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Patterns of Exploration in Rats Distinguish Lisuride from Lysergic Acid Diethylamide

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ADAMS, L. M. AND GEYER, M. A. *Patterns of exploration in rats distinguish lisuride from lysergic acid diethylamide.* PHARMACOL BIOCHEM BEHAV **23**(3) 461–468, 1985.—In order to further validate a previously proposed animal model of the effects of LSD in humans, doses of 5, 15, 30 and 60 μg/kg lisuride (a non-hallucinogenic congener of LSD) were studied using a behavioral pattern monitor (BPM). The BPM provided both quantitative measures of crossovers, rearings, and holepokes and qualitative measures of spatial patterns of locomotion. A holeboard chamber connected to a homecage provided two test situations. Rats were tested either with (free exploration) or without access to the homecage (forced exploration). In both situations, lisuride exhibited a biphasic dose-response curve for horizontal locomotion (low dose suppression and high dose enhancement), while rearing was significantly reduced at all doses. Lisuride also produced a dose-dependent increase in the perseverative quality of locomotor patterns. A comparison of these results with our previous studies with lysergic acid diethalmide (LSD) indicate that, with the exception of rearings, lisuride fails to mimic LSD's characteristic effects on exploratory activity. Rather, lisuride exhibited many similarities to the dopamine angonist apomorphine.

Lisuride LSD Apomorphine Exploration Neophobia Hallucinogens Animal model

LISURIDE hydrogen maleate is an isolysergic acid derivative which has been used clinically in the treatment of migraine because of its peripheral serotonin (5-HT) antagonistic actions [11] and, more recently, in Parkinson's patients and hyperprolactinemics for its dopamine (DA) agonist actions [9]. Lisuride differs from LSD only in the substitution of an amino function in an 8 S position (c.f. [11,21]). Despite its close structural similarity fo LSD, lisuride does not appear to produce the perceptual alterations in man seen with LSD [11].

We recently proposed [3] an animal model of acute hallucinogenic activity, based on LSD's effects on rat exploratory activity [1,3] in which the animal behavior was suggested to be analogous to a characteristic acute effect of hallucinogens in humans; namely, an enhanced responsiveness to the environmental setting, particularly those aspects of the environment that are perceived as being aversive [5, 19, 25]. Briefly, the major effect of LSD in rats was a suppression of exploration of novel (neophobia) and open (agoraphobia) areas which was not attributable to a sedative-like reduction in the rate of locomotor or investigatory responses. This effect was dose-dependent within a moderate dose-range (20–160 μg/kg) and exhibited tolerance to the same extent and rate as reported for LSD's effects in humans [3]. More recent studies [2] revealed that both the indoleamine hallucinogen, N, N-dimethyltryptamine (DMT), and the phenylethylamine hallucinogen, 2,5-dimethoxy-4-methylamphetamine (DOM), also potentiate unconditioned avoidance of novel and central areas by rats.

The present studies were designed to further test the pharmacological specificity of the proposed model behavior by characterizing the effects of a non-hallucinogenic congener of LSD in the same behavioral paradigms. Lisuride appeared to be the ideal compound for this comparison because it is so similar to LSD in terms of structure and neurochemical effects and because it has been demonstrated to be centrally active in humans at doses comparable to LSD [15]. This last factor is of particular importance since many congeners of LSD lack hallucinogenic activity simply because they do not pass the blood-brain barrier (e.g., bufotenin) or have low biological activity (e.g., 2-Bromo-LSD).

METHOD

Animals

Male Sprague-Dawley rats weighing 275–300 g (Charles River Lab.) were used. In order to conduct behavioral testing during the active phase of these nocturnal animals, the housing facility was kept on a reversed 12/12 hour light/dark cycle (lights off from 10 a.m. to 10 p.m.). Testing was conducted between 11:30 a.m. and 4 p.m. For the forced exploration test, animals were housed in pairs. For the free exploration test, rats were individually housed in metabolic cages identical to those used for "homecages." Animals were

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allowed a 5 day period for acclimation to the animal room then handled every other day (between 1 and 4 p.m.) for a week prior to testing.

Drugs

Lisuride hydrogen maleate (Schering, Berlin) was prepared fresh daily, in nitrogen-bubbled isotonic saline, 30 min prior to the first test session. Following dilution, the drug was kept in refrigerated syringes until 15 min prior to injection. Drugs were administered subcutaneously (1.0 ml/kg).

