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Activity of a Non-Hallucinogenic Ergoline Derivative, Lisuride, in an Animal Behavior Model for Hallucinogens

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Abstract. The behavioral effects of IP administration of lisuride, a non-hallucinogenic iso-lysergic acid amide analog structurally related to *d*-lysergic acid diethylamide (LSD), were examined in 15 cats. Ten animals were given saline or 6.25, 12.5, 25, 50, or 100 µg/kg of lisuride and observed for 1 h by a rater blind to dose. There was a statistically significant effect of lisuride dose on the frequency of occurrence of the behaviors limb flicking, grooming, and abortive grooming. A time-course study with five cats at the most effective lisuride dose, 50 µg/kg, revealed that the frequencies of occurrence of these behaviors reached a maximum during the first 2 h post dose, and were comparable to frequencies after saline by 6 h post dose. An acute tolerance study with four cats scored for 90 min post dose revealed no significant tolerance to a 50 µg/kg lisuride test dose administered 6, 24, or 72 h after an initial 50 µg/kg dose. Acute cross tolerance studies with four cats scored for 90 min after an initial dose of 50 µg/kg of LSD or of lisuride, followed 24 h later by 50 µg/kg of lisuride or LSD, revealed no significant cross tolerance. The potency of lisuride relative to LSD was evaluated in six cats that were scored for 60 min following 25 and 50 µg/kg of LSD and of lisuride. On a molar basis, scores after lisuride were 51 % and 67 % those after LSD for limb flicking and grooming. These results indicate that lisuride, a non-hallucinogenic iso-lysergic acid derivative, is a false positive in the animal behavior model for hallucinogens.

Key words: Lisuride – LSD – Cats – Behavior – Hallucinogens

An animal behavior model for studying the actions of *d*-lysergic acid diethylamide (LSD) and related hallucinogens in the cat has been proposed by two of the present authors (Jacobs et al. 1976; 1977a). The model behaviors consist most conspicuously of limb flicking and abortive grooming, which occur with a near-zero hourly frequency in saline-treated cats, but with a significantly higher frequency following acute administration of the hallucinogens LSD, psilocin, N,N-dimethyltryptamine (DMT), mescaline, or 2,5-dimethoxy-4-methylamphetamine (DOM, STP) (Jacobs et al. 1977b). Specificity of the model behaviors for such hallucinogens is supported by the fact that they are not seen in response to single doses of amphetamine, atropine, caffeine, chlorpheniramine or Δ^9-tetra-hydrocannabinol (Jacobs et al. 1977a). Further contributing to the validity or utility of the model is evidence that the frequency of occurrence of the model behaviors is dose-dependent; that doses effective in the cat are similar to those effective in man; that LSD produces a rapidly-developing tolerance after acute administration to the cat, as it does in man; and that the behaviors are easy to quantify, reliable, and sensitive to dose.

The emergence of these behaviors may be related to inactivation of central serotonergic neurotransmission since, for example, hallucinogens depress the activity of serotonin (5HT)-containing raphe neurons (Aghajanian et al. 1970). Furthermore, the model behaviors are elicited by p-chlorophenylalanine (a 5HT synthesis inhibitor) (Trulson and Jacobs 1976), methysergide (a 5HT receptor blocker) (Jacobs et al. 1977a; J. L. Marini, unpublished observations), and 5,7-dihydroxytryptamine (a 5HT neurotoxin) (M. E. Trulson and B. L. Jacobs, unpublished observations).

Lisuride is a particularly suitable drug for testing the specificity and validity of the proposed model. It is a synthetic ergoline derivative structurally related to LSD (for structure see, e.g., Kehr and Speckenbach 1978) and, like LSD, low doses of lisuride reduce brain serotonin turnover (Pieri et al. 1978) and have a powerful depressant action on 5HT-containing raphe neurons; indeed, lisuride is 5–10 times as potent as LSD in depressing 5HT-neuronal activity (Rogawski and Aghajanian 1979). However, in numerous clinical trials lisuride has never been reported to produce hallucinations after acute administration (25–300 µg/man), and hallucinatory side effects have been reported rarely after chronic administration of high doses (100 to greater than 1,000 µg/man) (Somerville and Herrmann 1978; Schachter et al. 1979). Given its structural similarity to LSD, its extreme potency on the brain 5HT system, and its lack of hallucinogenicity, we decided to study its properties in the cat behavior model.

