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USEFULNESS OF AN ANIMAL BEHAVIORAL MODEL IN STUDYING THE DURATION OF ACTION OF LSD AND THE ONSET AND DURATION OF TOLERANCE TO LSD IN THE CAT

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SUMMARY

LSD elicits a number of emergent behaviors in the cat, including limb flicking, abortive grooming, investigatory and hallucinatory-like behaviors, which we have proposed as an animal behavior model for studying the actions of LSD and related hallucinogens. These emergent behaviors were used in the present study to investigate the duration of action of LSD, as well as the onset and duration of tolerance. A dose of 10 μg/kg of LSD produced significant behavioral changes for up to 4 h, while a dose of 50 μg/kg produced changes lasting for at least 8 h. Tolerance to a test dose of 50 μg/kg of LSD is virtually complete one day after a single 50 μg/kg dose, and lasts for approximately 5 days. Tolerance to a test dose of 50 μg/kg of LSD one day after a single dose of 10 μg/kg is quite marked, and lasts for approximately 3 days. A significant tolerance to a test dose of 50 μg/kg of LSD occurs within 2 h after a single injection of 10 μg/kg. The limb flick was found to be the most sensitive index in all tests: it showed the longest time-course, as well as the most rapid and longest-lasting tolerance. These studies demonstrate that the LSD-induced behavioral syndrome in the cat parallels important parameters of the action of LSD in humans, and thus enhances the usefulness of the model.

INTRODUCTION

In the preceding paper we proposed an animal behavior model for studying the parameters and mechanisms of action of LSD and related hallucinogens. This model consists of quantifying the occurrences of limb flicking, abortive grooming, investigatory or play behavior, and hallucinatory-like behavior in the cat following drug administration. The utility of any animal model is dependent on whether it parallels the effect in humans. Therefore we hypothesized that the validity of the pre-

sent model would be strengthened if the LSD-induced behavioral changes in cats paralleled important parameters of the action of LSD in humans.

Two of the best known aspects of the action of LSD in humans are its long duration of action and the dramatic tolerance which develops to its repeated administration. Moderate doses of LSD produce discriminable physiological and psychological effects lasting for 6–8 h, while higher doses produce changes lasting up to 24 h[2,12,19]. The duration of these effects is consistent with the relatively long half-life of LSD in human plasma of 3 h[1]. Since the half-life of LSD in cat plasma is known to be approximately 2 h[6], we predicted that high doses of LSD would induce behavioral changes lasting for at least 8 h.

Repeated daily administration of LSD to humans produces a marked tolerance to the physiological and psychological effects within 1–3 days which lasts for 5–6 days[1,7,13]. Examination of the literature on the effects of LSD on animal behavior reveals that several studies have investigated the phenomenon of tolerance, but that few have done so systematically. Considerable ambiguity exists in both the human and animal literature concerning the drug regimen required to induce tolerance, as well as the duration of tolerance[2,5,8–10,12,13,25]. In addition, very little is known about the rapidity of onset of tolerance to LSD.

Previous studies on the duration of action and development of tolerance to LSD have utilized non-specific behavioral measures such as the disruption of either rope climbing or bar pressing[5,8,9,25]. While these studies have made important contributions to our knowledge of the action of LSD, no definitive conclusions can be drawn from them because the behavioral measures employed are not a specific reflection of the action of hallucinogens. Since we have demonstrated that the behavioral syndrome in the cat is elicited only by LSD and structurally and/or functionally related hallucinogens, these behavioral changes provide useful measures for studying the phenomenon of tolerance to those drug effects which are *specific* to these hallucinogens.

METHODS

Duration of behavioral effects

Two groups of female cats (N = 7/group) weighing 2.7–3.8 kg received a single intraperitoneal injection of LSD tartrate at a dose of either 10 or 50 μg/kg (dose expressed as the salt). Behavioral observations by "blind" raters were made during hours 1, 2, 3, 4, 6, 8 and 24 following drug administration. The behavior was scored for limb flicking, abortive grooming, investigatory or play behavior, hallucinatory-like behavior, head and body shakes, staring, and grooming as described in the preceding paper. Although treading or kneading, rubbing, and vocalization were scored in the present study, the data will not be reported, since these behaviors did not show a dose-related change in the previous study.