Apparatus

The behavioral pattern monitor (BPM) chambers have been described in detail elsewhere [1, 3, 6]. Each of the four chambers consisted of a 30.5×61 cm black plastic box with walls 38 cm high, a stainless steel floor and touchplate (15 cm above the floor) that detected wall rearings. The chamber ("holeboard") had three floor holes and seven wall holes. Holepokes were detected by an infrared photobeam in each of the 10 holes. A "homecage" was connected to the chamber by a sliding door and was enclosed in its own anteroom. A 4×8 perpendicular array of photobeams for the holeboard chamber and 2×2 array for the homecage served to localize the animal's position with 3.8 cm resolution (c.f. [1]). The presence of the animal in the doorway was detected by an additional photobeam ("entry-beam"). Each assembly was enclosed in a ventilated wooden box. A microprocessor system checked the status of the beams and circuits in each chamber every 100 msec.

Procedure

Forced exploration test. Sixty experimentally naive rats were used. For an experimental session, four animals were brought to the test room under blackout curtains 1 hr before test start. The door between the homecage and holeboard chamber was sealed shut. Each animal was administered saline, 5, 15, 30 or 60 μg/kg (free base dose) lisuride and returned to holding cages for a 10 min wait. The rats were then placed in the right front corner of the holeboard chamber, and the chamber lid was immediately closed. Following a 60 min period of data collection, the animals were removed and the boxes thoroughly cleaned.

Free exploration test. Thirty-six experimentally naive rats were randomly assigned to one of three groups to be tested following administration of saline; 5, 15, 30, or 60 μg/kg (free base dose) lisuride. Test procedures were identical to those described above except that the rats were injected and immediately placed in the homecage. Following a 10 min acclimation period, the sliding door was opened remotely and the computer was then signalled to start data collection from that chamber. Three additional rats were treated with 90 μg/kg lisuride to more thoroughly characterize patterns of locomotion in the free exploration test.

Visual observations. Additional animals given saline (n=3), 15 (n=4), or 60 (n=4) μg/kg lisuride were used for visual observations. The forced exploration procedure was followed with the exception that a 15 watt red light illuminated the holeboard chamber. Animals were observed through fish-eye viewing lenses mounted in the lids of the enclosure. Events were recorded for a 2 min period every 6 min. Another 15 animals were treated with saline, 15, 30, 60 and 120 μg/kg lisuride (n=3 per group) and their core temperature monitored with a YSI Tele-thermometer and rectal probe just prior to injection and at 20 min intervals thereafter. Room temperature was maintained at the same level used for behavioral testing (20.5±1°C).

Data Analysis

Data collection. The data analysis procedures have been described in detail elsewhere [1, 3, 6]. The raw data were translated into frequencies and durations of events cumulated over 10-min blocks. X-Y position was calculated and used to define an animal's position in 1 of 8 equally sized sectors and one of 9 unequally sized regions (c.f. [1]).

Activity measures. The two types of locomotor activity measures derived from these data were: photobeam breaks (the total number of X-Y beam breaks) and crossovers (the total number of sector entries). For holepokes and rearings, a distinction was made between repeated and varied events. A repeated holepoke is the second of two consecutive holepokes into the same hole, which has not been preceded by an interposed crossover, a rear, or a holepoke into a different hole. All others are varied holepokes. Repeated rearings have a similar definition. The mean duration per response (MDPR) was calculated by dividing the cumulated response duration over the entire session by the corresponding number of events.

Regional Analysis. For the free exploration test, the nine regions were collapsed into front, middle, and rear thirds of the chamber (with respect to the homecage). The centermost region was also analysed separately. For the forced exploration test, the regions were pooled into center, corner, and wall regions (c.f. [6]). The nine regions were also used to define three basic types of "traverses" (crossings from one end of the holeboard to the other) along a "short wall," "long wall," or through the "center." Additionally, "half long-wall" and "half center" traverses (reversal of direction prior to completion of a traverse) were cumulated separately. Thus, the ratio of half to full long-wall traverses indicates the degree of perseveration since a high ratio indicates that the animal frequently initiates a new directional change prior to completion of an old one. Conversely a low ratio indicates a high degree of perseveration. The same distinctions can be made for center traverses.

Free exploration measures. The amount of time spent in and number of wholebody entries into the holeboard were cumulated over 10-min blocks. The latency of the first whole-body entry into the holeboard (entrytime) was also recorded. To correct for individual differences in time spent in the holeboard chamber, rate measures were computed for each subject by dividing the number of responses per hour session by the time spent in the holeboard. Additionally, the ratio of repeated to varied entry-beam breaks (those followed by a whole-body entry into the holeboard or a retreat to the rear of the homecage) provided a measure of the proportion of entry-beam breaks due to partial entries (vacillation in the entry-way). Such measures have been shown to reflect the degree of "conflict" behavior resulting from the competing tendency to approach or avoid a novel environment [20].

