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Evidence for a Direct Dopaminergic Effect of Lisuride

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SCHECHTER, M. D. *Evidence for a direct dopaminergic effect of lisuride.* PHARMACOL BIOCHEM BEHAV **21**(2) 185–189, 1984.—The discriminative stimulus properties of the clinically important ergot derivative lisuride hydrogen maleate were studied by training 2 groups of rats to discriminate 0.04 mg/kg lisuride from saline and 0.16 mg/kg apomorphine from saline. Dose-response and substitution tests between these groups showed that lisuride and apomorphine are discriminated similarly by both groups and that lisuride is 5 to 9 times more potent. The dopaminergic agonists *d*-amphetamine, quipazine, bromocriptine, cocaine and cathinone did not substitute for lisuride. In antagonism studies, only the dopamine receptor blocker haloperidol attenuated the lisuride cue; the serotonin receptor blockers pirenperone and BC-105 were ineffective. These data indicate that the primary central action mediating the discriminative stimulus effects of lisuride was direct activation of dopamine receptors.

Drug discrimination Lisuride Apomorphine Amphetamine Bromocriptine Quipazine Cocaine Cathinone Dopamine Pirenperone Haloperidol

THE drug discrimination procedure consists of training animals to indicate whether or not they have received administration of a specific drug. Typically, food-deprived rats are trained to press one lever to receive food when the drug has been administered or to press an alternate lever to receive food when a vehicle control has been administered. When discrimination is learned and retained, tests with other drugs can be conducted and this testing can provide information concerning the similarity of stimulus properties of other drugs to that of the training drug. In addition, the mechanism(s) which might be involved in the action of the training drug can be studied by means of chemical or neuropharmacological manipulations.

This sensitive and specific behavioral paradigm has been employed by various investigators to evidence the dopaminergic activity of lisuride. Thus, Holohean *et al.* [8] trained twelve rats to discriminate between 0.25 mg/kg apomorphine and saline and found that lisuride produced a pattern of responding similar to that observed after apomorphine, whereas White and Appel [27,28] trained rats to discriminate between lisuride and saline and found that various doses of the dopaminergic agonist apomorphine produced discriminative responses like that of the trained drug state. The purpose of the present investigation was to independently replicate these studies and to expand the results by administering indirect dopamine agonists to lisuride-trained rats in an endeavor to investigate the pre- or postsynaptic site of action for the dopaminergic effects of lisuride. In addition, serotonergic antagonists and numerous other drugs were administered to these rats to further elucidate the site and mechanism of action of the centrally-mediated discriminative stimulus produced by lisuride.

METHOD

Subjects

Fourteen experimentally-naive male ARS/Sprague-Dawley rats weighing 330–440 g at the beginning of experimentation were used. They were housed in individual living cages and their weights were adjusted, by daily rationing of commercial rat chow, to approximately 80 to 85% of their free-feeding weights as determined by daily weighing of two control free-feeding rats purchased at the same time as experimental animals from the supplier (Zivic-Miller, Allison Park, PA). Water was continuously available in the home cages which were kept at a constant temperature (20–22°C) and maintained on a 12-hour light/12-hour dark daily cycle.

Apparatus

The experimental space consisted of four identical standard rodent operant chambers (Lafayette Instruments Corp., Lafayette, IN) each equipped with two operant levers located 7 cm apart and 7 cm above the grid floor. A food pellet receptacle was mounted 2 cm above the grid floor at an equal distance between the two levers. The test cage was housed in a sound-attenuating cubicle equipped with an exhaust fan and 9 W house-light. Solid-state programming equipment (LVB Corp., Lehigh Valley, PA) was used to control and record the sessions and was located in an adjacent room.

