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Apomorphine and Haloperidol, but not Domperidone, Affect Penile Reflexes in Rats[1]

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PEHEK, E. A., J. T. THOMPSON, R. C. EATON, T. J. BAZZETT AND E. M. HULL. *Apomorphine and haloperidol, but not domperidone, affect penile reflexes in rats.* PHARMACOL BIOCHEM BEHAV 31(1) 201–208, 1988.—Previous studies have shown that systemic administration of the dopamine agonist apomorphine produced a biphasic effect on erection in the freely moving rat, with lower doses facilitating, and high doses inhibiting, erection. However, those studies did not distinguish between erection per se and seminal emission. The present results demonstrate that apomorphine produces a similar biphasic effect on penile reflexes in the restrained, supine rat, while facilitating seminal emission in a monophasic fashion. Haloperidol, a centrally-acting dopamine antagonist, either blocked the effects produced by apomorphine administration, or had actions opposite to those of apomorphine. Domperidone, a dopamine antagonist that does not readily penetrate the blood-brain barrier, did not antagonize apomorphine's effects, and did not affect penile responses when administered alone. These results suggest that dopamine receptors in the central nervous system regulate genital responses, and that effects on penile reflexes and seminal emission can be experimentally dissociated.

Dopamine Apomorphine Haloperidol Domperidone Penile reflexes Seminal emission Copulatory behavior Male rat

SYSTEMIC administration of apomorphine (APO), a dopamine (DA) agonist, was reported to produce biphasic effects on ex copula penile erection in the freely moving rat, with low to moderate doses facilitating, and high doses inhibiting, erection [3, 11, 20]. Pretreatment with either haloperidol (HAL) or sulpiride, centrally acting DA antagonists, blocked the increases in erection produced by APO [3,11]. Prior treatment with domperidone (DOM), a DA antagonist that does not cross the blood-brain barrier when administered acutely [14], did not antagonize the APO-induced facilitation of erection [3,11]. This latter finding suggested that the effects of APO administration were due to actions on the central, rather than the peripheral, nervous system.

Other investigators have found that moderate doses of systemically administered APO decreased the number of intromissions required for ejaculation and reduced the latency to ejaculate in copula, suggesting that the ejaculatory threshold had been reduced [1, 4, 9, 17, 18]. HAL blocked this effect [1], whereas DOM did not [9], supporting the hypothesis that APO acted centrally to alter copulatory performance.

It is possible that the APO-induced decrease in ejaculatory threshold may be related to changes in genital responses. However, a simple relationship between ejaculatory threshold and ex copula genital responses cannot be inferred from ex copula studies utilizing the freely moving rat, because no distinction was made in those studies between erection per se and seminal emission. This distinction is important, since others have found opposite pharmacological effects on these two responses [5, 15, 16, 21]. For example, administration of RDS-127, a mixed DA/5-HT agonist, inhibited penile reflexes (including erection), but facilitated seminal emission [21]. This agent also reduced the ejaculatory threshold in copula [6].

Tests of penile responses in the restrained, supine rat allow one to distinguish readily between penile reflexes and seminal emission. Penile reflexes occur spontaneously following exposure of the glans penis in the rat, and consist of erections and flips (anteroflexions of the glans penis) [12,19]. Erections vary in intensity from mild engorgement of the body of the glans to an intense flaring of the tip of the glans into a cup-like shape. On rare occasions in untreated

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rats, seminal emission also occurs. Sachs [19] has provided evidence suggesting that these responses occur in copula. Removal of the perineal ischiocavernosus muscle prevented the display of flips ex copula and severely impaired the ability to intromit. Excision of the bulbocavernosus muscle eliminated the formation of intense, cup-like erections ex copula and prevented the impregnation of females, although copulatory behavior appeared normal and a normal seminal plug was ejaculated. Sachs suggested that the function of cups was to position the seminal plug around the female's cervix, thereby facilitating impregnation.

One aim of the present studies was to clarify the role of DA receptors in the regulation of genital responses by examining the effects of systemically administered APO on penile reflexes and seminal emission in the restrained, supine rat. In order to ascertain whether APO's actions were pharmacologically specific to the DA receptor, the effects of HAL, administered either alone or prior to APO administration, were also examined. The hypothesis that APO's effects on genital responses were due to actions on the central nervous system (CNS) was tested by comparing the relative abilities of HAL and DOM to block APO's actions. Additionally, the relationship, if any, between the effects of APO on copulatory behavior and genital responses was examined.