Pattern analysis. X-Y position data were used to produce video displays of the animal's X-Y position changes, rearings, and holepokes, which could be viewed from 20 to 1 times real-time speed with relative temporal relationships preserved. The same data files were also used to produce hard copy plots on a Zeta plotter.

Statistical analyses. Repeated-measures and mixed-

TABLE 1

COMPARISON OF LISURIDE'S EFFECTS IN THE FORCED AND FREE EXPLORATION TESTS

	Forced Exploration						Free Exploration			
	Dose (μg/kg)						Dose (μg/kg)			
	0	5	15	30	60	F-Ratio (*df* 4,45)	0	15	60	F-Ratio (*df* 2,32)
Crossovers	1998 ±203	1050* ±125	947* ±83	1651 ±223	2672* ±329	12.62	50.72 ±2.79	23.10* ±2.99	43.97 ±5.80	15.64
Rearings	152 ±16	67† ±7	33† ±6	25† ±4	33† ±7	38.13	3.70 ±0.23	0.88* ±0.15	1.00* ±0.33	57.50
Holepokes	204 ±30	92† ±16	73† ±8	84† ±15	119‡ ±12	9.50	4.59 ±0.63	1.28* ±0.17	1.35* ±0.24	20.53
Var/Rep§ Holepokes	1.12 ±0.17	1.22 ±0.15	1.15 ±0.22	2.17* ±0.22	2.63* ±0.16	4.17	1.48 ±0.15	2.30 ±0.42	4.64† ±0.64	17.37
n =	10	10	10	10	10		14	11	10	

Values shown are group means ± S.E. for 60 min totals (forced exploration), and total counts per total time in holeboard (counts per min) (free exploration). F-ratios for effect of treatment from mixed design ANOVAs ($p<0.001$ for all measures).

*Significantly different from control ($p<0.05$) by Duncan's test.

†Significantly different from control ($p<0.01$) by Duncan's test.

‡Significantly less ($p<0.01$) than control and significantly greater ($p<0.05$) than 15 μg/kg group (Duncan's).

§Ratio of varied to repeated holepoke frequency.

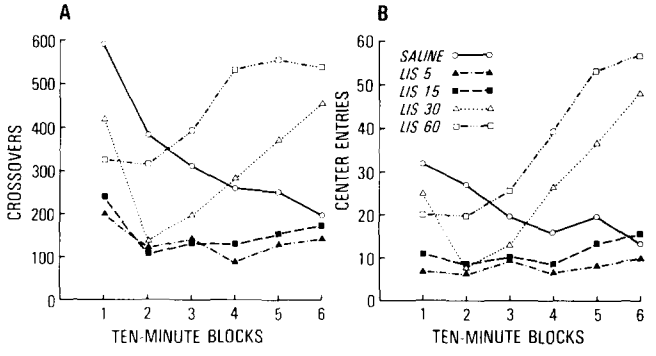

FIG. 1. Dose-dependency of lisuride's effect on the temporal distribution of (A) crossovers and (B) center entries in the forced exploration test. Points shown are group 10-min totals of rats treated with saline of 5, 15, 30, or 60 μg/kg lisuride.

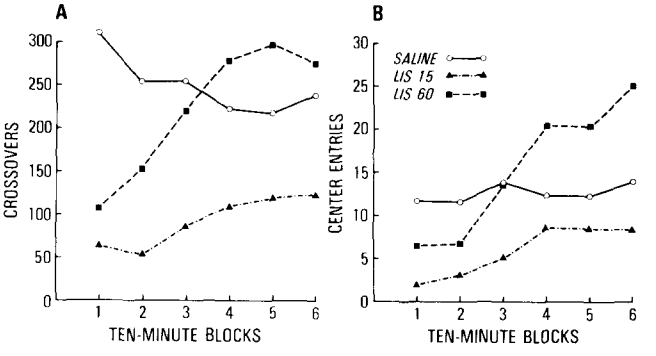

FIG. 2. Effect of lisuride on the temporal distribution of (A) crossovers and (B) center entries in the free exploration test. Points shown are group means for 10-min blocks of rats treated with saline, 15, or 60 μg/kg lisuride.

design analyses of variance (ANOVA) were performed for selected variables. Specific comparisons between groups were made using the Duncan's Multiple Range Test while the F-test was used for within group comparisons [14].