Discriminative Training

Drug discrimination training was based upon procedures

described in detail elsewhere [18]. There were two training phases. In the first phase, the food-deprived rats learned to press the lever indicating saline control administration and received a food reward (45 mg Noyes pellet) for each correct response, fixed ratio 1 (FR1) schedule. This schedule was made progressively more difficult, in daily 15 min sessions, over 10 days until an FR10 schedule was achieved. Throughout lever press training, all rats received daily intraperitoneal (IP) injections of saline (0.9% sodium chloride) 15 min prior to being placed into the two-lever operant box. Immediately following the attainment of the FR10 schedule after saline administration, the opposite lever was activated and rats received a food reward for each correct response, fixed ratio 1 (FR1) schedule, after the IP administration of an equal volume of saline (1 ml/kg body weight) containing either 0.04 mg/kg lisuride (n=8) or 0.16 mg/kg apomorphine hydrobromide (n=6). Daily sessions, of 15 min duration, were continued over 8 days with drug administration until an FR10 schedule was attained. In order to minimize effects due to any possible position preference, the rats in each group were divided into two subgroups. For one subgroup responding on the left lever was reinforced by delivery of food pellets in every session following drug injection, whereas the other group was reinforced with food after responding on the right lever following drug injection. Responses on the opposite lever were reinforced with food pellets after saline injection.

Phase II discrimination training then began. Subjects were trained 5 days per week with reinforcement in a pseudorandom sequence. Thus, in each two week period, there were five days with drug lever (D) and five days with saline lever (S) correct. The pattern was D,S,S,D,D; S,D,D,S,S. The training criterion was reached when the animal selected the appropriate lever, according to the drug state imposed, on eight of ten consecutive session.

Dose-Response Relationships

After the rats attained the discriminative training criterion with each of the two agents, testing and training sessions of 15 min duration with alternating administrations of either 0.04 mg/kg lisuride and saline or 0.16 mg/kg apomorphine and saline were continued on Mondays, Wednesdays and Fridays. It was intended that if a rat was observed to make more than two incorrect lever selections in any of 10 consecutive maintenance sessions, the data on that rat's performance would be deleted from the results. This, however, did not occur in the eight lisuride-trained animals and occurred in only one of the six animals trained to discriminate apomorphine. On Tuesdays and Thursdays, the rats of each group were injected IP with one of several different doses of either apomorphine or lisuride then used for initial training and, 15 min later, they were placed into the experimental chamber. They were allowed to lever press, without receiving reinforcements, until ten presses were made on either lever. To preclude training at a drug dose different than employed to train the animals, the rats were immediately removed from the experimental chamber once the total responses on one lever reached 10 presses. Each of the test doses of drugs was tested in each animal on two occasions with each test preceded both by a drug and a saline maintenance session. The lever first pressed ten times was designated as the "selected" lever and the percentage of rats choosing the drug-correct lever constitutes the quantal measurement (below).

Lisuride to Apomorphine and Apomorphine to Lisuride Transfer Experiments

Once the dose-response relationships for apomorphine and lisuride were established, various doses of each were administered to animals trained with the other. Thus, lisuride was administered to apomorphine-trained animals and apomorphine was administered to lisuride-trained animals IP and, 15 min later, the ability of the animals to press the lever previously associated with their trained drug was tested. Each of the doses of these test drugs was tested on two occasions preceded by both a drug and saline maintenance session and the animals were immediately removed upon making ten responses on either lever.

Substitution Tests

Subsequently, testing days (Tuesdays and Thursdays) were used to investigate the ability of the lisuride-trained rats to discriminate numerous drugs evidenced to act upon dopaminergic neurons, viz., *d*-amphetamine, bromocriptine, cocaine, (±)-cathinone and quipazine, as well as three tricyclic antidepressants, at doses reported in the literature to produce behavioral effects.

Antagonism Studies

In antagonism tests, the apomorphine- and lisuride-trained rats were administered the dopaminergic antagonist haloperidol prior to receiving either lisuride, apomorphine or saline and were tested under the same extinction conditions for lever selection. In addition, the lisuride-trained rats were administered two putative serotonin receptor blockers, pirenperone and BC-105 (pizotifen) prior to lisuride or saline.

Drugs

All drugs were administered IP in an equal volume of 1 ml/kg with the identity of the test drug unknown to the experimenter (technician). Lisuride hydrogen maleate (Schering AG), freshly prepared apomorphine hydrobromide (Sigma), *d*-amphetamine sulfate (Sigma), bromocriptine (CB-154) (Sandoz), amitriptyline (MS&D), desipramine (Merrill), imipramine (Ciba-Geigy), haloperidol (McNeil), pirenperone (Janssen), BC-105 (Sandoz), cocaine (NIDA), ±-cathinone (provided by Dr. Richard Glennon, Medical College of Virginia) and quipazine (provided by Dr. John Rosecrans, Medical College of Virginia) were all dissolved in sterile saline and doses were calculated as base. The order of administration of all test drugs was random throughout the study.