Duration and onset of tolerance

For investigating the duration of tolerance, female cats were administered a

single dose of LSD tartrate, either 10 or 50 μg/kg, i.p., and then given a test dose of 50 μg/kg of LSD at 1, 3, 5, 7 or 14 days later (separate groups for each time point). Behavioral observations during a 1 h period were made by "blind" raters, as described above. In the study of the onset of tolerance, female cats were administered either a single dose of LSD tartrate (2.5 or 10 μg/kg, i.p.) or saline (1 ml, i.p.), and then given a test dose of 50 μg/kg of LSD at 2, 6 or 24 h later (separate groups for each time point), or at 24 h only, in the case of the 2.5 μg/kg dose. Behavioral observations were taken during the 1 h period immediately following the 50 μg/kg dose of LSD.

LSD assay

In order to determine whether there is a metabolic component to the development of tolerance, LSD concentrations were measured in the brain and plasma of control and tolerant cats. Female cats were administered lysergic acid diethylamide tartrate (10 μg/kg, i.p.) or saline (1 ml, i.p.) either 2 or 24 h prior to a dose of 50 μg/kg of LSD (N = 5/group). Fifteen minutes later the cats were anesthetized with sodium pentobarbital (35 mg/kg, i.p.) and the brains were removed (30 min post LSD injection), and frozen on dry ice. Plasma samples were also obtained at the time of sacrifice. The brains and plasma were assayed for LSD within 6 h, using the method of Axelrod et al.[6]. The reported values have not been corrected for recovery of LSD, which was 90.6% ± 1.8%.

RESULTS

Duration of behavioral effects

The 50 μg/kg dose of LSD produced behavioral changes lasting for at least 8 h, while the 10 μg/kg dose produced changes lasting up to 4 h. Analyses of variance revealed significant time-related changes in limb flicking ($P < 0.01$) and abortive grooming ($P < 0.025$) following both doses of LSD. Investigatory or play behavior also showed significant time-related changes at either dose of LSD (Fig. 1).

Limb flicking was the most persistent behavior, following both doses of LSD. It still occurred at a frequency significantly above baseline 8 h after 50 μg/kg and 4 h after 10 μg/kg doses of LSD ($P < 0.05$ Dunnett's test). By contrast, the frequency of abortive grooming, investigatory and hallucinatory-like behavior returned to baseline levels within 3–4 h following either 10 or 50 μg/kg doses of LSD.

Grooming, head and body shakes, and staring also showed significant time-related changes following each dose of LSD ($P < 0.05$, Anova) (Table I).

During the first 2–3 h after LSD administration, many of the cats were continually bounding about their cages, occasionally falling off their perches, and appeared very attentive and responsive. This general arousal effect disappeared within the first 2–3 h following drug administration. The disjunctive nature of behavior following LSD administration was also no longer apparent after the first 2–3 h. In the time period from 4 to 8 h after LSD administration, the cats became relatively inactive and were resting quietly in their cages, only occasionally moving about. Even though