RESULTS

Locomotion

In the forced exploration test, lisuride had a biphasic effect on crossover activity, reducing activity at doses of 5 and 15 μg/kg and increasing activity at 60 μg/kg (Table 1). As seen in Fig. 1A, lisuride's enhancement of locomotor activity occurred only in the latter half of the hour session (resulting in a significant treatment-by-trials interaction, $F(20,225) = 12.12$, $p<0.001$), with both the 30 and 60 μg/kg groups being lower than controls in the first 10–20 min of the session and higher in the last 20–30 ($p<0.05$, F-test). The late increase in locomotion seen in the 30 and 60 μg/kg groups was due specifically to an increase in entries into the center region (Fig. 1B), resulting in a significant treatment-by-trials interaction, $F(20,225)=9.37$, $p<0.001$, for center entries. Since the 5 and 15 μg/kg groups exhibited the same low level of activity as the 30 μg/kg group from 10–30 min, but only the 30 μg/kg group exhibited hyperactivity from 30–60 min, this hyperactivity appears to reflect a temporally biphasic drug effect or impairment of habituation rather than a rebound increase in exploratory activity due to a lack of stimulus satiation.

When rats were tested using the free exploration procedure, 60 μg/kg lisuride still produced a biphasic temporal effect on crossovers (Fig. 2A, $F(10,160)=5.12$, $p<0.001$) and center entries (Fig. 2B, $F(10,160)=2.79$, $p<0.01$), while 15 μg/kg lisuride reduced the number of crossovers and center entries throughout the session. As shown in Fig. 3, rats

TABLE 2
LISURIDE DOSE-RESPONSE: FORCED EXPLORATION

Activity Measure	Dose (μg/kg) 0	5	15	30	60	F-Ratio	$p<$
Mean Duration	20.2	14.9	14.5	10.5†	12.6†	2.65	0.05
Repeated Rearings	±3.1	±1.9	±2.3	±1.9	±2.5		
Half/Full‡	2.14	1.88	1.73	1.07*	0.48*	6.34	0.001
Long-wall Traverse	±0.33	±0.25	±0.42	±0.17	±0.14		
Half/Full‡	1.58	1.35	0.99*	0.88*	0.48†	6.33	0.001
Center Traverse	±0.28	±0.20	±0.11	±0.14	±0.05		

Values are group means ± S.E. (n=10 per group) for transforms on 60 min totals. F-ratios for effect of treatment (*df* 4,45) and corresponding *p* values from a one-way ANOVA.
*Significantly different from control ($p<0.05$) by Duncan's test.
†Significantly different from control ($p<0.01$) by Duncan's test.
‡These measures are inversely proportional to the degree of perseveration of peripheral (long-wall) and central locomotion.

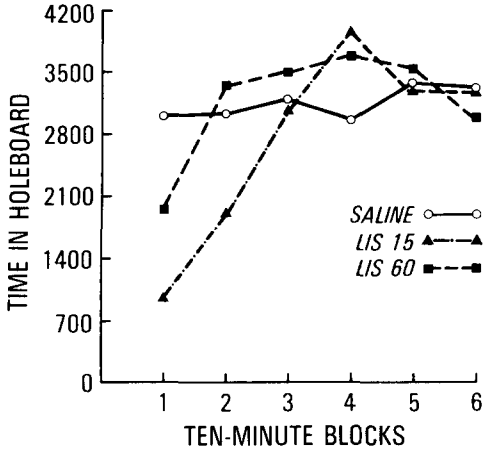

FIG. 3. Effect of doses of 15 and 60 μg/kg lisuride on time spent in the holeboard (tenths of sec) in the free exploration test. Points shown are group means per 10-min block.

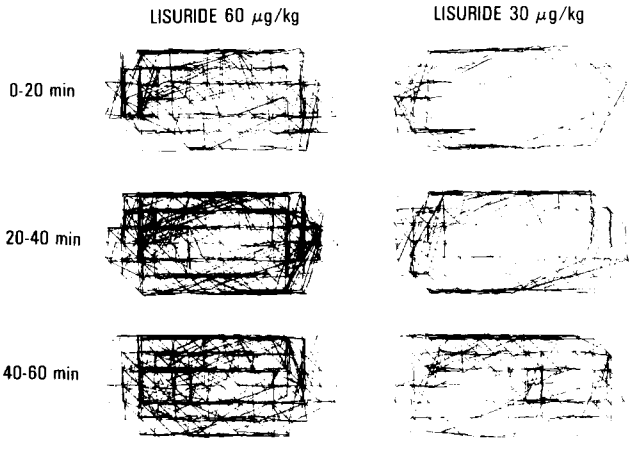

FIG. 4. Computer generated plots of sequential changes in X-Y position over 20-min intervals summarize the locomotor patterns of rats treated with 60 and 30 μg/kg lisuride in the forced exploration test.

treated with lisuride spent less time in the holeboard in the beginning of the session resulting in a significant treatment-by-trials interaction, $F(10,160)=3.64$, $p<0.001$. However, specific comparisons revealed that while the 15 μg/kg group spent less time in the holeboard in the first 20 min of the session ($p<0.01$, F-test), the 60 μg/kg group did not differ from control. As shown in Table 1, even after correcting for individual differences in time spent in the holeboard, the 15 μg/kg group exhibited a reduced rate of crossover activity relative to both controls and the 60 μg/kg group.