Materials and Methods

Experiments were conducted in New Haven and Princeton under comparable conditions. Animals, housed in an air-conditioned room with a 12 h (7 a.m. to 7 p.m.) light-dark cycle, had free access to water and Purina Cat Chow, were observed in their home cages, and lived in their cages for at least six weeks before receiving drugs. Cages contained a wooden perch, litter pan, and food and water dishes. Saline and drug studies were conducted at the same time of day for each cat, and animals were studied only when in good health. At least six days elapsed between

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experiments, except for tolerance studies, and for consecutive dose-response trials with six animals at 6.25 and 12.5 µg/kg lisuride, which were separated by 72 h.

Experiments in the New Haven laboratory employed ten cats (five males, 4.1–6.0 kg; five females, 2.9–4.1 kg), and included the dose-response study ($N = 10$), LSD response at 25 and 50 µg/kg ($N = 6$), and the LSD-lisuride cross tolerance experiment ($N = 4$). Experiments in the Princeton laboratory employed five cats (females, 2.0–3.8 kg) and included duration of lisuride action ($N = 5$), all lisuride tolerance studies ($N = 4$), the lisuride-LSD cross tolerance experiment ($N = 4$), and the activity of orally-administered lisuride ($N = 3$).

Animals were scored for the behaviors limb flicking, grooming, abortive grooming, head plus body shaking, staring, investigate-playing, and yawning, using criteria described previously (Jacobs et al. 1976; 1977a). Scoring was for 60 min post drug for dose-response studies, 90 min post drug for tolerance, cross tolerance and oral dose studies, and as described below (Results) for duration-of-action observations. The dose-response study was scored blind to dose; other experiments were scored with a knowledge of drug and dose.

Except for three oral doses, all experiments used IP injection of 1 ml/kg of physiological saline, or of LSD (as bitartrate, Sandoz, Basle or NIDA, Rockville) or lisuride (as hydrogen maleate, Schering AG, Berlin) in saline. For oral doses, lisuride was dissolved in saline and administered in a small amount of moistened cat food at a dose of 100 µg/kg. Solutions of drugs were prepared fresh daily and were protected from light. Doses are reported in µg of salt per kg of body weight. Lisuride hydrogen maleate (MW 455) contains 1 mol of free base (MW 339) per mole of salt, or 74.5% of free base by weight; LSD bitartrate (MW 861) contains 2 mol of free base (MW 323) per mole of salt, or 75.0% of free base by weight. Hence, equal weights of the salts correspond to nearly equal weights of the free bases, or to 6.4% more LSD than lisuride on a molar basis.

Statistical analysis employed one-way analysis of variance (ANOVA) for repeated measures for each behavior, followed by related measure *t*-tests for differences between control and experimental conditions, as in an earlier study (Jacobs et al. 1977a).

Results

During lisuride dose-response trials, cats showed pupillary dilation and were invariably awake and alert, with arousal and onset of other drug-related behaviors apparent by 10–20 min post-drug. In general, the animals tolerated doses of 6.25–100 µg/kg of lisuride well, with no vomiting or diarrhea, although they typically defected during lisuride, but not saline, sessions. After lisuride, many cats showed bilateral ear twitching, as well as foot shuffling or tapping, in which body weight was shifted from one forelimb to the other, or one forepaw was tapped on the floor several times in succession. Gagging, retching, salivation or rhinorrhea were occasionally observed. Acute motor dysfunction (collapse with brief inability to sit or stand) was seen in a few cases, generally at the higher doses; more common were one or two occurrences per session of impaired balance or unsteady gait, again usually at the higher doses. Throughout these studies the cats showed no signs of drug-related illness, and their weights were stable (± 0.1 kg).

