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Lack of Specificity of an Animal Behavior Model for Hallucinogenic Drug Action[1]

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WHITE, F. J., A. M. HOLOHEAN AND J. B. APPEL. *Lack of specificity of an animal behavior model for hallucinogenic drug action.* PHARMAC. BIOCHEM. BEHAV. **14**(3) 339–343, 1981.—It has been proposed recently that the occurrence of drug-induced limb-flicking (LF) and abortive grooming (AG) in cats can serve as a viable animal behavior model for the actions of hallucinogens in humans. If this is the case, such behaviors should occur reliably following the administration of drugs that produce hallucinations in humans and should not occur after administration of other, non-hallucinogenic drugs—a hypothesis that was examined in the present experiment. The frequency of LF and AG were observed in 12 cats which were given a wide range of doses of the potent hallucinogen, d-LSD (0.01–0.16 mg/kg), as well as several other compounds. The results showed that three non-hallucinogenic agents which are related to LSD in various ways, the ergot derivative lisuride, the serotonin agonist, quipazine, and the dopamine agonist, apomorphine, significantly increased LF frequency. Lisuride and quipazine also caused AG. Cocaine did not elicit either behavior. Thus, it was concluded that the proposed model cannot be regarded as specific to hallucinogenic drugs. In addition, the frequency of these behaviors, as well as their reliability and robustness, were shown to be partly dependent on the environment in which observation occurs.

Hallucinogens LSD Lisuride Quipazine Apomorphine Cocaine Specificity Cats
Behavior Limb-flick Abortive-groom Reliability Animal models Robustness

WHILE it has been known for some time that d-lysergic acid diethylamide (LSD) elicits many responses in cats [31], the occurrence of two previously unreported behaviors, limb-flicking (LF) and abortive grooming (AG), has recently been proposed as an animal model for studying the actions of LSD and related hallucinogens [13, 14, 15]. The LF and AG measures were said to represent a viable animal behavior model for the actions of hallucinogens in humans because they satisfied a variety of criteria including (1) specificity; the behaviors occurred only in response to hallucinogenic drugs, (2) reliability; they were consistent across time, and (3) robustness; they occurred in every animal tested [13].

Perhaps the most important criterion for establishing the validity of an animal behavior model of hallucinogenic drug action is the demonstration of specificity; that is, the changes in behavior occur *only* in response to the administration of such drugs. Thus, it has been shown that the hallucinogens LSD, N,N-dimethyltryptamine (DMT), psilocybin and mescaline increase the frequency of LF and AG, whereas compounds from other drug classes, such as d-amphetamine, caffeine, atropine and chlorpheniramine, do not [13, 14, 15]. Although these results support the specificity of the model, more stringent tests should include agents which are structurally or functionally related to hallucinogens but which do not produce hallucinations in humans. The only structurally related compounds tested thus far are tryptamine, brom-LSD (BOL), and methysergide (UML). Tryptamine did not elicit either LF or AG [13, 14, 15], whereas BOL [10,15] and UML [15] produced only minimal effects at the doses tested.

In order to test more thoroughly the question of specificity we have administered a variety of non-hallucinogenic compounds to cats and compared their efficacy in eliciting LF and AG to that of LSD. These included: (1) quipazine, a direct acting serotonin (5-HT) agonist which is similar to LSD in several behavioral tests [1, 2, 18, 37, 40, 41, 42], but reportedly is not hallucinogenic ([23], Villareal, cited in [43]); (2) apomorphine, a potent dopamine (DA) agonist [4,6] which may be viewed as similar in structure to LSD [22] and shares some behavioral properties with LSD [8, 9, 24, 33], but is not hallucinogenic [4]; and (3) lisuride, a congener of LSD which produces almost all of the biochemical [17,25] and electrophysiological changes [27,38] seen after LSD administration, but is not hallucinogenic [11, 12, 20, 29, 34]. Cocaine, a non-hallucinogenic CNS stimulant that acts via release of the catecholamines and inhibition of their re-uptake [7,21], was tested as a "positive control"; that is, a centrally active compound that is neither structurally nor functionally related to LSD.

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In order to assess the reliability of the LF-AG measures, certain doses of LSD and lisuride were re-administered and test-retest reliability measures (Pearson's product-moment correlation) were computed for each of these behaviors. While two previous studies have addressed the question of reliability [10,35], they reported only that the mean hourly LF frequency was relatively stable across repeated administrations of LSD; no measure of reliability was reported.