In contrast to the biphasic dose-response curve for horizontal locomotion, all doses of lisuride tested produced a large reduction of rearing activity in the forced exploration test (Table 1). This reduction in rearings was fairly consistent across time, though most marked in the first 20 min of the session, $F(20,225)=21.49$, $p<0.001$. The mean duration of repeated rearings was also significantly reduced at doses of 30 and 60 μg/kg (Table 2). Similarly, in the free exploration test, both the 15 and 60 μg/kg doses reduced the rate of rearing activity (Table 1). The reduction of rearing duration in the high dose groups may be related to lisuride's peculiar effect on posture (see visual observations below).

Investigatory Responding

As shown in Table 1, the dose-response curve for lisuride's effect on holepoking in the forced exploration test was intermediate between that seen for crossovers and rearings. Beyond 15 μg/kg, holepoke frequency begins to increase, with the 60 μg/kg group making significantly more holepokes than the 15 μg/kg group. This slight upswing in the dose-response curve is suggestive of a biphasic effect on holepoking with the dose-response curve shifted to the left of the curve for horizontal locomotion. Doses of 30 and 60 μg/kg lisuride also significantly increased the ratio of varied to repeated holepokes (Table 1), suggesting that although

TABLE 3

COMPARISON OF THE EFFECTS OF LISURIDE AND LSD ON EXPLORATORY ACTIVITY

	Lisuride			LSD*		
Forced Exploration	Low (5–15)†	Med (30)	High (60–80)	Low (10)	Med (20–30)	High (80–160)
Crossovers	↓	0	↑	↑	↓	↓↓
Holepokes	↓	↓	0	0	↓	↓↓
Rearings	↓	↓↓	↓↓	0	↓	↓↓
Center Entries	↓	0	↑	0	↓	↓↓
Patterns	NA	Stped	Stped	Norm	Rand	"Stped"
Free Exploration (Rates are Counts per min in Holeboard)						
Crossover Rate	↓		0	0	0	0
Holepoke Rate	↓		↓	0	0	0
Rearing Rate	↓↓		↓↓	↓	↓	↓↓
Time in Holeboard	↓		0	↑	↓	↓↓
Patterns	NA		Stped	Norm	Rand	NA

Symbols: ↓ decrease; ↑ increase; 0, no effect; blank, not measured.

Abbreviations: Normal (Norm), random (Rand), stereotyped (Stped), NA (not measureable because rats either never entered the chamber [free exploration] or were too inactive for pattern analysis [forced exploration]).

*Summary of results of from [1,3].

†Dose ranges in μg/kg free base.

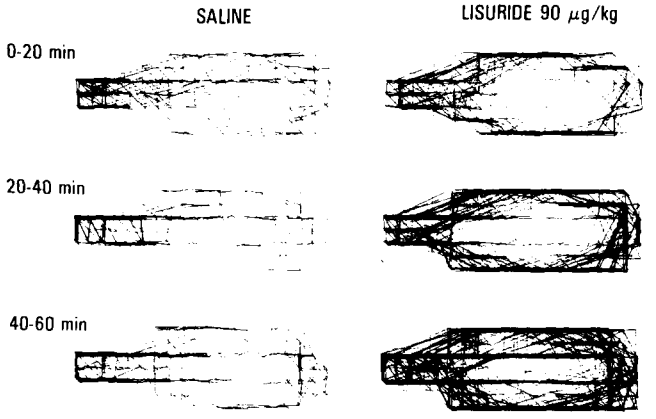

FIG. 5. Computer-generated summaries of sequential changes in X-Y position reveal differences in the locomotor patterns of a rat treated with saline and one treated with 90 μg/kg lisuride in the free exploration test. The plots summarize activity over 20-min intervals. The homecage is depicted on the left.

fewer holepokes are made, more of them are exploratory. Similarly, in the free exploration test, the 60 μg/kg group exhibited a significantly greater varied/repeated holepoke ratio (Table 1). However, in contrast to the forced exploration test, both the 15 and 60 μg/kg doses reduced the frequency of holepoking to the same extent (Table 1).