Figure 1 gives the results of the dose-response study with ten cats on the behaviors for which a statistically significant dose effect was found by ANOVA: Limb flicking ($F_{5,40} = 2.98$, $P < 0.025$); grooming ($F_{5,45} = 2.50$, $P < 0.05$); abortive grooming ($F_{5,45} = 6.67$, $P < 0.01$). The ANOVA result for limb flicking is based on data from nine animals. One cat (a female, whose limb flick scores increased from 15 per hour at 6.25 µg/kg to 66 per hour at 50 µg/kg) accounted for 80% of the variance in the limb flick data and was omitted from the ANOVA for this behavior; when its data were included, the dose effect did not achieve statistical significance at the 0.05 level. Relative to saline control, limb flicking and abortive grooming were significantly increased at all doses except 6.25 µg/kg; grooming was increased only at 25 and 50 µg/kg (see Fig. 1). After saline, mean ± SE scores for the other behaviors were: shakes ($N = 10$) 5.2 ± 1.1; stares ($N = 8$) 0; investigate-play ($N = 8$) 2.3 ± 1.3; yawns ($N = 8$) 0.45 ± 0.21. None was significantly increased relative to saline by any dose of lisuride. As observed after LSD (Jacobs et al. 1977a) there was a large inter-animal variation in behavior frequencies following lisuride. Comparing scores for the five females and five males used in the dose-response study revealed no sex difference in any behavior (data not shown).

The scores illustrated in Fig. 1 were converted to percent of maximum response by subtracting the average saline score, and dividing by the score at 50 µg/kg. Expressed in this way, limb flicking and grooming show half-maximal response at about 12.5 µg/kg (27 nmol/kg in terms of free base), and abortive grooming shows a half-maximal response near 25 µg/kg (55 nmol/kg).

Figure 2 gives the results of duration-of-action studies for limb flicking, grooming, and abortive grooming after 50 µg/kg of lisuride. Observations were made for the first 60 min post dose, and for subsequent 45-min epochs correspond-

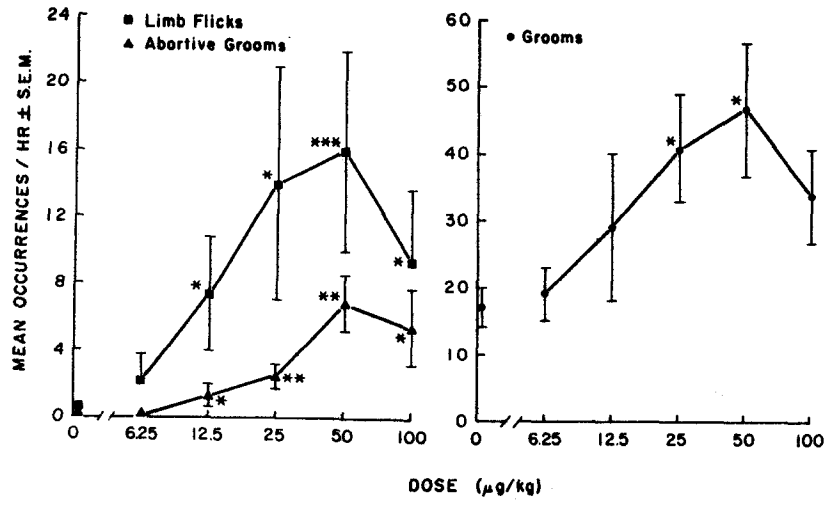

Fig. 1
Mean hourly frequencies ± SE of selected behaviors for ten cats administered saline or lisuride hydrogen maleate. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$

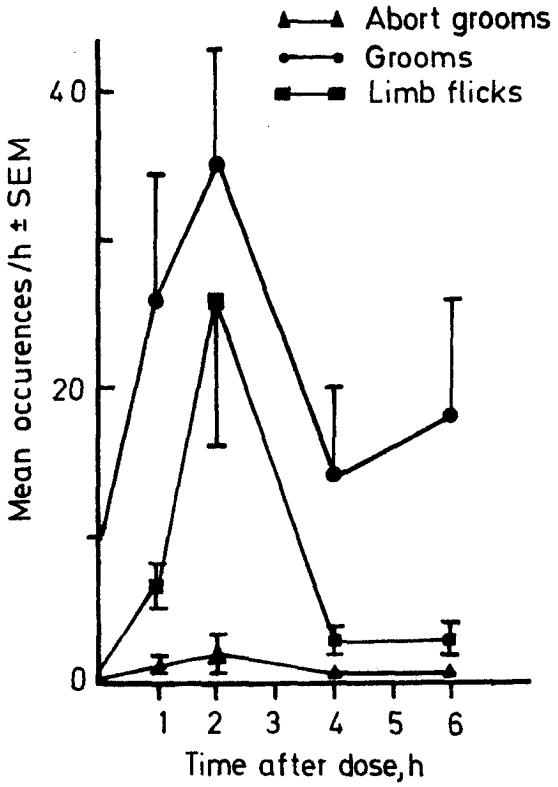

Fig. 2. Mean hourly frequencies ± SE of selected behaviors for five cats as a function of time after a dose of 50 µg/kg of lisuride hydrogen maleate