GENERAL METHOD

Subjects

Adult male Long-Evans rats, weighing from 350–600 g and obtained from Blue Spruce Farms (Altamont, NY), were used. All animals were housed singly in a temperature and humidity controlled environment, with food and water available ad lib. A 14/10 light/dark cycle was in effect, with lights off at 11:00 hr.

Female rats of the same strain were used as stimulus animals in copulatory behavior tests and were housed separately from the males. Females were ovariectomized and brought into behavioral heat with a single SC injection of estradiol benzoate (20 μg) administered 48 hours before behavioral testing.

Surgical Procedures

Unless otherwise mentioned, all subjects in ex copula experiments had severed suspensory ligaments. This ligament is attached bilaterally to the base of the penis underneath the skin. Severing the ligament facilitates maintained exposure of the glans penis from the penile sheath. In addition, this procedure allows one to observe the movements of the penis as the penile body engorges with blood and its distal end rises up out of the penile sheath before a cluster of reflexes, and recedes down following the cluster (termed "ups" and "downs," respectively) (Sachs, personal communication).

Drug Administration

Apomorphine hydrochloride, obtained from Sigma Chemical, was dissolved immediately before administration in sterile saline with 0.2% ascorbic acid to prevent oxidation. Control injections for APO administration consisted of the saline/ascorbic acid vehicle. All injections were given IP in a volume of 1 ml/kg. Testing began 10 min after APO administration, and 30 min after HAL or DOM injections.

Behavioral Testing

All testing was done during the dark period of the light cycle, between 11:00 and 17:00 hr.

Copulatory behavior tests. Copulatory behavior was assessed in the male's home cage. Males were screened for copulatory behavior twice before receiving a preexperimental baseline test. Each test lasted for 30 min following the first vaginal intromission, or for a total of 30 min, if no intromissions occurred (unless otherwise noted). The numbers and times of each mount, intromission, and ejaculation were recorded. Intromissions were distinguished behaviorally from mounts by the presence of a rapid, springing dismount. Ejaculations were distinguished from mounts and intromissions by a deep thrust followed by a slow dismount and a 5–10 min period of inactivity. Measures derived from the data were: number of ejaculations, numbers of mounts and intromissions preceding each ejaculation, latency to the first mount, latency to the first intromission, ejaculation latency (time from the first intromission of an ejaculatory series to the subsequent ejaculation), length of the postejaculatory refractory period (time from the ejaculation to the following intromission), interintromission interval (the average time between intromissions), and intromission ratio (the number of intromissions divided by the total number of mounts and intromissions).

Ex copula tests. Each rats was restrained in a supine position in a device fashioned from a piece of rain gutter pipe (dimensions, 8.5 by 5.5 cm; length, 20 cm). The lower portion of his body protruded from this device, and was restrained by the use of masking tape. Rats were handled and acclimated to this procedure before any testing began.

In order to evoke penile reflexes, the penile sheath was retracted and maintained in this position. Usually, reflexes spontaneously occur within five to ten min following exposure of the glans. The resultant responses occur in discrete clusters, separated by 15 sec or longer. Within a cluster, usually two to six reflexes are displayed, with a duration from 0.5 to 2 sec for each reflex. Two major classes of responses, erections and flips, may occur. Three gradations of erections were scored: E1, engorgement of just the base of the glans; E2, tumescence involving both the base and the tip of the glans; E3, engorgement involving the base as well as an intense flaring of the tip of the glans so that the diameter of the tip was greater than that of the base of the glans (also termed a cup) (Sachs, personal communication). Flips (dorsiflexions) were classified as "partial" or "full" in the present studies. A flip was classified as a "full flip" if the penis traveled past the line perpendicular to the rat's body.

A test lasted 15 min from the first reflex (i.e., an erection or flip), or 20 min if no reflexes occurred. Rats were given at least three screening tests. Only animals that consistently displayed reflexes on the screening tests were used as subjects.