Locomotor Patterns in the Forced Exploration Test

Video plots revealed a biphasic temporal effect of 60 μg/kg lisuride on locomotor patterns. Between 10 and 20 min after test start, animals treated with 60 μg/kg lisuride began to circle the perimeter. From 20–40 min, all animals in this group continuously circle the chamber, reversing direction every two or three revolutions (Fig. 4). As summarized in Table 2, this perseverative circling resulted in a significant reduction in the ratio of half to full long-wall traverses. In contrast, the last 15 min of the session consists of a great number of traverses through the center, both diagonally and longitudinally (Fig. 4). The ratio of half to full center traverses was also significantly reduced by the 60 μg/kg dose (Table 2) suggesting that the center traverses were also "perseverative" in that, once initiated, the traverses were continued until a wall was reached.

Although the locomotor patterns of controls have been described in detail elsewhere [1,3], it should be noted that some control animals also circle the chamber. However, this "circling" differs from that seen in lisuride-treated animals in that, beyond the first 3–5 min of the session, it is characteristically "hesitant" (i.e., with animals back-tracking before half a revolution is made) and discontinuous (i.e., with interspersed pauses).

The locomotor patterns of the 5 and 15 μg/kg groups were similar and quite distinct from the 60 μg/kg group. At approximately 8 min, there was an abrupt shift to a much slower locomotor rate. Subsequently, the animals made few excursions, stayed close to the walls, and made frequent and protracted stays in their "home" areas. While most animals in the 5 μg/kg group continued this trend throughout the session, 66% of the 15 μg/kg group exhibited a shift at 45–50 min to more rapid activity with fewer pauses in the home area and correspondingly more excursions.

The 30 μg/kg group was more heterogenous than the 60 μg/kg group. As might be expected from its position on the biphasic dose-response curves (Table 1), the 30 μg/kg dose appeared to be on the threshold between the depressant effects of 15 μg/kg and the excitatory effects of 60 μg/kg, with

some animals exhibiting patterns indistinguishable from the 60 μg/kg group and others being more similar to the 15 μg/kg group. During the first 20 min of the session their excursions were mostly confined to the walls (Fig. 4). Circling of the chamber was seen from 20–45 min but to a lesser degree than the 60 μg/kg group (Fig. 4). Similarly, the increased locomotor rate in the last 15 min was associated with a preponderance of diagonal traverses through the center (Fig. 4). Furthermore, as shown in Table 2, the ratios of full length to half length traverses revealed a steady progression from normal to highly stereotyped locomotion across the entire dose range.

Visual Observations in the Forced Exploration Test

During the first 20–30 min, the rats treated with 60 μg/kg lisuride alternated frequently between laying down, crawling, and normal locomotion. All animals circled the perimeter of the chamber, while continuously sniffing the floor or making pokes into wall holes. Locomotion (in either posture) consisted of intermittent bursts of forward locomotion. At approximately 35 min, the rats resumed a normal posture and new behaviors emerged, such as entries into the center, rearings along the walls, and jumping in the air (with 180 degree turns). The "crawling" behavior did not appear to reflect a motor impairment since when a rat treated with 60 μg/kg lisuride was tested in an "open field" it was found that placing a piece of cardboard on the floor caused the rat to immediately resume normal posture upon contacting the new surface, and when enticed with a food pellet above his head he was able to rear up without touching the walls.

By contrast, rats treated with 15 μg/kg lisuride spent much of the time slowly traversing a wall or sitting in a backwall region. At times, their quiescent posture (ears down) was interrupted by head swaying or an abrupt 90 degree jerk of the head with ears erect. From 30–45 min, the animals appeared to become somnolent, laying motionless, with head resting on the floor and ears down. However, beyond 45 min, head-swaying and jerking resumed, and some animals began chasing and biting their tails, darting forward, and pouncing, with ears erect the entire time.

Locomotor Patterns in the Free Exploration Test

Most rats treated with 15 μg/kg lisuride spent the majority of time in the homecage. Generally, the first full entry into the holeboard did not occur until 20 min from test start, as reflected in the significant increase in latency to first entry (median entrytime: Saline=64.6 sec, LIS15=514.4 sec, LIS60=46.9 sec; $p<0.01$ LIS15 vs. Saline). They also spent significantly less time in the entryway region than controls or animals in the 60 μg/kg group (mean entry-way duration: Saline=359.6 sec, LIS15=186.2, LIS60=456.6 sec; $F(1,26)=10.80$, $p<0.001$), instead alternating between the rear and middle portions of the homecage. Once having entered, a full excursion (all the way to the rear of the holeboard and back to the homecage) was generally made, followed by another prolonged stay in the homecage. Thus, excursions were generally all or none, and there was no significant increase in conflict activity in the entry-way (mean number repeated/varied entry-beam breaks: Saline=0.097, LIS15=0.115, LIS60=0.117, $F(1,26)=2.22$, n.s.).