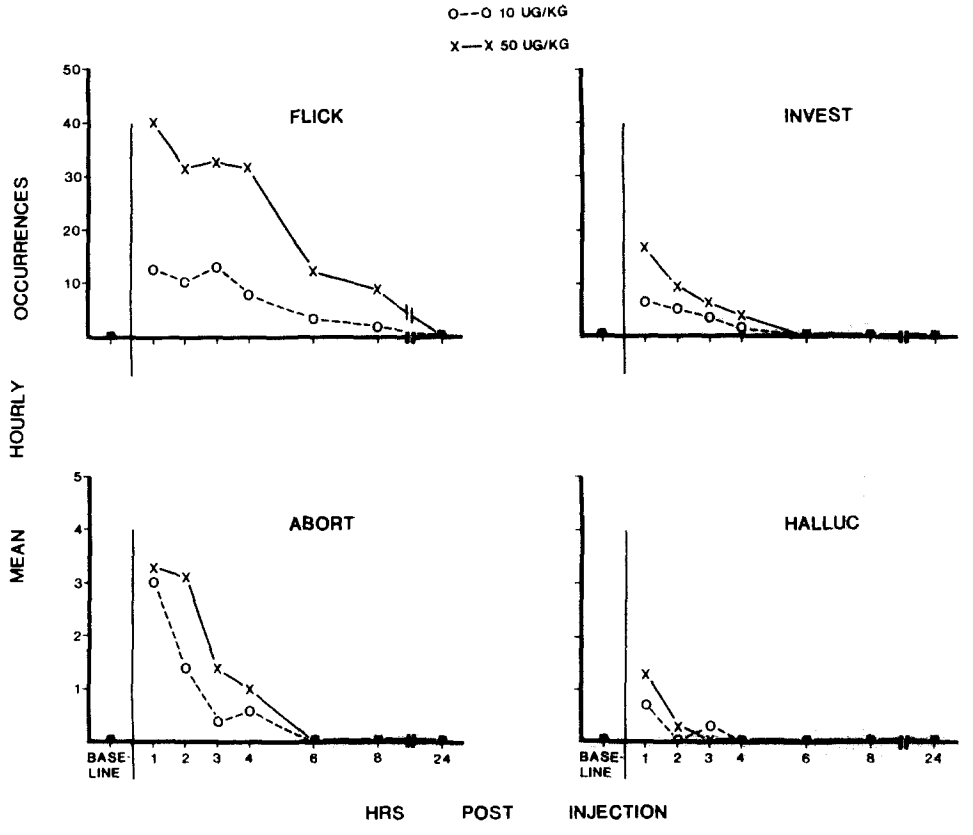

Fig. 1. Duration of the behavioral effects of LSD. Cats received a single injection of 10 or 50 μg/kg of LSD, and the frequencies of occurrence of limb flicking (Flick), abortive grooming (Abort), investigatory or play behavior (Invest) and hallucinatory-like behavior (Halluc) were recorded during hours 1, 2, 3, 4, 6, 8 and 24 post-injection. Baseline refers to saline control values. Data are means for 7 cats.

the cats were resting quietly in their cages during this period, limb flicks were still being emitted at a rate significantly above baseline levels. This argues against an arousal interpretation of the limb flicking behavior. The limb flick, therefore, appears to be the most sensitive measure, since it persists after the subsidence of all other behavioral changes produced by LSD.

Duration of tolerance

A single 50 μg/kg dose of LSD produces a long-lasting tolerance which is maximal at 1 day and persists for approximately 5 days (Fig. 2.) In the case of limb flicking, tolerance to a test dose of 50 μg/kg of LSD one day after a single dose of 50 μg/kg of LSD is virtually complete, and a substantial tolerance (80.5% below baseline) is present at 3 days post-injection ($P < 0.05$, Dunnett's test). Five days post-injection, the mean number of limb flicks is still 29.2% below baseline, but this was not a statistically significant effect ($P > 0.05$, Dunnett's test). By comparison, the tolerance to a test dose of 50 μg/kg of LSD following a single dose of 10 μg/kg of

TABLE I

*Duration of the behavioral effects of LSD**

Behavior	*Saline*	*Dose of LSD (μg/kg)*	*Hours post-injection*						
			1	*2*	*3*	*4*	*6*	*8*	*24*
Grooming	11.1 ± 4.8	10	9.1 ± 2.2	15.6 ± 3.3	18.4 ± 4.8	15.7 ± 3.7	7.6 ± 3.3	5.9 ± 1.8	3.3 ± 1.8
		50	18.0 ± 5.3	13.0 ± 5.0	22.6 ± 7.1	15.6 ± 6.2	2.9 ± 1.0	3.7 ± 1.9	6.0 ± 1.3
Shakes	6.6 ± 2.4	10	15.6 ± 4.6**	12.9 ± 3.5	9.6 ± 2.4	6.9 ± 1.8	5.6 ± 2.7	2.9 ± 1.5	1.3 ± 0.9
		50	29.3 ± 6.5	18.6 ± 5.8	21.6 ± 5.0	16.4 ± 4.8	5.4 ± 2.4	6.7 ± 3.1	4.4 ± 1.1
Stares***	2.0 ± 1.1	10	2.9 ± 1.3**	2.4 ± 1.0	2.0 ± 0.9	1.7 ± 0.6	0.0 ± 0.0	0.3 ± 0.3	0.7 ± 0.5
		50	20.3 ± 6.9	10.4 ± 3.5	7.9 ± 1.6	5.4 ± 1.6	0.4 ± 0.4	0.3 ± 0.3	2.9 ± 1.6