During experimental tests, the time of the first reflex, and the numbers of ups, downs, and seminal emissions, as well as the numbers and types of erections and flips were recorded with the aid of an Esterline-Angus event recorder. If a seminal emission was present upon sheath retraction, it was removed and included in the number of seminal emissions per test. A cluster was defined as beginning with an up, and ending with a down, unless 15 sec or more intervened between successive reflexes. In the latter case, the successive reflexes were considered as belonging to two separate clusters. Measures derived from the data included: the latency to the first reflex, the number of clusters, the intercluster interval (the average time between clusters, obtained by dividing the time from the end of the first cluster of a test to the beginning of the last cluster by the number of clusters

TABLE 1

EFFECTS OF SYSTEMICALLY ADMINISTERED APOMORPHINE ON PENILE RESPONSES

	Vehicle	100 μg/kg APO	300 μg/kg APO	500 μg/kg APO
RL	470.77 ± 106.26	79.00 ± 37.1*	289.20 ± 120.11	316.11 ± 66.06
RT	37.41 ± 5.32	49.30 ± 7.98	26.60 ± 13.20	7.67 ± 1.79‡
CT	12.09 ± 1.24	11.50 ± 1.44	6.60 ± 2.99	3.78 ± 0.72‡
ET	28.73 ± 3.75	33.80 ± 4.53	18.00 ± 7.93	7.11 ± 1.79‡
E1	10.91 ± 1.60	8.60 ± 1.29	7.20 ± 2.35	4.89 ± 1.51*
E2	14.05 ± 2.36	14.20 ± 2.00	5.40 ± 2.77	2.22 ± 1.62‡
E3	3.77 ± 1.18	11.00 ± 2.72*	5.40 ± 4.19	0.00 ± 0.00
FT	8.68 ± 2.17	15.50 ± 4.00§	8.60 ± 5.34	0.56 ± 0.44‡
PF	7.82 ± 2.06	10.80 ± 2.20	5.40 ± 2.77	0.56 ± 0.44‡
SE	0.09 ± 0.06	1.00 ± 0.30†	0.20 ± 0.20	0.33 ± 0.24

Values are the means ± S.E.M. for significantly affected variables. RL, latency to the first reflex (sec); RT, total number of reflexes; CT, total number of clusters; ET, total number of erections; E1, number of E1s; E2, number of E2s; E3, number of E3s (cups), FT, total number of flips; PF, number of partial flips; SE, number of seminal emissions.

*$p<0.05$, †$p<0.02$, ‡$p<0.01$, §$p<0.10$ (all relative to vehicle).

minus one), the number of seminal emissions, the total number of reflexes, the numbers of erections and flips, and the numbers of ups, downs, E1s, E2s, E3s (cups), partial flips, and full flips.

Data Analysis

All experiments employed counterbalanced, repeated measures designs, unless otherwise noted. In a given experiment, data from males that failed to respond on each experimental trial were excluded from statistical analyses. Measures derived from the data were analyzed by either a repeated measures ANOVA, followed by Newman-Keuls pariwise comparisons, or by a Student's *t*-test. Log transforms were performed on latency and interval data before parametric statistics were employed.

EXPERIMENT I

The first experiment attempted to replicate the findings of others, demonstrating that systemic administration of APO reduced ejaculatory threshold [1, 4, 9, 17, 18].

METHOD

Eighteen sexually experienced males were used. All tests occurred at one week intervals. In the first part of this experiment, all animals received 0, 50, 100, and 300 μg/kg APO on separate, counterbalanced copulatory behavior tests. Subsequently (part two), 17 of these same animals received 0 and 500 μg/kg APO on separate, counterbalanced tests. In part two, tests ended after the first intromission following the first ejaculation. All data were analyzed by paired *t*-tests.

RESULTS AND DISCUSSION

Confirming the work of others, the administration of 500 μg/kg APO reduced the number of intromissions preceding the first ejaculation [vehicle, 9.71; 500 μg, 6.71; $t(16)=4.04$, $p<0.001$]. The number of mounts in the first ejaculatory series was also reduced by this dose [vehicle, 5.24; 500 μg, 3.18; $t(16)=2.28$, $p<0.05$]. Lower doses of APO did not significantly affect copulatory behavior.

EXPERIMENT II

This experiment investigated the effects of three doses of systemically administered APO on penile reflexes and seminal emission. Corresponding to previous reports utilizing the freely moving rat, it was hypothesized that a biphasic effect on penil reflexes would be observed, with a moderate dose facilitating, and a higher dose inhibiting, penile reflexes.