METHOD

Subjects

Twelve adult mongrel female cats, weighing between 2.2 and 3.9 kg were used as subjects. After being obtained from a local animal shelter (Lexington County Pound), each cat underwent an extensive, eight week evaluation and preventive treatment program (vaccines, etc.) at the University of South Carolina Central Animal Care Facility. Upon arrival at the laboratory, cats were housed individually in stainless steel cages in a separate colony room maintained at constant temperature (21–23°C), humidity (40–50%) and lighting condition (12 hr light-dark cycle). Each cage contained a wooden perch, a litter pan and two troughs, one containing Wayne cat chow and the other containing tap water. Litter trays and water troughs were cleaned daily; cages were changed and sanitized weekly. For approximately six hours a day, all cats were allowed free access to and from cages for exercise and play.

Apparatus

Cats were observed in an isolated chamber which was a 92 cm cube with wire mesh floor supported over a removable litter pan. Observations were made through a one-way mirror mounted as one wall. Two 20 W fluorescent bulbs illuminated the inside of the chamber. The chamber was ventilated by a small blower which also provided a masking noise.

Procedure

Experimentation began eight weeks after the cats were brought into the laboratory (16 weeks after they were obtained from the pound). For each experimental session, one cat received an intraperitoneal (IP) injection (0.5 ml/kg) of either isotonic saline solution (0.9% NaCl), de-ionized water (DI-H_2O) or one of the five drugs chosen for study: d-lysergic acid diethylamide tartrate (0.01, 0.02, 0.04, 0.08 and 0.16 mg/kg), lisuride hydrogen maleate (0.01, 0.02, 0.04, 0.08 and 0.16 mg/kg), quipazine maleate (0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg), apomorphine HCl (0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg), and cocaine HCl (5.0, 10.0 and 20.0 mg/kg). All doses are expressed as the weight of the salt. Apomorphine was dissolved in DI-H_2O; all other drugs were dissolved in saline. The first session for each cat was a saline session; afterwards, the treatment regimen proceeded according to a random sequence. At least six days intervened between consecutive sessions for each cat. At the end of all other testing, each cat was retested with the most active dose of LSD (0.08 mg/kg) and lisuride (0.02 mg/kg) in order to determine the test-retest reliability of the LF and AG measures.

Behavioral observations were made during the hour immediately following drug administration by raters who were "blind" to the treatment. Raters were instructed to observe the animals for one hour and to record their observations in fifteen minute segments. They were told to look especially for two behaviors: LF—lifting and rapidly snapping or flicking the paw outward from the body, and AG—orienting to the body surface as if to groom but not emitting the grooming response (i.e. biting, licking, or scratching), or emitting the response without actual body contact [13, 14, 15]. Data sheets provided space for LF and AG counts as well as general observations about the cat's behavior during each of the four 15 minute periods. Animals were returned to their home cages immediately after the session.

Statistical Procedures

Data from each drug treatment were analyzed using a randomized block (mixed effect model) analysis of variance [19]. Individual comparisons were made using Dunnett's procedure for comparing each treatment level (dose) to its control with $\alpha=0.05$ as the error rate experimentwise [5]. Test-retest reliability was evaluated by means of the Pearson product-moment correlation [3].

RESULTS

The results are presented in Table 1. Because cocaine failed to elicit either LF or AG (at the 20 mg/kg dose one cat emitted one LF and another emitted two LF), these data are not included in the table. The LF and AG responses were characterized by extreme between-subjects variability. Thus, in addition to variance estimates (SEM), the table also includes an indication of the number of cats emitting at least one response at each dosage level.

Inspection of the mean LF/hr rates for LSD and lisuride reveals a curvilinear dose-response relationship (inverted-U). Following LSD, LF reached maximum frequency at 0.08 mg/kg whereas, following lisuride, maximal LF occurred at 0.02 mg/kg; LF frequency decreased at higher doses of both drugs. The ANOVA revealed a significant effect of dose for both LSD, $F(5,55)=3.37$, $p<0.01$, and lisuride, $F(5,55)=4.40$, $p<0.005$. Both 0.04 and 0.08 mg/kg of LSD produced significant increases in LF as compared with saline controls; 0.02, 0.04 and 0.08 mg/kg of lisuride increased LF significantly (Dunnett's test).

Quipazine, $F(5,55)=5.79$, $p<0.001$, and apomorphine, $F(5,55)=3.77$, $p<0.005$, also produced significant dose effects. Both 2.0 and 4.0 mg/kg of apomorphine produced significant increases in LF; 1.0, 2.0 and 4.0 mg/kg of quipazine increased LF significantly (Dunnett's test).