Measurements

The lever pressed 10 times first was designated as the "selected" lever. The percentage of rats selecting the lever appropriate for the training drug was the quantal measurement of discrimination. In addition, the total number of lever presses on both levers made before ten presses on either lever were counted constitutes the quantitative measurement, i.e., the number of responses on the drug-correct lever divided by total responses made prior to ten responses times 100. The advantages in using both measurements have been discussed by Stolerman and D'Mello [23]. The quantal data for the dose-response experiments were analyzed by the method of Litchfield and Wilcoxon [12] which employs probit vs. log-dose effects and generates ED50's and tests for parallelism.

TABLE 1

DOSE-RESPONSE AND TRANSFER TO LISURIDE IN APOMORPHINE-TRAINED RATS

Treatment	Dose (mg/kg)	No. of Trials	Quantal	Quantitative (±SEM)
Saline	—	20	6.7	11.0 (4.9)
Apomorphine	0.24	2	90.0	79.0 (7.4)
	0.16	20	83.3	77.3 (5.3)
	0.08	2	80.0	66.8 (9.2)
	0.04	2	50.0	51.8 (9.0)
Lisuride	0.08	2	100.0	82.8 (2.7)
	0.04	2	90.0	82.6 (6.7)
	0.02	2	80.0	72.7 (3.2)
	0.01	2	60.0	60.8 (10.1)
	0.005	2	30.0	35.5 (1.1)

n=5.

TABLE 2

DOSE-RESPONSE AND TRANSFER TO APOMORPHINE IN LISURIDE-TRAINED RATS

Treatment	Dose (mg/kg)	No. of Trials	Quantal	Quantitative (±SEM)
Saline	—	16	2.8	11.1 (1.8)
Lisuride	0.08	2	93.8	81.4 (4.9)
	0.04	16	91.7	74.1 (1.8)
	0.02	2	81.3	67.9 (6.4)
	0.01	2	56.3	50.7 (3.9)
	0.005	2	18.8	23.5 (9.4)
Apomorphine	0.24	2	93.8	80.8 (1.1)
	0.16	2	68.8	64.2 (10.6)
	0.08	2	56.3	55.2 (13.4)
	0.04	2	12.5	12.9 (4.2)

n=8.

RESULTS

Discriminative Learning

Discriminations were rapidly acquired; the average number of sessions to meet criterion (8 out of 10 correct consecutive sessions) was 20 for the rats in the lisuride group and 23 for the rats in the apomorphine group.

Dose-Response Relationship and Transfer to Lisuride in Apomorphine-Trained Rats

Alternating maintenance sessions with 0.16 mg/kg apomorphine and saline produced 83.3 and 6.7% quantal responding on the apomorphine-correct lever, respectively (Table 1). Administration of one higher (0.24 mg/kg) and 2 lower (0.08 and 0.04 mg/kg) doses of apomorphine indicated that decreasing doses produced decreasing discriminative performance both in terms of quantal and quantitative measurements.

Test trials with lisuride doses, ranging from 0.005 to 0.08 mg/kg, indicated that the rats perceive lisuride as they do apomorphine and that this transfer (generalization) is dose-dependent. When the quantal data for apomorphine and lisuride are graphed and subjected to the method of Litchfield and Wilcoxon [12], the ED50 for apomorphine is 0.034 (95% confidence limits: 0.014–0.085) mg/kg and the ED50 for lisuride in apomorphine-trained rats is 0.0085 (0.0047–0.0151) mg/kg. The dose-response lines are parallel within 95% statistical limits, i.e., the fSR (3.65) > SR (1.05), and lisuride is 4.94 times (significant at $p>0.05$) more potent than apomorphine.

Dose-Response Relationship and Transfer to Apomorphine in Lisuride-Trained Rats

Alternating administrations of 0.04 mg/kg lisuride and saline produced 91.7 and 2.8% quantal responding on the lisuride-correct lever, respectively (Table 2). Decreasing doses of lisuride produced decreasing quantal and quantitative measurements and the ED50 for lisuride was 0.0099 (95% confidence limits: 0.0059–0.0166) mg/kg.