* Data are presented as means ± S.E.M. for 7 cats.
** Significant change from saline control ($P < 0.05$, Dunnett's test).
*** Analysis of variance revealed a significant dose × time interaction ($P < 0.01$).

TABLE II

*Duration of tolerance following a single dose of LSD**

			Inter-LSD injection interval (days)				
Behavior	*Baseline*	*Dose*	*1*	*3*	*5*	*7*	*14*
Groming	9.0 ± 3.3	10	3.9 ± 2.1	16.3 ± 3.9	16.1 ± 4.9	18.9 ± 5.8	--
		50	1.9 ± 1.5	11.3 ± 6.3	19.7 ± 9.1	17.1 ± 7.3	19.0 ± 6.1
Shakes	24.1 ± 3.7	10	4.4 ± 2.1**	18.0 ± 4.3	20.1 ± 6.1	24.1 ± 6.7	--
		50	2.9 ± 1.6	12.6 ± 4.7	15.4 ± 2.6	25.9 ± 4.6	29.3 ± 6.5
Stares	9.8 ± 2.7	10	3.3 ± 1.8	6.0 ± 1.7	7.1 ± 2.6	6.3 ± 2.7	--
		50	1.4 ± 0.9	3.3 ± 1.8	9.6 ± 4.7	12.4 ± 4.5	20.3 ± 6.9

* A single dose of either 10 or 50 μg/kg of LSD was administered, and test doses of 50 μg/kg of LSD were administered to separate groups of cats at 1, 3, 5, 7 and 14 days later.