Both LSD, $F(5,55)=4.83$, $p<0.001$, and lisuride, $F(5,55)=2.59$, $p<0.05$, showed a significant effect of dose on AG. However, none of the individual means for LSD were significantly higher than saline and only the 0.16 mg/kg dose of lisuride (12.6/hr) produced a significant increase in AG (Dunnett's test). Neither quipazine nor apormorphine produced a significant effect of dose on AG. Only the 4.0 mg/kg dose of quipazine produced a significant increase in AG when compared with saline; no dose of apomorphine had a significant effect (Dunnett's test).

Other interesting behaviors also occurred following various drug treatments. For example, LSD caused either of two general patterns of response; (1) the cat remained in one place (usually a corner of the chamber), sometimes shivering, and would either stare intently and engage in visual tracking or attempt to bury its head; or (2) the cat was highly active and engaged in LF, AG, grooming, staring, visual tracking, head or body shaking, investigatory behavior and "hallucinatory-play" behavior, i.e. pouncing or batting apparently at "objects" unseen by the observer. The first of these patterns resembles that reported by Schneider and Sigg

TABLE 1

EFFECTS OF VARIOUS AGENTS ON LIMB-FLICK (LF) AND ABORTIVE GROOM (AG) RESPONSES IN CATS

Drug	Dose (mg/kg)	LF*			AG*		
		Mean	SEM	#R†	Mean	SEM	#R†
Saline		0.8	0.6	2	0	0	0
LSD	0.01	9.8	4.1	8	0.9	0.9	1
	0.02	7.5	4.4	7	1.8	1.0	4
	0.04	19.0‡	6.7	7	1.9	1.1	4
	0.08	25.0‡	11.2	8	0.9	0.7	2
	0.16	7.5	4.3	4	1.2	0.7	3
Retest	0.08	13.6	7.3	7	5.0	4.6	3
Lisuride	0.01	10.3	5.2	8	4.7	3.4	4
	0.02	31.0‡	8.9	11	2.7	1.2	6
	0.04	24.0‡	9.0	10	2.7	1.3	4
	0.08	18.3‡	4.5	11	8.1	5.2	9
	0.16	7.7	2.7	9	12.6‡	5.4	8
Retest	0.02	17.6	5.9	9	3.1	2.0	5
Quipazine	0.25	0.1	0.2	1	0.2	0.2	0
	0.50	1.3	0.8	4	0.2	0.2	1
	1.00	5.3‡	2.2	6	0.2	0.2	1
	2.00	6.9‡	2.4	7	0.8	0.5	2
	4.00	7.3‡	1.7	9	3.7‡	1.1	6
DI H_2O		0.3	0.1	3	0	0	0
Apomorphine	0.25	0.2	0.2	1	0	0	0
	0.50	0.7	0.5	2	0	0	0
	1.00	0.9	0.8	2	0	0	0
	2.00	12.3‡	6.3	8	0.5	0.4	2
	4.00	10.3‡	3.9	8	2.3	1.8	5

*Data represents mean hourly LF or AG frequency ±SEM for 12 cats.
†Represents the number of cats emitting at least one response.
‡Significantly greater than control (Dunnett's test).

[30] following injections of the hallucinogenic compound ibogaine HCL while the second pattern is consistent with reports of Jacobs *et al.* [13, 14, 15] concerning LSD.

Lisuride induced a dichotomy of response similar to that of LSD and, in addition, produced some behavioral changes which were different. The cats were typically more explorative but emitted less "hallucinatory play" behavior than after LSD. They also engaged more often in a variety of behaviors which are often subsumed under the category of stereotypy, i.e., continuously sniffing, gnawing and scratching. Several instances of awkward movements, unsteady balance or gait and vibratory tail flicks were also observed.

Apomorphine, especially at higher doses, induced intense stereotypy, especially sniffing and gnawing. In addition, the cats were extremely active and often engaged in bizarre movements such as repetitively stepping forwards and backwards. A considerable amount of "hallucinatory-play" behavior and visual tracking occurred in most cats at the higher doses. There was also occasional gagging, salivation, rhinorrhea and emesis.

The typical response to quipazine was similar to the immobile response to LSD described above. The cats sat in one place (usually a corner of the chamber), while constantly staring in one direction or engaging in visual tracking. There was frequently a large amount of head shaking. Most LF and AG occurred during infrequent periods of active exploration. Gagging, salivation, rhinorrhea and emesis also occurred at higher doses. Following cocaine, the cats were almost invariably immobile, sitting mostly in one spot.