METHOD

Fourteen rats from Experiment I that responded consistently on reflex screening tests and had intact suspensory ligaments were used. Tests following drug administration were given at four-day intervals. In each of the three parts of this study, males were randomly divided into two equal groups, with one group receiving APO and the other receiving vehicle. If penile responses appeared to be altered following APO administration in a given part, then all animals received the opposite treatment in order to achieve a repeated measures design. In the first part of this experiment, animals received 0 and 500 μg/kg APO on separate, counterbalanced tests. Subsequently (part two), these same males were randomly divided into two independent groups, with one group receiving 0 and the other 300 μg/kg APO. Since 300 μg/kg APO produced no observable trends, a second counterbalancing test was not employed for this dose. These same animals then received 0 and 100 μg/kg APO on separate, counterbalanced tests (part three). Data from parts one and three were analyzed by paired *t*-tests, while data from part two were analyzed by independent groups *t*-tests. Since a relatively large proportion of animals did not respond on one or more tests, data from only those animals that responded on both trials of a given part were used for repeated measures analyses of that part.

RESULTS AND DISCUSSION

Since there were no significant differences between the vehicle means in the three parts of this experiment, these means were averaged for tabular, but not statistical, purposes.

The administration of 100 μg/kg APO decreased the la-

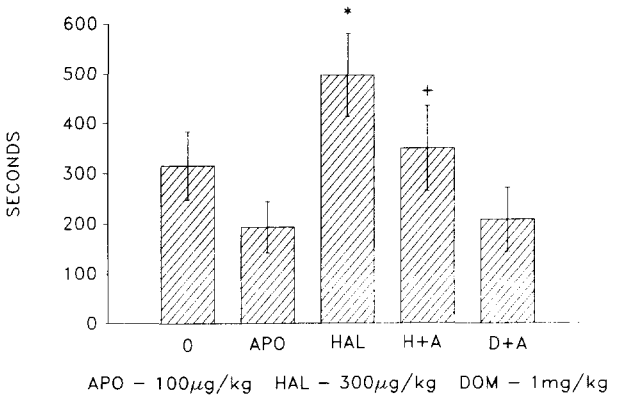

FIG. 1. Effects of IP administration of vehicle (0), apomorphine (APO), haloperidol (HAL), haloperidol followed by apomorphine (H+A), and domperidone followed by apomorphine (D+A) on the latency (sec) to the first penile reflex (means±S.E.M.). *$p<0.05$ relative to all other treatments. +$p<0.05$ relative to HAL.

tency to the first reflex, $t(9)=2.75, p<0.05$, and increased the number of cups, $t(9)=2.31, p<0.05$, and seminal emissions, $t(9)=3.21, p<0.02$ (see Table 1). There was also a trend towards an increased number of flips with this dose, $t(9)=2.15$, $0.05<p<0.1$ (see Table 1). Injections of 300 μg/kg APO did not affect penile responses.

Administration of 500 μg/kg APO decreased the total number of reflexes, $t(8)=6.52, p<0.01$, as well as the number of clusters, $t(8)=5.41, p<0.01$ (see Table 1). Contributing to the decrease in reflex total were decreases in the total numbers of erections, $t(8)=5.73$, $p<0.01$, and flips, $t(8)=4.44$, $p<0.01$ (see Table 1). Among erections, both the numbers of E1s, $t(8)=2.53, p<0.05$, and E2s, $t(8)=4.49, p<0.01$, were reduced (see Table 1). Among flips, the number of partial flips was decreased, $t(8)=4.51, p<0.01$ (see Table 1). There were no differences in the percentages of animals responding or displaying seminal emission following administration of any dose of APO. Following injections of 500 μg/kg APO (but not other doses), the rats struggled vigorously upon restraint. It is thus posssible that the inhibition of reflexes produced by this dose indirectly resulted from an increase in agitation, rather than from a direct action of APO on the neural substrate(s) responsible for penile reflexes.

The present results demonstrate that APO produces a biphasic effect on penile reflexes. A moderate dose facilitated penile reflexes, as evidenced by a decrease in reflex latency and an increase in the number of cups. A higher dose inhibited the display of reflexes, as seen by a decrease in the numbers of reflexes and clusters.

EXPERIMENT III

This experiment examined the effects of systemically administered HAL on penile reflexes and seminal emission. In addition, the relative abilities of HAL and DOM to block the facilitative effects of 100 μg/kg APO were compared. A dose of DOM (1 mg/kg), that was found previously not to affect penile responses, was employed (Pehek, Thompson and Hull, unpublished observations). It was hypothesized that HAL would inhibit penile reflexes, and that HAL, but not DOM, would antagonize the effects of 100 μg/kg APO.