** Significant changes from baseline control ($P < 0.05$, Dunnett's test).

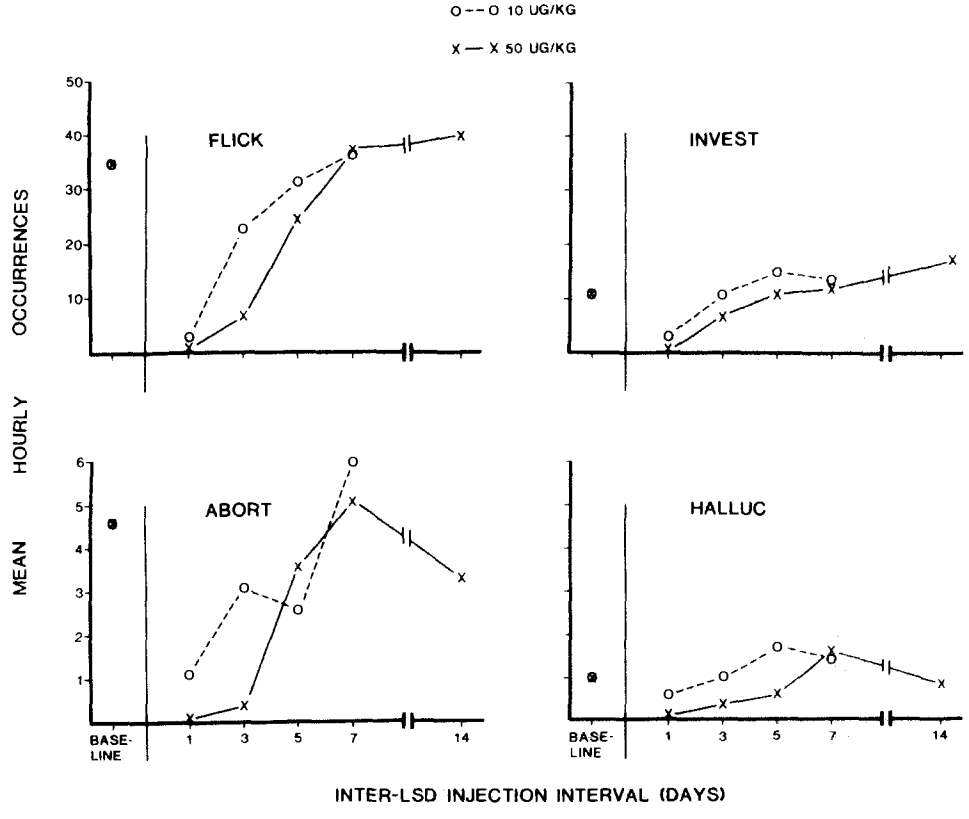

Fig. 2. Duration of tolerance to LSD. Cats received a single injection of 10 or 50 μg/kg of LSD and then a test dose of 50 μg/kg of LSD 1, 3, 5, 7 or 14 days later. The frequencies of occurrence of limb flicking (Flick), abortive grooming (Abort), investigatory or play behavior (Invest) and hallucinatory-like behavior (Halluc) were recorded during the hour immediately after the test dose. Baseline refers to the values from 50 μg/kg of LSD in an untreated cat. Data are means for 7 cats.

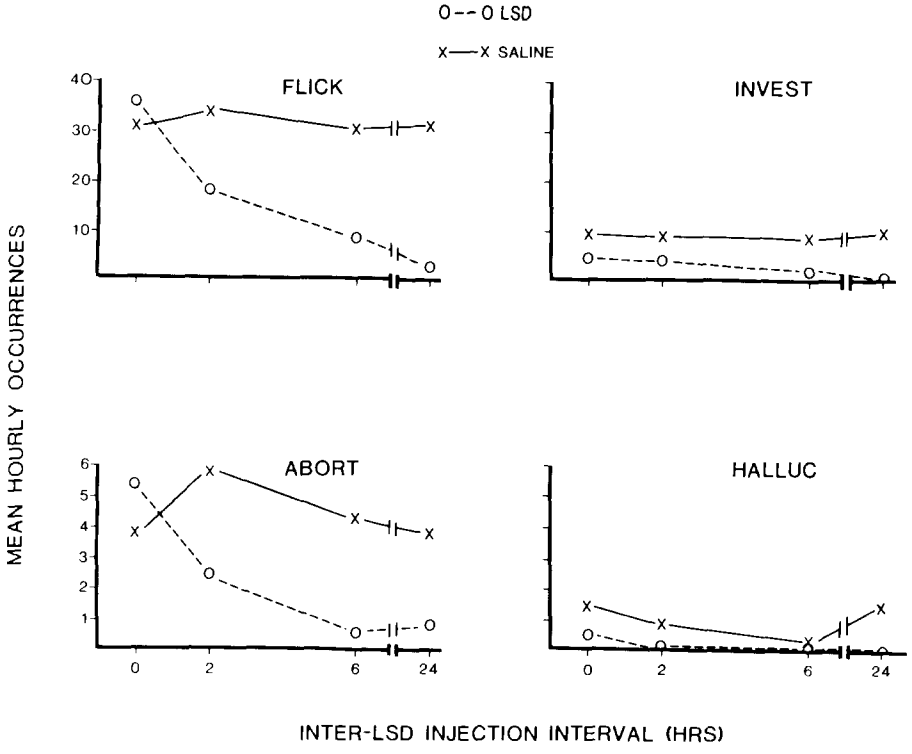

Fig. 3. Onset of tolerance to LSD. Cats received a single injection of saline or 10 μg/kg of LSD and then a test dose of 50 μg/kg of LSD 2, 6 or 24 h later. The frequencies of occurrence of limb flicking (Flick), abortive grooming (Abort), investigatory or play behavior (Invest) and hallucinatory-like behavior (Halluc) were recorded during the hour immediately after the test dose. Data are means for 7 cats.