Like controls, rats treated with 60 μg/kg spent the first 10 min of the session making partial entries (half-body only) and partial excursions (less than half the distance to the rear of the holeboard). From 20–40 min, the rats made lengthy and direct excursions along the walls, with some circling which generally included the homecage. From 40–60 min, more center entries were seen and circling had virtually ceased.

As illustrated in Fig. 5, rats treated with 90 μg/kg lisuride were even more active than the 60 μg/kg group and circled the chamber for the first 20–40 min, consistently including the homecage in the circular pattern. Further, the same spatio-temporal evolution seen in the forced exploration test for 60 μg/kg (activity confined to the walls 0–20 min and center entries 40–60 min) was seen at the 90 μg/kg dose. For comparison, a saline-treated animal's locomotor routes are shown in Fig. 5. It can be seen that, as previously described [1], controls establish preferred routes of locomotion (particularly down the center of the holeboard) but do not exhibit stereotyped circling.

Lisuride's Effect on Body Temperature

Observational measures also revealed that lisuride reduced core body temperature at all doses tested. There was no significant difference among groups for pre-injection temperature (mean±SE in degrees Celsius: saline=377±0.5, 15 μg/k=37.2±0.2, 30 μg/kg=37.5±0.4, 60 μg/kg=37.3±0.08, 120 μg/kg=37.4±0.2). Rats treated with 15 μg/kg exhibited a progressive drop in temperature, maximal at 40 min post-injection (35.9±0.12) with return to baseline by 120 min (37.0±0.04). Rats treated with doses of 30, 60, or 120 μg/kg did not differ significantly from each other at any time-point, therefore their means were pooled. At high doses lisuride produced a maximal drop from 37.37±0.035 to 35.1±0.035 at 60 min post-injection; and at 120 min post-injection, body temperature was still below baseline (36.0±0.15).

DISCUSSION

Comparison With LSD

The major findings of our previous studies with LSD are summarized in Table 3. In most respects, the behavioral effects of lisuride were quite distinct from the effects of LSD. First of all, as noted in Table 3, in forced exploration tests, LSD suppresses locomotion only at moderate doses (30 μg/kg), and continues to suppress locomotion with increasing dose. This pattern contrasts with lisuride's biphasic dose-response curve, with low doses reducing and high doses increasing crossover activity (Table 3). When tested in the free-exploration paradigm, LSD's reduction of locomotion was found to be directly related to its reduction of time spent in the holeboard since LSD did not alter the rate of crossover activity [1,3]. Additionally, the initial period of avoidance of the holeboard was associated with an increase in conflict activity. In the same paradigm, 15 μg/kg lisuride actually reduced the rate of crossover activity (Table 3) and the initial reduction of time spent in the holeboard was associated with prolonged stays in the rear of the homecage rather than conflict activity. Thus, while the locomotor suppressant effects of 30–80 μg/kg LSD can be solely attributed to its reduction of time spent in the holeboard (neophobia) [1,3], lisuride appears to have an actual sedative effect at low doses. A similar distinction was seen for holepokes. While LSD produced a dose-dependent decrease in holepokes in the forced exploration test (Table 3), lisuride showed a biphasic dose-dependency, particularly with regard to varied holepokes. Additionally, lisuride reduced the rate of holepoking in the free exploration test at both low and high doses; whereas LSD does not alter holepoke rate at any dose

(Table 3). Visual observations also indicated a primarily sedative effect of 15 μg/kg lisuride. Only at 45–50 min did they become more alert, exhibiting a phase of locomotor bursts (pouncing, jumping, and darting) similar to that seen with 125 μg/kg apomorphine (Adams and Geyer, unpublished observations). Lisuride's biphasic dose-dependency is consistent with clinical studies showing that, in humans, 1 μg/kg lisuride induces an EEG profile indistinguishable from CNS depressants, while higher doses induce an EEG profile more similar to CNS stimulants, such as amphetamine [15].