METHOD

Twenty-eight males that responded consistently on penile reflex screening tests were used. Rats received vehicle, 100 μg/kg APO, 300 μg/kg HAL, HAL plus APO, and DOM (1.0 mg/kg) plus APO, on separate, counterbalanced tests spaced five or six days apart. On each test, a DA antagonist or vehicle was administered 30 min to the start of testing, followed by APO or vehicle 10 min prior to testing. HAL was kindly donated by McNeil Laboratories and was obtained in solution form at a concentration of 5 mg/ml (pH 3.0–3.4). This solution was diluted with PEG 300:saline (1:9) to 300 μg/ml. DOM was kindly donated by Janseen Pharmaceutica and was suspended in a solution consisting of PEG 300:acidified saline (1:9). The saline was acidified with lactic acid to a pH of 3.4, comparable to the pH of the 300 μg/ml HAL solution. Control injections for DA antagonists consisted of this PEG 300:acidified saline vehicle. If a male did not display penile reflexes on a given test, a value of 1200 sec was assigned for his reflex latency on that test.

RESULTS AND DISCUSSION

One animal failed to display penile reflexes on all five tests, and thus was excluded from data analyses. HAL injections increased the latency to the first reflex, and this effect was blocked by APO, $F(4,104)=5.54, p<0.001$ (see Fig. 1). APO injections did not significantly decrease reflex latency, although 67% of the animals had shorter latencies following APO administration relative to vehicle injections.

HAL decreased the total number of reflexes, $F(4,104)=6.90, p<0.001$, which included a reduction in both erections, $F(4,104)=4.80, p<0.005$, and flips, $F(4,104)=5.66$, $p<0.001$ (see Table 2). APO injections antagonized HAL's decrease in erections, but not its decreases in flips and total reflexes (see Table 2). Among erections, HAL administration reduced the number of E2s, and this effect was blocked by treatment wtih APO, $F(4,104)=4.21, p<0.005$ (see Table 2). The number of clusters was decreased following HAL, relative to APO injections, $F(4,104)=3.12$, $p<0.025$ (see Table 2).

APO administration increased the number of seminal emissions, and this effect was antagonized by HAL but not DOM pretreatment, $F(4,104)=4.62$, $p<0.005$ (see Fig. 2). APO injections also increased the number of full flips; this effect was blocked by pretreatment with either HAL or DOM, $F(4,104)=6.14, p<0.0001$ (see Table 2). There were no differences in the numbers of animals responding or displaying seminal emission between treatments.

The results of the present study demonstrate that systemic administration of the DA antagonist HAL impairs several measures of penile reflexes. In contrast, a 100 μg/kg dose of the DA agonist APO facilitated penile reflexes in Experiment II. This dose of APO blocked the effects of HAL on reflex latency and number of erections. These results suggest that the effects of APO and HAL on penile reflexes are pharmacologically specific to the DA receptor. The administration of 100 μg/kg APO did not antagonize all of the effects of 300 μg/kg HAL, possibly due to an insufficient dose of agonist in relation to antagonist.

The facilitation of seminal emission by 100 μg/kg APO was antagonized by HAL, but not DOM, suggesting that actions on CNS DA receptors were responsible for this effect. A central site of action is also implicated in the effects of DA agents on penile reflexes, since HAL inhibited reflexes in this study, whereas DOM did not in previous work.

TABLE 2

THE EFFECTS OF SYSTEMIC ADMINISTRATION OF APOMORPHINE (100 μg/kg), HALOPERIDOL (300 μg/kg), AND DOMPERIDONE (1.0 mg/kg) ON PENILE REFLEXES

	Vehicle	APO	HAL	HAL+APO	DOM+APO
RT	54.44‡	55.48‡	38.41*	44.04	51.52
	±5.67	±4.16	±3.92	±4.81	±4.38
CT	11.70	12.63	9.63§	10.52	11.85
	±1.00	±0.85	±1.00	±1.06	±0.79
ET	38.52	38.22	27.56*	32.56	36.07
	±3.98	±2.51	±2.73	±3.36	±2.93
E2	19.44	20.93	14.52*	16.48	19.74
	±1.95	±1.74	±1.52	±2.09	±2.01
FT	15.93‡	17.26‡	10.85*	11.48	15.00‡
	±2.01	±2.18	±1.65	±2.06	±2.08
FF	4.04	7.63†	3.11	3.44	4.30
	±0.93	±1.50	±0.80	±0.92	±1.02

Values are the means ± S.E.M. for significantly affected variables. RT, total number of reflexes; CT, total number of clusters; ET, total number of erections; E2, number of E2s; FT, total number of flips; FF, number of full flips.

