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The effects of intracranial administration of the dopamine agonist apomorphine on penile reflexes and seminal emission in the rat

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Previous studies employing systemic administration of the dopamine agonist apomorphine have shown that the dose response curves for apomorphine's effects on penile reflexes and seminal emission differ, suggesting that experimentally separable populations of dopamine receptors regulate these two responses. The present experiments examined the locations of central nervous system DA receptors mediating genital responses in the restrained, supine rat by injecting apomorphine into the medial preoptic area and the paraventricular nucleus through chronic, indwelling cannulae. Medial preoptic area injections facilitated penile reflexes, but not seminal emission, while paraventricular injections facilitated seminal emission. These results suggest that systemically administered apomorphine may facilitate penile reflexes by acting on the medial preoptic area and may enhance seminal emission by acting on the paraventricular nucleus.

INTRODUCTION

Systemic administration of the dopamine (DA) agonist apomorphine (APO) produces a biphasic effect on penile reflexes. Injections of moderate doses facilitate penile responses (including erection) in the rat, monkey and human[1,8,16,17,25,30,34], whereas higher doses impair such responses in the rat[1,25]. In contrast, seminal emission is affected in a monophasic fashion (facilitated) by systemic APO administration[25]. These effects are blocked by pretreatment with centrally acting DA antagonists (e.g. haloperidol), but not by domperidone, a DA antagonist that does not cross the blood–brain barrier[1,8]. These results suggest that central nervous system (CNS) dopamine receptors are involved in the regulation of genital responses. Furthermore, since the dose–response curves for APO's effects on penile reflexes and seminal emission differ, experimentally separable populations of CNS dopamine receptors may regulate these two behaviors[25].

One site where APO may act to facilitate penile reflexes is the medial preoptic area (MPOA). Lesions of this area abolish or severely impair male copulatory behavior in all species examined to date (reviewed in Hart and Leedy[10]). Electrical stimulation of the MPOA facilitates copulation in the male rat and monkey[19,24,28]. Erection is thought to be induced primarily by activity in parasympathetic fibers (reviewed in Benson[2]), and electrical stimulation of the MPOA results in responses indicative of parasympathetic activation, including erection[11,12,18,31]. This area receives a small projection from the incertohypothalamic DA system, which originates in cell group A14 of the periventricular hypothalamus[4]. We have shown that microinjections of APO into this area facilitate male copulatory performance in tests with a female[14], whereas MPOA injections of

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the dopamine antagonist *cis*-flupenthixol block the actions of apomorphine and, at higher doses, impair male sexual behavior[26a].

One site where systemically administered APO may act to facilitate seminal emission is the paraventricular nucleus (PVN) of the hypothalamus. Seminal emission is induced by activity in sympathetic fibers (reviewed in Kimura[15]) and electrical stimulation of the PVN produces responses indicative of sympathetic activation[11,12]. Oxytocinergic neurons with cell bodies in the PVN have been shown to project directly to the dorsal commissural nucleus in the upper lumbar cord[37]. This spinal nucleus is the origin of the hypogastric sympathetic nerve input to the genitalia[9]. The PVN is innervated by periventricular catecholaminergic neurons[3] and some of these fibers appear to be dopaminergic[3,7]. Evidence indicates that this area also contains DA cell bodies[7,37]. Recently, Melis, Argiolas, and Gessa[23] have shown that injections of APO into the PVN enhanced erection in the freely moving rat. It is unclear, however, whether seminal emission was affected by such injections.

The aim of the present experiments was to investigate the effects of microinjections of APO into the MPOA and the PVN on genital responses in the restrained, supine rat. Use of this behavioral testing paradigm allows one to readily distinguish between types of penile reflexes (including erection) and seminal emission. It was hypothesized that penile reflexes would be facilitated by intra-MPOA injections and that seminal emission would be enhanced after PVN administration.

MATERIALS AND METHODS

Subjects

Adult male Long–Evans rats, obtained from Blue Spruce Farms (Altamont, NY), and weighing 350–400 g, were used. Animals were housed singly in a temperature- and humidity-controlled environment, with food and water available ad libitum. A 14:10 light:dark cycle was in effect, with lights off at 11.00 h. Animals were handled daily so that microinjections could be accomplished without anesthesia. All behavioral testing was done during the dark period, between 11.00 and 17.00 h.