LSD is not as pronounced or long lasting. Tolerance under these conditions is quite marked at one day post-injection (90.9% below baseline, $P < 0.05$, Dunnett's test), and although still 40.3% below baseline 3 days post-injection, this decrease was not significant ($P > 0.05$, Dunnett's test).

Abortive grooming showed a similar pattern of tolerance (Fig. 2): 50 μg/kg of LSD produced a significant tolerance at one (97.8% below baseline) and 3 days (91.2% below baseline) post-injection ($P < 0.05$, Dunnett's test), while a single dose of 10 μg/kg of LSD produced a significant tolerance only at one day (76.1% below baseline) post-injection ($P < 0.05$). In the case of hallucinatory-like behavior and investigatory behavior, large, but not significant, decreases were observed 1–3 days after doses of 10 and 50 μg/kg of LSD. Similarly, grooming and staring showed large, but not significant, tolerance one day after LSD (Table II). Head and body shaking, however, showed a significant tolerance effect on day 1 (89.9% below baseline, $P < 0.05$, Dunnett's test) following a single dose of 50 μg/kg of LSD (Table II).

While only a few of the behaviors showed a statistically significant tolerance effect, the general behavioral state of these cats was dramatically different under the tolerance condition. All 7 of the behaviors which were quantified were greatly de-

TABLE III

*Onset of tolerance to LSD**

Behavior		*Inter-LSD injection interval (h)*			
		0	*2*	*6*	*24*
Grooming	Saline	10.7 ± 3.8	12.3 ± 4.1	18.8 ± 4.9	10.7 ± 3.6
	LSD	15.8 ± 4.2	15.7 ± 4.6	10.9 ± 3.1	2.9 ± 1.4
Shakes	Saline	21.0 ± 4.7	25.7 ± 5.1	28.2 ± 4.9	21.0 ± 4.4**
	LSD	17.3 ± 4.3	7.4 ± 2.2	5.6 ± 2.0	2.5 ± 1.2
Stares***	Saline	5.0 ± 1.7	7.2 ± 2.4	3.3 ± 1.3	5.0 ± 1.6
	LSD	10.0 ± 3.3	3.6 ± 1.5	3.7 ± 1.4	1.2 ± 0.5

* Each cat received a single injection of LSD (10 μg/kg, i.p.) and then a test dose of LSD (50 μg/kg) 0, 2, 6, or 24 h later.

** Significant change from 0 h control ($P < 0.05$, Dunnett's test).

*** Analysis of variance revealed a significant dose × time interaction ($P < 0.05$).

creased one day after the initial dose of LSD, especially at the higher initial dose (50 μg/kg) (see Fig. 2 and Table II). Furthermore, many of the tolerant cats did not show the typical arousal effect elicited by LSD administration. In addition, the general disjunctive nature of behavior produced by LSD was greatly diminished in tolerant animals.

Onset of tolerance

A significant tolerance was observed as early as 2 h after administration of a single dose of LSD (Fig. 3). Limb flicking showed tolerance to a test dose of 50 μg/kg of LSD 2 h after a single dose of 10 μg/kg of LSD (50.4% below baseline, $P < 0.05$, Dunnett's test). Furthermore, cats receiving 50 μg/kg of LSD 2 h after 10 μg/kg did not show the typical arousal response seen following 50 μg/kg of LSD alone. The tolerance is much more marked at 6 h after the initial dose of LSD (77.2% below baseline, $P < 0.001$), and reaches a maximum at 24 h (93.0% below baseline, $P < 0.001$). Abortive grooming does not show a significant tolerance at 2 h post-injection, but shows a marked tolerance at 6 (90.6% below baseline) and 24 h (84.9% below baseline) after a single dose of LSD ($P < 0.025$, Dunnett's test). Investigatory and hallucinatory-

TABLE IV

*LSD concentration in brain and plasma of tolerant cats**

	Saline control	*Inter-LSD injection interval (h)*	
		2	*24*
Brain (ng/g)	29.1 ± 2.3	29.3 ± 2.0	26.2 ± 2.0
Plasma (ng/ml)	193.0 ± 4.0	197.3 ± 7.7	188.6 ± 8.6

* Cats were given a single injection of LSD (10 μg/kg, i.p.) or saline (1.0 ml) either 2 or 24 h prior to receiving a test dose of 50 μg/kg of LSD, and brain and plasma samples were obtained for assay 30 min after the last LSD injection.

like behavior showed no significant tolerance at any time point. The only other behavior to show a significant tolerance effect was head and body shakes at 24 h post-injection (85.6% below baseline, $P < 0.05$, Dunnett's test) (Table III).