The data for the LSD and lisuride re-tests are also presented in Table 1. The correlations for the most active doses of LSD and lisuride were poor. The correlation for LF at the 0.08 mg/kg dose of LSD ($r=.46$) was not significantly different from no correlation, $t(10)=2.2$; AG reliability ($r=-.12$) was also not significant, $t(10)=-0.37$. At the 0.02 mg/kg dose of lisuride the reliability correlation for LF was lower than for LSD ($r=.15$) and also was not significantly different from no correlation, $t(10)=0.48$; reliability for AG was also very poor ($r=-.24$) and was not significant, $t(10)=-0.79$.

DISCUSSION

The results demonstrate that, whereas LF and AG may occur following hallucinogens such as LSD, these behaviors

also occur following several other agents which do not possess hallucinogenic properties in humans; lisuride, quipazine and apomorphine significantly increased the frequency of LF while lisuride and quipazine also increased AG. Although it might be argued that the relatively large doses of apomorphine (2.0–4.0 mg/kg) and quipazine (1.0–4.0 mg/kg) that were active in this experiment are not relevant to doses typically employed in humans and that, at larger doses, these drugs may be hallucinogenic, this argument does not hold for lisuride. Even at relatively large doses (0.60 mg, PO) lisuride is not typically hallucinogenic in humans [11, 12, 20, 29, 34]. Thus, drug-induced LF and AG in cats cannot be considered a *specific* model of hallucinogenic drug action; activity in the model is not necessarily associated with hallucinogenic activity in humans.

In this study, lisuride was about four times as potent as LSD in inducing LF and AG. This finding is in agreement with other reports comparing the potencies of lisuride and LSD on a variety of measures, including inhibition of the firing of 5-HT containing raphe cells, [27,38] and DA containing substantia nigra cells [38], the "serotonin syndrome" [32], circling behavior [26], drug discrimination [39] and effects on both 5-HT and DA biochemistry [17,25].

Both quipazine and apomorphine produced increases in LF similar to those reported for hallucinogenic drugs that are less potent than LSD such as psilocybin [15], psilocin [16], mescaline [16], N,N-dimethyltryptamine (DMT) [16] and 5-methoxy-N,N-dimethyltryptamine (5-MeODMT) [36]. This is not surprising since both quipazine and LSD are 5-HT agonists which share many behavioral properties [1, 2, 18, 37, 40, 41, 42]. Similarly, apomorphine has been found to be difficult to differentiate from hallucinogens with several behavioral procedures [8, 9, 33], probably because of its structural similarity to LSD [22]. Cocaine administration produced a response similar to that reported for acute d-amphetamine administration [15], i.e. a lack of activity (including LF and AG).

In terms of the test-retest reliability of the LF-AG model, the correlations for the two administrations of the most active doses of LSD and lisuride were not significant, indicating a lack of reliability. However, it is possible that intervening drug administrations between the first and second LSD and lisuride injections and continued exposure to the testing chamber may have contributed to the poor correlations. In this regard, it is interesting that both LSD and lisuride showed a decline in LF frequency from the first to the second administration.

In terms of the robustness of the LF-AG model, the present results, like those of Rusterholz *et al.* [28], indicate that a considerable amount of response variability exists between cats. This wide variation is typified by the observation that *no* LF were observed in four cats at the 0.08 mg/kg dose of LSD, while another cat emitted 127 LF at this dose. Thus, unlike the original report of Jacobs *et al.* [15], which indicated that every cat emitted at least one LF at the three most active doses of LSD, in this study several of the cats failed to emit a single LF after the most active doses of LSD; one cat never flicked following any dose of LSD. AG was even less robust since most cats seldom emitted this response. Because the major procedural differences between these studies was a different experimental environment, i.e. Jacobs *et al.* [13, 14, 15] observed cats in their home cages whereas we used an observation chamber, we administered 0.08 mg/kg LSD on two occasions (one week apart) and observed the cats in their home cages. Interestingly, both the mean LF frequency (65.4/hr) and AG frequency (9.5/hr) increased significantly over the frequencies observed for LSD in the chamber (correlated t-tests). In addition, the LF results were robust (every cat emitted at least 12 LF) and reliable [Mean_2=67.8; r=.78, $t(10)$=3.92]. Thus, the test chamber used in this study may have inhibited the responsiveness of some cats and caused greater variability and less reliability as compared to responsiveness in the home cage. These results suggest that the test environment can be an important determinant of the reliability and robustness of the LF response.

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