Surgery and cannulae

Implantation of cannulae was performed under sodium pentobarbital anesthesia (55 mg/kg) using a Kopf stereotaxic frame. Each animal received one guide cannula, ending 1 mm above the structure of interest, with coordinates chosen from the atlas of Pellegrino, Pellegrino, and Cushman[27] (incisor bar 5 mm above the interaural line). Briefly, a small hole was drilled in the skull above the appropriate structure and a cannula was lowered to the appropriate depth. Four screws were inserted into the skull surrounding the cannula, which provided anchorage for an assembly constructed of dental cement that surrounded both the screws and the cannula.

Cannulae were cut from 23 gauge thin-wall stainless steel tubing, and were sanded on a rotary disk to an appropriate length. An obturator of the same length, constructed from 27 gauge stainless steel tubing, prevented entry of foreign material into the cannula. A collar of 23 gauge tubing was crimped to the end of the obturator, to prevent descent further than the end of the guide cannula. A piece of polyethylene tubing (PE-50) surrounded and extended slightly from the collar to prevent loss of the obturator. An injection cannula was constructed from 27 gauge stainless steel tubing and, during drug injections, protruded 1 mm beyond the edge of the guide cannula in the brain. The other end of the injection cannula was inserted into a 1 m length of polyethylene tubing (PE-20), which, in turn, was connected to a 1 ml syringe during drug injections. At this time, the syringe was held in a Harvard microinfusion pump.

At the time of cannula implantation, each male's suspensory ligament was excised. This ligament is attached bilaterally to the base of the penis underneath the skin. Severing the ligament facilitated maintained exposure of the glans penis from the penile sheath.

Drugs

Apomorphine HCl (Sigma) was dissolved immediately before administration in sterile saline with 0.2% ascorbic acid to prevent oxidation.

Procedures

Males were given 3 screening tests for penile reflexes. Only those males that displayed reflexes on

two out of 3 screening tests were used. One week following surgery, males were given a single postoperative baseline test. Thereafter, tests following intracranial injections were given at one-week intervals. At the time of drug administration, the obturator was replaced with the injection cannula. The injection volume was 0.5 μl delivered over a 30 s period. In order to minimize diffusion back up the guide cannula, the injection cannula was left in place for 30 s following drug administration, and then replaced with the obturator. Behavioral testing occurred immediately following injection.

During behavioral testing, each rat was restrained in a supine position in a metal restraining device (circumference, 8.5 cm 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 occurred within 5 to 10 min following exposure of the glans. The resultant responses occurred in discrete clusters, separated by 15 s or longer. Within a cluster, usually 2 to 6 reflexes were displayed, with a duration from 0.5 to 2 s for each reflex. These reflexes consisted of erections (engorgement of the glans), flips (anteroflexions of the penis), and cups (intense erections in which the tip of the glans flared dramatically so that the diameter of the tip was greater than that of the base of the glans). On rare occasions in untreated animals, seminal emission was displayed during such tests.

A test lasted 15 min from the first reflex or 20 min if no reflexes occurred. During tests, the time of the first reflex and the numbers of erections, flips, cups, and seminal emissions 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.

All experiments employed counterbalanced, repeated measure designs. Data from males that failed to respond on each experimental trial were excluded from statistical analyses. Log transforms were performed on latency data before parametric statistics were employed.

Histology

Following each experiment, males were decapitated and their brains were removed and frozen in an American Optical cryostat. Forty-μm sections were cut, mounted on glass slides, stained with Cresyl violet, and examined with a projection magnifier. Only those animals with a histologically verifiable cannula in the relevant structure were included in data analyses.

Experiment 1. Effects on genital responses of intra-MPOA APO.

Twenty-six males had cannulae in the left MPOA (AP, 2.4; ML, 0.2; DV −7.0). The subjects were randomly divided into two independent groups. One group received vehicle and 0.1 μg APO on separate tests while the second group received vehicle and 1.0 μg APO on separate tests. Subsequently, 7 animals were randomly chosen from the first group and received vehicle and 1.0 μg APO on two separate counterbalanced tests in order to increase the number of animals in this treatment condition. Six other animals from the first group and all animals in the second group then received counterbalanced treatments with vehicle and 2.0 μg APO. Statistical analyses (2-factor ANOVAS) revealed that prior drug treatment had no effect on subsequent performance under a different treatment condition (i.e. there was no main effect for prior treatment condition and no interaction between prior and subsequent treatment). The Student's *t*-test for dependent groups was then used to statistically compare each drug dose with its relevant vehicle control.