ing to 75–120, 195–240, and 315–360 min post dose, although the data in Fig. 2 are all on an hourly basis. Only limb flicking showed a significant change of frequency with time after dose ($F_{3,12} = 7.65$, $P < 0.01$). The behavior frequencies peak 60–120 min post lisuride and return to saline frequencies by 6 h, making possible unambiguous interpretation of tolerance and cross tolerance data for times 6 h or more after initial drug administration. Note that in general these results are comparable to those reported after 10 µg/kg of LSD (Trulson and Jacobs 1977).

Table 1 gives the results of acute lisuride tolerance trials using doses of 50 µg/kg. There was no statistically significant reduction in scores for a test dose given 6, 24, or 72 h after the initial dose. Although the large variance in these data precludes identification of a weak tolerance effect, analogous experiments in the same laboratory using LSD have invariably resulted in nearly complete tolerance at 24 h (e.g., Trulson and Jacobs 1977). Dose-response trials were repeated after 8–14 drug-free days for four of the six cats that had received low lisuride doses 72 h apart (see Materials and Methods), and there was no evidence of tolerance: Original data: Limb flicks, 2.3 ± 1.7; grooms, 44 ± 30; abortive grooms, 2.5 ± 1.2. Repeat trial: Limb flicks, 4.5 ± 4.1; grooms, 12 ± 9.1; abortive grooms, 0.8 ± 0.6. The high mean grooms score and large variance in the original data were primarily due to one animal with a score of 117 grooms per hour.

Table 1 also presents scores for lisuride-LSD and LSD-lisuride cross tolerance trials 24 h after an initial dose. There was no statistically significant cross tolerance in either study, but 24 h after lisuride, the LSD limb flick score was reduced

Table 1. Results of lisuride tolerance, lisuride-LSD, and LSD-lisuride cross tolerance experiments

Experiment	Mean occurrences ± SE per 90 min, $N = 4$		
	Limb flick	Groom	Abortive groom
Lisuride tolerance, 6 h			
First dose	14 ± 2.9	40 ± 20	7.0 ± 5.9
Second dose	15 ± 4.1	43 ± 21	11 ± 7.8
Lisuride tolerance, 24 h			
First dose	21 ± 8.0	38 ± 16	3.0 ± 1.8
Second dose	24 ± 9.7	57 ± 20	8.0 ± 2.5
Lisuride tolerance, 72 h			
First dose	28 ± 14	65 ± 35	3.5 ± 2.6
Second dose	26 ± 8.5	49 ± 25	4.8 ± 1.7
Cross tolerance studies, 24 h			
LSD after lisuride	33 ± 9.4	28 ± 24	2.8 ± 0.99
LSD reference	47 ± 14	7.8 ± 5.7	0.75 ± 0.55
Lisuride after LSD	37 ± 20	44 ± 21	2.5 ± 1.4
Lisuride reference	56 ± 28	93 ± 38	6.3 ± 2.4

All experiments used 50 µg/kg of LSD bitartrate or lisuride hydrogen maleate

by 30%, and 24 h after LSD, lisuride scores were reduced by 30, 50, and 60% for limb flicking, abortive grooming, and grooming, respectively, relative to reference scores for the same cats.

Table 2 gives scores for selected behaviors for six cats that received 25 and 50 µg/kg doses of both lisuride and LSD. The behaviors appeared the same whether elicited by lisuride or LSD. At one or both doses, lisuride was significantly more active than saline for abortive grooming or grooming, and LSD for grooming, limb flicking, and shakes. Lack of statistically significant differences relative to saline for behaviors like limb flicking after lisuride probably are due to the large variance in the data.

From these data, lisuride's potency can be compared to LSD's across both doses for limb flicking, grooming, and shakes. On a molar basis, raw scores for lisuride correspond to 52% of LSD's on limb flicking and shakes, and 85% on grooming. Correcting the respective raw scores for activity after saline results in lisuride scores 51, 17, and 67% of those of LSD.