*$p<0.05$ relative to each treatment except for HAL+APO, †$p<0.05$ relative to each treatment, ‡$p<0.05$ relative to HAL+APO, §$p<0.05$ relative to APO.

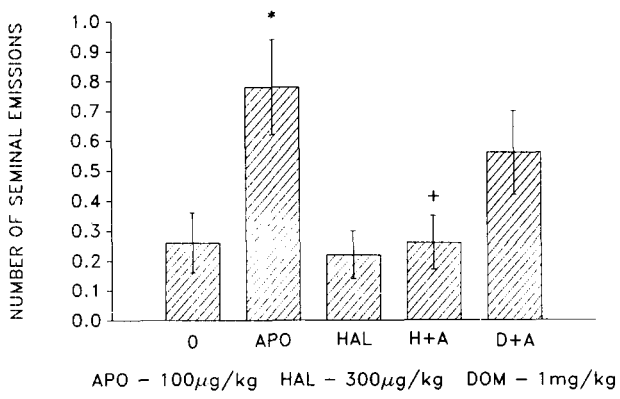

FIG. 2. Effects of IP administration of vehicle (0), apomorphine (APO), haloperidol (HAL), haloperidol followed by apomorphine (H+A), and domperidone followed by apomorphine (D+A) on the number of seminal emissions (means±S.E.M.). *$p<0.05$ relative to all treatments except for D+A. +$p<0.05$ relative to APO.

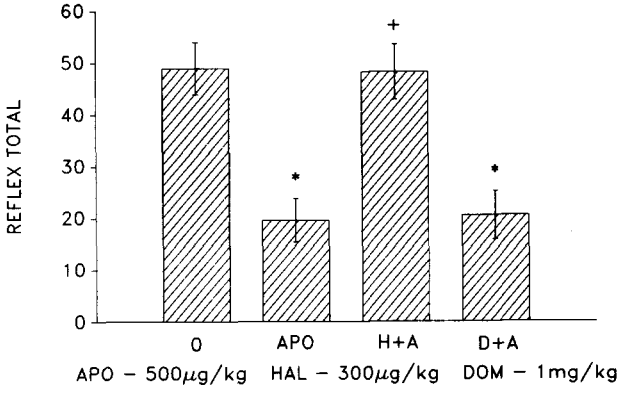

FIG. 3. Effects of IP administration of vehicle (0), apomorphine (APO), haloperidol followed by apomorphine (H+A), and domperidone followed by apomorphine (D+A) on the total number of reflexes (means±S.E.M.). *$p<0.05$ relative to 0 and H+A. +$p<0.05$ relative to APO and D+A.

In general, the results with DOM plus APO paralleled the results with APO alone in the present study. DOM did block APO's facilitation of full flips. However, this result may have been a random occurrence, since it is unclear how actions on peripheral DA receptors (located on blood vessels and postganglionic sympathetic nerve terminals; see [13]) would result in changes in a reflex regulated by striated muscles.

EXPERIMENT IV

This experiment examined the relative abilities of HAL and DOM to block the inhibition of penile reflexes produced by systemic administration of 500 μg/kg APO. It was hypothesized that administration of HAL, but not DOM, would block APO's effects.

METHOD

Twenty-three males from Experiment III were used. Rats received vehicle, 500 μg/kg APO, HAL (300 μg/kg) plus APO, and DOM (1.0 mg/kg) plus APO, on separate, counterbalanced tests spaced five or six days apart. Drug preparation and injection times were the same as in Experiment III.

RESULTS AND DISCUSSION

There were no differences in the percentages of animals

TABLE 3

THE EFFECTS OF SYSTEMIC ADMINISTRATION OF HALOPERIDOL AND DOMPERIDONE ON 500 μg/kg APOMORPHINE-INDUCED INHIBITION OF PENILE REFLEXES

	Vehicle	APO	HAL+APO	DOM+APO
CT	11.52 ± 1.23	5.13 ± 1.13*	11.30 ± 1.17†	5.09 ± 0.94*
ET	35.26 ± 3.65	14.30 ± 3.13*	35.74 ± 3.87†	14.26 ± 3.50*
E1	15.83 ± 2.26	6.39 ± 1.56*	11.17 ± 1.50†	7.09 ± 1.71*
E2	16.74 ± 1.89	6.61 ± 1.76*	22.35 ± 2.55†	6.83 ± 1.88*
FT	13.61 ± 2.00	5.26 ± 1.39*	12.39 ± 1.86†	6.22 ± 1.46*
PF	10.57 ± 1.67	4.00 ± 1.11*	9.65 ± 1.33†	5.74 ± 1.44*
UP	14.09 ± 1.70	5.26 ± 1.32*	11.39 ± 0.92†	4.65 ± 1.16*
ICI	182.16 ± 59.48	412.49 ± 67.27*	152.31 ± 49.69†	334.23 ± 55.80*

Values are the means ± S.E.M. CT, total number of clusters; ET, total number of erections; E1, number of E1s; E2, number of E2s; FT, total number of flips; PF, number of partial flips; UP, number of "ups"; ICI, intercluster interval (sec).
*$p<0.05$ relative to vehicle, †$p<0.05$ relative to APO.

