On the other hand, while low doses of LSD have an effect on raphe neurons which acts to decrease the serotonergic input to their postsynaptic neurons, high doses of LSD have the opposite functional effect on these same postsynaptic neurons: a direct serotonin agonist effect⁴⁷. These opposing effects of high and low doses of LSD may account for the significant decreases in virtually all behaviors seen in response to the highest doses of LSD. Thus, while low doses of LSD may disinhibit the activity of postsynaptic neurons, high doses may directly inhibit their activity.

If the emergent behaviors seen in response to LSD are a manifestation of the depression or inactivation of the activity of the brain serotonin system, then other compounds which functionally inactivate this system should also elicit these behaviors. This inactivation could be accomplished by a depression of raphe unit activity, by a decrease in brain serotonin, or by a blockade of serotonin receptors. Consistent with this hypothesis, we have previously reported that cats administered the serotonin-depleting drug, *p*-chlorophenylalanine, manifest limb flicking and abortive grooming⁴⁶. It should be recalled that the presumptive central serotonin receptor blocker methysergide produced moderate LSD-like effects in high doses. We further hypothesized that only those compounds which inactivate the brain serotonin system will elicit these behaviors. Using electrophysiological criteria, any hallucinogen which can be shown to consistently depress the activity of raphe neurons should be effective. This electrophysiological criterion has been demonstrated in the case of *N,N*-dimethyltryptamine⁴, bufotenine⁵, psilocin⁵, and 5-methoxy-*N,N*-dimethyltryptamine³⁷. We have recently tested several of these compounds and found that they do elicit the emergent behaviors. In addition, our recent data indicate that although serotonin inactivation may be a sufficient condition for eliciting the emergent behaviors, their frequency of occurrence may be greatly increased if the test drug also exerts a dopaminergic action (e.g., LSD or STP).

Usefulness of the model

As will be shown in the following paper, one of the major applications of this model is in the investigation of the parameters of action of hallucinogenic drugs. These studies demonstrate that the model is an effective tool in examining the duration of action of LSD, and the onset and duration of tolerance to LSD. Cross-tolerance could also be investigated with this model. The development of cross-tolerance between two compounds may be a probe into the similarity of the neuronal substrates of their

actions. Because some of the behaviors, such as limb flicks, give reliably quantifiable data, the degree of cross-tolerance, if less than total, could be assessed.

Relative potency of hallucinogenic compounds could be examined by comparing both the dose necessary to produce the emergent behaviors and the magnitude of the response elicited. In the same vein, the model could be used to predict whether as yet untested compounds would have hallucinogenic potency in humans.

Blocking the action of hallucinogens could also be explored through the use of the model. These studies would potentially be of interest both clinically and for basic research. If the emergent behaviors are a manifestation of the depression of the activity of the brain serotonin system, as suggested above, then compounds which act in a reciprocal fashion should block the syndrome. Compounds which selectively increase the functional activity in serotonin-mediated synapses of the cat should be effective blockers, whereas those compounds which increase the activity of other transmitters should be less effective (or ineffective) blockers. Compounds with known dopamine receptor blocking action, such as the phenothiazines, would also be expected to decrease the behavioral effects of those hallucinogens with known dopaminergic actions.

Finally, the model could be used to determine whether a correlation exists between the depression of raphe unit activity and the behavioral changes induced by LSD, by recording raphe unit activity in freely moving cats. A dose of LSD which is just at the threshold of producing behavioral effects significantly different from saline could be examined to see if it significantly depresses raphe unit activity. Also, a range of doses of LSD could be examined to see whether the quantifiable behavioral changes positively correlate with the degree of depression of raphe unit activity. Such an experiment would also provide a major test of the hypothesis that inactivation of the brain serotonin system is a necessary precondition for the hallucinogenic effects of LSD.

CONCLUSION

We propose that the emergent behaviors in the cat, especially limb flicking and abortive grooming, represent a viable animal behavior model for studying the actions of those hallucinogens which inactivate the brain serotonin system. This model fulfills all the criteria for a valid model that were discussed in the introduction. *Specificity*: these behaviors are seen exclusively in response to LSD and related hallucinogens. *Dose dependent*: the behaviors significantly increased in frequency in a dose-dependent manner. *Human range*: limb flicking showed a significant increase in frequency in response to a dose of 2.5 $\mu\text{g/kg}$ LSD, while the other 3 emergent behaviors significantly increased in response to a 10 $\mu\text{g/kg}$ dose. *Parallel major parameters*: the following paper describes the usefulness of the model in examining the duration of action of LSD, and the onset and duration of tolerance to LSD. *Sensitive*: the sensitivity of the model is indicated by the fact that significant changes are observed in response to 2.5 and 10 $\mu\text{g/kg}$ doses. *Robust*: the changes in limb flicking and abortive grooming were observed in every animal tested. *Reliable*: the following

paper reports that the mean frequency of limb flicks in response to a 50 $\mu\text{g/kg}$ dose of LSD is stable when tested over a period of several weeks. *Quantifiable and easy to score*: one of the important advantages of this model is that the scoring and quantification of the behaviors, especially limb flicking and abortive grooming, requires only a trained observer with pencil and paper.

ACKNOWLEDGEMENTS

This research was supported by National Institute of Mental Health Grants MH 13445 and MH 23433.

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