Substitution of 0.04–0.24 mg/kg apomorphine in lisuride-trained rats indicated a dose-related decrease in discriminative performance with decreasing doses. The ED50 for apomorphine in these lisuride-trained rats was 0.076 (0.054–0.139) mg/kg. Analysis of the lisuride and apomorphine dose-response curves by the probit method [12] indicates that lines are parallel within statistical limitations, i.e., fSR(2.53) > SR(1.04) and that lisuride is 8.7 times (and significantly) more potent than is apomorphine.

Substitution Tests

Administration of various drugs that act as direct and indirect dopamine agonists to lisuride-trained rats produced saline-appropriate quantal responding and, in no case, was the quantitative results statistically similar (*t*-test of means) to that of lisuride (Table 3). Furthermore, administration of a behaviorally-active dose of each of three tricyclic antidepressants did not produce significant responding upon the lisuride-appropriate lever.

Antagonism Tests

The results of antagonism tests are shown in Table 4. In apomorphine-trained rats, 0.2 mg/kg haloperidol administered 10 minutes prior to test drugs blocked the apomorphine cue and the substitution of lisuride for apomorphine. Likewise, haloperidol, at the same dose and time-course, blocked both apomorphine and lisuride cues in lisuride-trained rats. In addition, the putative serotonergic receptor blockers pirenperone and BC-105 administered 45 minutes prior to lisuride did not significantly decrease the lisuride cue in lisuride-trained rats.

DISCUSSION

The results of these studies indicate that lisuride and apomorphine are capable of being discriminated and this discrimination can be used as a cue for a behavioral response by a common mechanism. Thus, in apomorphine-trained rats, lisuride produces discriminative effects similar to the trained drug, while in lisuride-trained rats, apomorphine produces similar effects. The parallelism of the dose-response curves generated in each group of these trained animals indicates that the mechanism and/or site of action of these two agents

TABLE 3

SUBSTITUTION EXPERIMENTS IN LISURIDE-TRAINED RATS

Treatment	Dose (mg/kg)	No. of Trials	Quantal	Quantitative (±SEM)
Lisuride	0.04	28	94.3	80.1 (9.2)
Saline	—	28	4.5	10.9 (5.6)
Quipazine	4.0*	2	37.5	40.7 (9.3)
	2.0	2	6.3	9.2 (8.8)
D-Amphetamine	1.2	2	25.0	34.2 (9.6)
	0.6	2	25.0	34.1 (1.8)
Bromocriptine	8.0*	2	25.0	29.4 (1.4)
	4.0	2	18.8	19.4 (1.4)
	2.0	2	12.5	18.7 (2.8)
Cocaine	10.0	2	25.0	36.6 (2.3)
Cathinone	2.4*	2	25.0	31.3 (3.9)
	1.2	2	12.5	26.6 (2.8)
	0.6	2	6.3	17.4 (10.5)
Amitriptyline	10.0	2	6.3	10.8 (8.4)
Desipramine	10.0*	2	31.3	35.2 (0.3)
Imipramine	10.0	2	25.0	28.1 (9.3)

*Partial disruption of behavior seen at this dose.
n=8.

are similar, since parallel dose-response lines are indicative of a common site/mechanism of action [11]. This confirms and extends previous work by Appel and his associates [8, 27, 28]. In addition, lisuride was observed to be approximately 5 to 9 times more potent than apomorphine in the animals tested. These potency ratios have previously been shown in other behavioral tests that predict dopaminergic activity, viz., contralateral turning in rats with lesions of the nigrostriatal dopamine system [4, 6, 15], in inducing emesis in dogs [9] and in producing stereotyped behavior in rats [2].

Administration of the indirect dopamine agonists, *d*-amphetamine and (±)-cathinone, did not produce lisuride-appropriate responses. In a previous study [1], a 1 mg/kg dose of *d*-amphetamine was observed to produce 50% responding in rats trained to discriminate 0.08 mg/kg lisuride from saline. Cathinone, a drug with discriminative properties similar to *d*-amphetamine [21], has never been administered to lisuride-trained animals and the present results indicate that it does not share a common discriminative stimulus cue.