Lisuride also differed from LSD in terms of its alteration of locomotor patterns. In both free and forced exploration tests, LSD disrupts the tendency of rats to establish preferred routes of locomotion [1,3]; whereas, doses of 30–90 μg/kg lisuride induce stereotyped routes of locomotion which are consistent from animal to animal both spatially and in their evolution across time. Although higher doses of LSD (80–160 μg/kg) do cause animals to initially circle the chamber [3], this circling appears to be a prolongation of the normal thigmotaxic response seen in controls since, for LSD, circling occurs only in the forced exploration test, it is specific to the first 10–20 min, and is confined to the walls (i.e., the oval and figure-eight patterns characteristic of lisuride-treated animals are not seen). Since in the free exploration test, rats always confine their micturation and defecation to the homecage, the fact that the characteristic patterns produced by lisuride and LSD occur in both test situations suggests that subtle differences in the peripheral effects of the two drugs (e.g., lisuride's greater diarrhetic effect) do not contribute to the pattern differences seen.

The only similarity between lisuride and LSD was the dose-dependent reduction of rearing activity (Table 3). In contrast to the biphasic dose-response curve for ambulation, lisuride continued to suppress rearing with increasing dose. However, while LSD suppressed total rearing only at doses of 30 μg/kg and greater, lisuride suppressed rearing even at 5 μg/kg. Further, rearing was suppressed to the same extent by 15, 30 and 60 μg/kg lisuride. The failure of lisuride to further suppress rearing beyond 15 μg/kg could be explained on the basis of a "floor" effect since this dose suppressed rearing to the same extent as the highest dose of LSD tested (160 μg/kg) [3]. Visual observations indicated that the suppression of rearing by 60 μg/kg lisuride was associated with the postural changes (crawling behavior) produced by the drug. This same "crawling" behavior was also seen with 30–160 μg/kg LSD [3] and has been noted by others for both lisuride [18] and LSD [10, 16, 31]. However, doses of 15 μg/kg lisuride did not cause animals to crawl. Therefore, it appears that suppression of rearing by doses of 5 and 15 μg/kg lisuride might reflect a different mechanism (e.g., a sedative effect) than that responsible for suppression of rearing at higher doses.

Comparison with apomorphine. The results of the present experiments are consistent with the biochemical [7, 17, 23], electrophysiological [24, 28, 30], and behavioral [22, 27, 29] evidence showing that lisuride is a more potent DA agonist than LSD. Low doses of lisuride reduced activity while high doses increased activity above controls. Lisuride also induced hypothermia, an effect previously reported for mice [13], as well as rats maintained at 4°C [14]. These same effects have been noted for the direct acting DA agonist apomorphine [12,22] as well as other ergots believed to be potent DA agonists, such as legotrile and bromocriptine [14,22]. Further, it has been shown that neuroleptics antagonize the hyperactivity induced by lisuride and apomorphine [22,27], presumably due to their DA antagonistic effects. Examination of the qualitative aspects of behavioral effects also reveals similarities between lisuride and apomorphine. For example, White and Appel [29] found that rats trained to discriminate lisuride from LSD generalize to apomorphine rather than the 5-HT agonist quipazine. Similarly, we found that the dose of lisuride (60 μg/kg) which produced hyperactivity induced a rotational pattern similar to that seen with locomotor-activating doses of apomorphine (1.0–2.0 mg/kg salt) [8]. Furthermore, the circling occurred with the same time of onset and offset as that seen with apomorphine; and showed the same abrupt transition at 40 min to more center-oriented activity [8]. The major difference between the high dose effects of the two drugs is that apomorphine-treated animals seldom reverse direction, and never make holepokes during the circling phase [8].

In summary lisuride did not share LSD's ability to potentiate neophobia, nor did it induce the type of randomized locomotor patterns seen with LSD. Lisuride instead showed many similarities (on both qualitative and quantitative measures) to the DA agonist apomorphine. This is consistent with lisuride's greater potency and efficacy in mimicking the electrophysiological and biochemical effects of DA agonists. In contrast, the suppression of rearing and associated postural alterations produced by 30 and 60 μg/kg lisuride are strikingly similar to those produced by comparable doses of LSD. In view of the similar potency of lisuride and LSD for suppression of raphe firing [24,28] and reduction of 5-HT turnover [17], the suppression of rearing produced by high doses of lisuride and LSD may be related to the effects of these drugs on the serotonergic system. This suggestion is supported by our recent observation [2] that suppression of rearing by the hallucinogen DOM is blocked by the 5-HT antagonist cyproheptadine. The finding that lisuride also suppresses rearing in still lower doses (5 and 15 μg/kg) without a concomitant postural alteration, suggests that the low-dose phenomenon may reflect a sedative action, perhaps due to a direct agonistic action at DA autoreceptors [26,28].

In conclusion, enhanced avoidance of novel and central area appears to be a valid indicator of hallucinogenic activity since LSD, DOM, and DMT all share this property; whereas, lisuride does not. Conversely, the reduction of rearing produced by hallucinogens is not a valid model behavior because the non-hallucinogenic ergot, lisuride, also produces this effect.

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