When a group of cats were administered a single dose of 2.5 μg/kg of LSD and then given a test dose of 50 μg/kg of LSD 24 h later, only the limb flick displayed a significant tolerance effect. The saline control values were 32.5 ± 5.0 flicks/h, and this was decreased to 13.7 ± 4.9 flicks/h under the tolerance condition. This represents a decrease of 57.8% ($P < 0.05$, *t*-test).

LSD assay

There were no significant differences in the levels of LSD in brain following 50 μg/kg of LSD at 2 (0.7% above control) or 24 h (10.0% below control) after a single dose of 10 μg/kg of LSD (Table IV). Similarly, no significant differences in plasma LSD levels were found at 2 (2.2% above control) or 24 h (7.5% below control).

DISCUSSION

The present data demonstrate that specific behavioral changes in the cat, especially limb flicking and abortive grooming, closely parallel the actions of LSD in humans. Several studies have reported that the behavioral and perceptual effects of of 1–2 μg/kg of LSD in humans last for approximately 8 h[2,12,20,23,24]. Our data in the cat revealed that a dose of 50 μg/kg of LSD produced a significant increase in limb flicking lasting for at least 8 h. Other components of the behavioral syndrome showed significant changes lasting 4–8 h post-LSD injection. At the 10 μg/kg dose of LSD, limb flicking was significantly increased for 4–6 h post-injection, while other behavioral measures were increased for 2–4 h. Thus, limb flicking seems to be the most sensitive measure of the action of LSD in the cat, and its time course of action most closely parallels the action of LSD in humans. The limb flick is also a highly reliable index. For example, the mean number of flicks emitted by a group of 7 cats on 3 different occasions separated by 3 weeks were 34.4, 37.9 and 40.0/h (Fig. 2, upper left panel).

A dramatic, long lasting tolerance develops to the psychological and perceptual effects of LSD following its repeated administration to humans. Cholden et al.[7] reported a significant tolerance to the second dose of LSD (100 μg/day) and complete tolerance to the third dose. This tolerance had completely disappeared within 5 days after the last dose of LSD. Isbell et al.[12] reported that tolerance to LSD develops after 3–4 consecutive days of LSD administration and disappears in an equal time period following discontinuation of LSD. Abramson et al.[1] reported similar findings. Thus, there is considerable agreement that tolerance to LSD in humans requires 2–4 days to develop and lasts for 3–4 days.

In studies using rats, Freedman et al.[8] reported that a dose of 130 μg/kg LSD per day produces virtually complete tolerance in 4 days, using the disruption of bar pressing for food as the behavioral measure. They also found that some rats show a significant tolerance effect after one day, and that no tolerance is demonstrable if 130

μg/kg of LSD is given once every 3 days. In subsequent studies, Freedman and his colleagues reported that the LSD induced suppression of bar pressing in rats shows complete tolerance to 130 μg/kg/day in 5–7 days[5,9]. They also found that when 3 successive doses of LSD (130 μg/kg) were given at 1 h intervals, the last injection is less disruptive than a single dose of 130 μg/kg, but the effect was not statistically significant. From these data they concluded that partial tolerance to LSD occurs within 3 h. Winter[25] reported that complete tolerance to LSD at a somewhat lower dose (96 μg/kg/day) occurs by the third day in rats, using a similar behavioral measure to that used by Freedman and his colleagues. Thus, these reports indicate that partial tolerance to the behavioral effects of LSD in rats develops within 1 day (possibly as early as 3 h) and is complete at some time between 3 and 7 days.