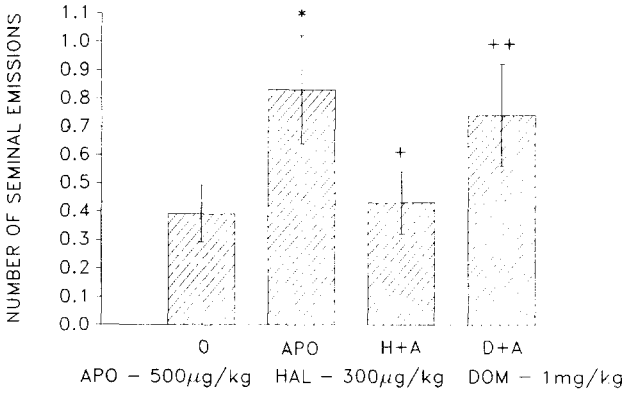

FIG. 4. Effects of IP administration of vehicle (0), apomorphine (APO), haloperidol followed by apomorphine (H+A), and domperidone followed by apomorphine (D+A) on the number of seminal emissions (means±S.E.M.). *$p<0.02$ relative to 0. +$0.05<p<0.10$ relative to APO. ++$0.05<p<0.10$ relative to 0.

responding or displaying seminal emission between treatments. All effects produced by APO administration were blocked by pretreatment with HAL, but not DOM. These effects included decreases in: the total number of reflexes, $F(3,66)=11.21$, $p<0.001$ (see Fig. 3), the number of clusters, $F(3,66)=11.25$, $p<0.001$, the number of erections, $F(3,66)=11.78$, $p<0.001$, the number of flips, $F(3,66)=6.40$, $p<0.001$, and the number of "up" movements of the penis, $F(3,66)=12.88$, $p<0.001$ (see Table 3). Since the number of "down" movements in a test is almost always equal to the number of "ups," this measure was not analyzed separately.

Among erections, the number of E1s, $F(3,66)=6.48$, $p<0.001$, and E2s, $F(3,66)=14.28$, $p<0.001$, were reduced by APO (see Table 3). Among flips, the number of partial flips was decreased, $F(3,66)=5.32$, $p<0.005$ (see Table 3). The intercluster interval was also lengthened, $F(3,66)=4.82$, $p<0.005$ (see Table 3).

APO increased the number of seminal emissions relative to vehicle, $t(22)=2.65$, $p<0.02$ (see Fig. 4). There was a trend towards blockade of this effect by HAL [APO relative to HAL plus APO: $t(22)=1.74$, $0.05<p<0.01$; HAL plus APO relative to vehicle: $t(22)=0.3$, ns], but not by DOM [APO relative to DOM plus APO: $t(22)=0.38$, ns; DOM plus APO relative to vehicle: $t(22)=1.78$, $0.05<p<0.1$] (see Fig. 4).

The administration of 500 μg/kg APO greatly inhibited the display of penile reflexes while facilitating seminal emission. These effects appear to be pharmacologically specific to the DA receptor, since they were blocked by HAL pretreatment. It is noteworthy that the administration of either 500 μg/kg APO in the present study or HAL in the previous study inhibited penile reflexes, while the combination of the two resulted in a mutual antagonism of each other's effects. The present results also suggest that APO alters genital responses by acting on the CNS, since DOM injections did not antagonize APO's effects.

GENERAL DISCUSSION

APO administration had a biphasic effect on penile reflexes in the supine rat, with a moderate dose facilitating, and a higher dose impairing, penile reflexes. In contrast to this biphasic effect on reflexes, APO injections facilitated seminal emission at both doses. These effects appear to be pharmacologically specific to CNS DA receptors since HAL, but not DOM, either blocked the actions of APO or produced effects opposite to those found following APO administration.