Quipazine, a drug with both serotonergic and dopaminergic properties in this behavior paradigm [20,26], had previously been shown to produce a partial (51%) transfer at a dose of 2 mg/kg in lisuride-trained animals [1]. However, in the present study, the highest, non-disruptive, dose of quipazine (4 mg/kg) produced 37.5% of total responding on the lisuride-correct lever. Likewise, bromocriptine in doses ranging from 2–8 mg/kg was found to produce essentially saline-appropriate responding when administered to lisuride-trained animals. This extends a previous investigation in which bromocriptine was not transferable in animals trained to discriminate apomorphine [8]. One possible explanation is that bromocriptine, which has been reported to possess both agonist and antagonist properties on dopaminergic receptors [7], may have blocked the dopamine-induced activation of adenylate cyclase [24] at the doses used.

The subsequent administration of 3 tricyclic antidepressants which have been shown to be discriminated in a similar paradigm [19] also produced saline-appropriate responding. The rationale for the use of these agents was in regard to their ability to affect serotonergic systems.

More important are the results from pre-treatment experiments with specific dopaminergic and serotonergic antagonists. Haloperidol, at a dose of 0.2 mg/kg, was observed to attenuate both the lisuride cue and apomorphine transfer in lisuride-trained animals and the apomorphine cue and lisuride transfer in apomorphine-trained animals without affecting saline discrimination. Previous work [1] had indicated that a dose of 0.05 mg/kg haloperidol reduced apomorphine discrimination. Likewise, the same dose of haloperidol reduced lisuride responding in a dose-effect antagonism study [27].

TABLE 4

ANTAGONISM TESTS WITH APOMORPHINE AND LISURIDE

Pretreatment		Dose (mg/kg)	Time (min)	Treatment	Dose mg/kg	No. of Trials	Quantal	Quantitative (±SEM)
Apomorphine trained rats (n=5)	Haloperidol	0.2	10	Saline	—	2	0.0	13.8 (6.0)
				Apomorphine	0.16	2	40.0	29.4 (18.6)
				Lisuride	0.04	2	20.0	25.7 (11.5)
Lisuride trained (n=8)	Haloperidol	0.2	10	Saline	—	2	0.0	20.0 (2.0)
				Apomorphine	0.16	2	12.5	23.0 (0.6)
				Lisuride	0.04	2	31.3	44.0 (1.2)
	Pirenperone	0.16	45	Saline	—	2	12.5	20.2 (5.2)
				Lisuride	0.04	2	81.0	69.0 (6.2)
		0.32	45	Saline	—	2	12.5	31.1 (2.6)
				Lisuride	0.04	2	81.0	63.8 (4.2)
	BC-105	1.0	45	Saline	8	2	0.0	13.0 (2.0)
				Lisuride	0.04	2	75.0	63.4 (1.4)

In light of the fact that lisuride has been reported to act at serotonin as well as dopamine receptors [27,28], the pretreatment with the specific serotonin antagonists BC-105 and pirenperone was investigated. Previous work [1] indicated that 3 mg/kg BC-105 did not antagonize 0.25 mg/kg apomorphine discrimination and doses of 1 to 4 mg/kg did not effect the action of lisuride on a fixed-ratio operant behavior task [14]. An effective dose (1 mg/kg) decreased lisuride responding to 75%. Likewise, pirenperone at a dose that was previously shown to antagonize the discriminative effects of LSD [3] had no effect on lisuride discrimination. Indeed, pretreatment with twice this dose did not significantly affect saline or lisuride discrimination.

In summary, this experimentation indicates that lisuride produces a discriminative cue in rats primarily by acting as a direct dopaminergic agonist in the central nervous system. There is also biochemical evidence for a direct dopaminergic agonist activity of lisuride [10,16]. In addition, the 5 to 9 times greater potency of lisuride when compared to apomorphine in the present study agrees with other similar actions of these agonists, including the inhibition of ^{3}H-spiroperidol in homogenates of rat caudate nucleus [25] and the inhibition of firing rates of nigral dopaminergic cells [22]. Thus, the primary central effect of lisuride appears to be dopaminergically-mediated and this finding is supported by the efficacy of lisuride in treating disorders of dopaminergic origin such as Parkinson's disease [17], acromegaly [13] and hyperprolactinemia [5].

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