Oral administration of 100 µg/kg of lisuride to three cats elicited mean scores of 20 ± 12 limb flicks, 1.7 ± 1.5 abortive grooms, 46 ± 18 grooms, and 52 ± 13 shakes during the 90 min following ingestion.

Discussion

The results show that lisuride is highly active in the cat behavior model. It produces dose-dependent, statistically significant increases in the frequencies of the principal model behaviors, with an effective dose range for limb flicking and grooming of at least 6–50 µg/kg (13–110 nmol free base/kg). Lisuride gives behavior frequency maxima at 25–50 µg/kg, with non-significantly lower scores at 100 µg/kg. At 25–50 µg/kg, its potency is 50–70% that of LSD's for limb flicking and grooming. In these respects lisuride is qualita-

Table 2
Comparison of selected behavior scores at 25 and 50 μg/kg LSD bitartrate and lisuride hydrogen maleate

Dose, μg/kg	Mean occurrences ± SE per 60 min, $N = 6$			
	Limb flicks	Grooms	Abortive grooms	Shakes
Saline	0.83 ± 0.64	21 ± 3.6	0.08 ± 0.09	5.6 ± 1.6
Lisuride, 25	18 ± 11	46 ± 12	3.0 ± 0.80*	7.8 ± 2.7
LSD, 25	37 ± 8.4**	62 ± 18**	11 ± 8.7	16 ± 4.8
Lisuride, 50	22 ± 9.8^{++}	62 ± 13**	6.5 ± 2.5***	8.5 ± 2.5^{+}
LSD, 50	43 ± 11***$^{++}$	71 ± 30	5.3 ± 2.2	17 ± 3.0***$^{+}$

* $P < 0.02$ vs saline. ** $P < 0.01$ vs saline. *** $P < 0.05$ vs saline
$^{+}$ $P < 0.05$ lisuride vs LSD. $^{++}$ $P < 0.02$, lisuride vs LSD

tively and quantitatively similar to LSD (Jacobs et al. 1976; 1977a, b), and is far more potent on a molar basis than the hallucinogens psilocin, DMT, and mescaline (Jacobs et al. 1977b). With respect to the cat behavior model, LSD and lisuride differ in that LSD produces a rapidly-developing tolerance (by at least 6 h post dose) which results in almost complete absence of model behaviors by 24 h post dose (Trulson and Jacobs 1977). In man, LSD is a powerful hallucinogen, while lisuride appears to be non-hallucinogenic (see Introduction).

The discrepancy between lisuride's activity in the model and its lack of hallucinogenicity in man is not an artifact of different routes of administration in the laboratory (IP) and clinic (PO). Thus, we found that orally-administered lisuride was very active in cats, and Schachter (M. Schachter, unpublished observations) found that IV doses of 5 – 15 μg of lisuride per person produced drowsiness or sleep, but no hallucinations, in a sample of 15 Parkinson's disease patients. Therefore, lisuride is a false positive in the model.

These results challenge the validity of the cat behavior model, both by showing that high behavior scores do not correspond to high hallucinogenic potency, and by demonstrating that hallucinogenicity in man is not a necessary condition for activity in the model, or equivalently, that activity in the model is not a sufficient condition for hallucinogenicity in man. Furthermore, the high potency of lisuride, which possesses the iso-lysergic acid stereochemical configuration, proves that elicitation of a high frequency of model behaviors by ergolines does not require the lysergic acid stereochemistry. Since the latter appears obligatory for characteristic hallucinogen-induced psychological effects in man (Cohen 1967), several important model behaviors, including limb flicking, do not have the stereochemical specificity for ergolines required of a rigorous animal model for LSD-like hallucinogens.

The properties of lisuride in the cat model should make it useful in studies of the pharmacology of grooming behaviors, as well as in studies of the mechanism of tolerance elicited by LSD. For example, the absence of such tolerance to lisuride proves that drug-induced production of a high frequency of model behaviors is not in itself sufficient to produce the degree of tolerance observed after LSD. However, the fact that lisuride is a false positive in the cat behavior model shows that inferences about the mechanism of action of hallucinogens based upon experiments with the model must be made with caution, as must predictions about hallucinogenicity of drugs in man based upon their activity in the model.

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