The effects of APO on reflexes in the restrained, supine rat appear to correspond generally to the results obtained by others in the freely moving rat [3, 11, 20]. However, a higher dose of APO (1.0 mg/kg SC) was required to inhibit erection in those previous studies, relative to the present ones (where 500 μg/kg APO IP inhibited erection). This discrepancy may reflect strain and/or route of drug administration differences, or the use of different behavioral scoring criteria. Regarding this latter possibility, studies of the effects of APO in the freely moving rat did not discriminate between erection independent of seminal emission, and seminal emission accompanied by erection, whereas the present studies did. Other investigators have found that administration of RDS-127 (a DA and 5-HT agonist) induced seminal emission in the freely moving rat, while erection independent of seminal emission was not seen [21]. As previously mentioned, this same agent facilitated seminal emission and inhibited penile

reflexes in the restrained rat [21]. Since 500 μg/kg APO induced seminal emission, while inhibiting erection in the present experiments, it is possible that previous studies in the freely moving rat reported a facilitation of "erection" at this dose when, in fact, seminal emission, accompanied by erection, was enhanced.

The perineal muscle excision studies of Sachs [19] demonstrated that erection is predominantly a vascular phenomenon in the rat, whereas flips and the intense flaring of the tip of the glans seen during cups result primarily from activity in the striated perineal musculature. Both erections and flips were affected by APO and HAL, but not DOM, administration in the present studies, suggesting that CNS DA receptors regulate the activity of both the autonomic and somatic motor components that produce penile reflexes.

The biphasic dose response curve for APO's effects on penile reflexes is probably not a result of differential stimulation of pre- and postsynaptic receptors by lower and higher doses (respectively), as others have suggested [10, 11, 20]. If a preferential stimulation of DA autoreceptors, and hence a resultant decrease in DA neurotransmission, mediated the facilitative effects of lower doses of APO, then 300 μg/kg HAL (a dose that blocks postsynaptic receptors) should have facilitated penile reflexes in the present study. In fact, the opposite occurred, namely an impairment of reflex activity. This conclusion corresponds to results obtained in other previous studies, suggesting a postsynaptic action of APO on erection in the freely moving rat [3,11]. For example, (+)3-PPP, a DA pre- and postsynaptic receptor agonist, facilitated erection, whereas (−)3-PPP, a DA presynaptic agonist and postsynaptic antagonist, did not affect erection [11].

It is possible that APO's biphasic effects on penile reflexes are due to differential stimulation of anatomically separate populations of DA receptors by lower and higher doses. Such a situation could result if, for example, a CNS area regulating the inhibition of reflexes had poorer access to the ventricular and/or vascular circulatory systems, relative to an area that promotes the display of reflexes. This hypothesis is supported by our recent findings that microinjections of APO into the medial preoptic area facilitated several measures of penile reflex ability, whereas injections into the lumbosacral subarachnoid space inhibited reflexes (unpublished observations).

In contrast to the biphasic effect on penile reflexes, APO had a monophasic effect on seminal emission. Since the dose response curves for these two behaviors differ, experimentally separable populations of DA receptors may regulate penile reflexes and seminal emission. Supporting this suggestion, previous pharmacological studies have shown that these two behaviors are often inversely related [5, 15, 16, 20]. Additionally, we have recently found that microinjections of APO into the paraventricular nucleus of the hypothalamus increased the incidence of seminal emission, whereas seminal emission was not affected by injections into either the medial preoptic area or the lubosacral subarachnoid space (unpublished observations).

Previous pharmacological studies have shown that treatments that facilitate ejaculation in copula, often facilitate seminal emission and inhibit penile reflexes ex copula [5, 6, 21]. Corresponding to these results, the only dose of APO that reduced the number of intromissions required for ejaculation (500 μg/kg), also facilitated seminal emission and inhibited penile reflexes in the present study. It has been suggested that the mechanism that regulates seminal emission ex copula also contributes to the determination of the male's ejaculatory threshold in copula [7]. This suggestion, as well as the possibility that a reduction in the number of intromissions is related to an impairment of penile reflex ability, remains to be tested further. If there is a relationship between genital responses ex copula and copulatory behavior, it is not always consistent. For example, administration of 8-OH-DPAT reduced ejaculatory threshold [2], while inhibiting seminal emission and erection [8] in the rat. Furthermore, in the present study 100 μg/kg APO facilitated seminal emission and penile reflexes, but did not affect copulatory behavior. These results suggest that neurotransmitter influences on genital responses and copulatory behavior can be experimentally dissociated.

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