Greater variability is found in the literature on tolerance to the behavioral effects of LSD in cats and monkeys. For example, Adey et al.[3] reported that a single injection of LSD (100 μg/kg) produced tolerance in cats lasting greater than 7 days, using a variety of behaviors such as head shaking as an index. Jarvik and Chorover[15] reported that tolerance to LSD using the delayed alternation test in the monkey occurs in one day after doses of 50–200 μg/kg and lasts for 1–2 weeks. On the other hand, Jonas and Downer[16] found no tolerance in the monkey even when LSD was administered at a high dose (1 mg/kg/day) for 4 consecutive days.

Much of this variability in the previous literature on the development of tolerance to LSD undoubtedly arises from the variety of behavioral indices used, as well as the different species and pretreatment regimens employed. More importantly, however, is the fact that none of the behavioral measures employed are a specific reflection of the action of hallucinogens. Since the behavioral syndrome in the cat is elicited only by LSD and related hallucinogens, these behavioral changes provide the opportunity to study the parameters of tolerance to those drug effects which are specific to these compounds. We have demonstrated in the present study that tolerance to the behavioral effects of LSD at a dose of 50 μg/kg is virtually complete within one day after a single dose of 50 μg/kg of LSD, and is very marked after a single dose of 10 μg/kg. Not only is the tolerance after the higher dose of LSD more pronounced, but longer lasting as well: the 50 μg/kg dose of LSD induced tolerance lasting for 3–5 days, while the 10 μg/kg dose produced tolerance lasting for only 1–3 days. A significant tolerance to a test dose of 50 μg/kg of LSD also occurs following a single dose of 2.5 μg/kg of LSD, which is in the human range of doses. Furthermore, the degree of tolerance at 24 h after the initial single dose of LSD is dose-related, i.e., a single dose of 10 μg/kg of LSD produces a greater tolerance than 2.5 μg/kg, and 50 μg/kg produces more tolerance than 10 μg/kg.

We also demonstrated that partial tolerance to a 50 μg/kg test dose of LSD following a single injection of 10 μg/kg of LSD develops very rapidly. Using the limb flick as a behavioral index, tolerance is significant within 2 h (50% below baseline) and is quite dramatic after 6 h (77% below baseline). As in the case of the duration of action of LSD, the limb flick proved to be the most sensitive measure of the effects of LSD in the cat, since limb flicking was the only behavior to show a significant tolerance at 2 h after the inital dose of LSD.

The rapid development of tolerance to LSD found in the present study is paralleled by the rapid development of tolerance to other drugs. For example, tolerance to the behavioral effects of barbiturates has been reported to occur within 26 h after a single injection[14]. Similarly, tolerance to the analgesic effects of morphine has been reported to occur within 24 h of a single injection[17]. Tolerance to the "running fit" produced by levorphanol occurs even more rapidly, showing a significant effect within 12 h[11]. The dramatic tolerance which occurs to LSD within 2 h may be the most rapidly developing drug tolerance reported using a behavioral index. On the basis of the present data, however, we cannot exclude interpretation of our results in terms of either tachyphylaxis or "behavioral tolerance".

Since a metabolic component has been ruled out for the tolerance to LSD, i.e., the brain and plasma levels of LSD were unchanged in tolerant cats, the tolerance is apparently attributable to a change in the central response to LSD. That is, if tolerance were due to greater peripheral metabolism of LSD, the brain levels of LSD would be decreased in tolerant cats. One possibility is that a change in receptor sensitivity occurs in the tolerant condition. A precedent has been established for the rapid change in receptor sensitivity by Axelrod and this associates who discovered that receptors in the pineal gland manifest a circadian change in sensitivity within 2 h after the transition from light to dark, and vice versa[18,21,22].

In conclusion, the present study demonstrates that the LSD-induced behavioral syndrome in the cat, especially the limb flick, parallels the duration of action and tolerance which occurs in humans, and thus greatly enhances the usefulness of the behavioral model. These data also indicate that tolerance to a *single dose* of LSD has a rapid onset (2 h) and is long lasting (5 days).

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