Experiment 2. Effects on genital responses of intra-PVN APO.

Eighteen males had cannulae in the left PVN (AP 0.4, ML 0.4, DV −7.3). Animals received vehicle, 0.1 μg, and 1.0 μg APO on separate tests. One-way repeated ANOVAS, followed by Newman–Keuls posthoc comparisons, were used to analyze the data. Nominal data were analyzed by Cochran's *Q* tests, followed by McNemar posthoc comparisons.

RESULTS

Experiment 1

Intra-MPOA APO administration facilitated several measures of penile reflex potential. Seminal emission was not affected (see Table I). Both the 1.0

TABLE I

The effects of apomorphine microinjections into the medial preoptic area on genital responses

Values are the means ± S.E.M. RT, total number of reflexes; CT, total number of clusters; ET, total number of erections; E3, number of cups; FT, total number of flips; SE, number of seminal emissions.

	Vehicle	*0.1 μg*	*Vehicle*	*1.0 μg*	*Vehicle*	*2.0 μg*
RT	53.55 ± 8.01	48.09 ± 8.55	46.40 ± 4.49	64.45 ± 4.74**	33.79 ± 5.62	54.95 ± 6.02***
CT	12.36 ± 1.32	10.73 ± 1.80	10.85 ± 0.95	13.20 ± 0.89*	7.68 ± 1.11	12.37 ± 1.20***
ET	39.18 ± 4.47	36.09 ± 6.47	35.10 ± 3.23	47.30 ± 3.57**	26.63 ± 4.35	40.00 ± 3.68***
CUP	1.00 ± 0.60	1.45 ± 0.70	0.40 ± 0.27	0.75 ± 0.23	0.32 ± 0.15	1.26 ± 0.44*
FT	14.36 ± 3.79	11.27 ± 2.95	11.30 ± 1.94	17.10 ± 1.88*	7.05 ± 1.66	14.79 ± 2.94**
SE	0.27 ± 0.14	0.36 ± 0.15	0.50 ± 0.17	0.75 ± 0.14	0.58 ± 0.14	0.74 ± 0.17

*$P < 0.05$; **$P < 0.02$; ***$P < 0.01$ (all relative to the preceding vehicle value).

and 2.0 μg doses reduced the latency to the first reflex (1.0 μg: $t_{19} = 2.81$, $P < 0.02$; 2.0 μg: $t_{18} = 2.81$, $P < 0.02$; see Fig. 1). The total number of reflexes was increased (1.0 μg: $t_{19} = 2.82$, $P < 0.02$; 2.0 μg: $t_{18} = 3.36$, $P < 0.01$), and there was a corresponding increase in the number of clusters (1.0 μg: $t_{19} = 2.32$, $P < 0.05$; 2.0 μg: $t_{18} = 3.12$, $P < 0.01$) (see Table I). The increased number of reflexes was due to an increase in the numbers of both erections (1.0 μg: $t_{19} = 2.83$, $P < 0.02$; 2.0 μg: $t_{18} = 3.39$, $P < 0.01$) and flips (1.0 μg: $t_{19} = 2.26$, $P < 0.05$; 2.0 μg: $t_{18} = 2.76$, $P < 0.02$) (see Table I). Contributing to the increase in the number of erections was an increase in the number of cups by the 2.0 μg dose ($t_{18} = 2.14$, $P < 0.05$; see Table I). The percentage of animals displaying reflexes was not affected.

Experiment 2

Intra-PVN APO administration facilitated seminal emission and erection, but did not affect other measures of penile reflexes (e.g. flips and cups; see Table II). Both doses of APO increased the incidence of seminal emission ($F_{2,34} = 7.53$, $P < 0.005$; see Fig. 2) and the percentage of males displaying seminal emission (vehicle: 11.11%; 0.1 μg: 50.00%; 1.0 μg: 61.11%; $Q_2 = 10.31$, $P < 0.01$). The 1.0 μg dose increased the total number of reflexes ($F_{2,34} = 3.84$, $P < 0.05$), and there was a corresponding increase in the number of clusters ($F_{2,34} = 3.74$, $P < 0.05$) (see Table II). The increase seen in reflex number following the 1.0 μg dose was due to an increase in the number of erections ($F_{2,34} = 8.83$, $P < 0.001$; see Table II). Many of these erections appeared to accompany seminal emission. When these erections (i.e. those within a reflex cluster

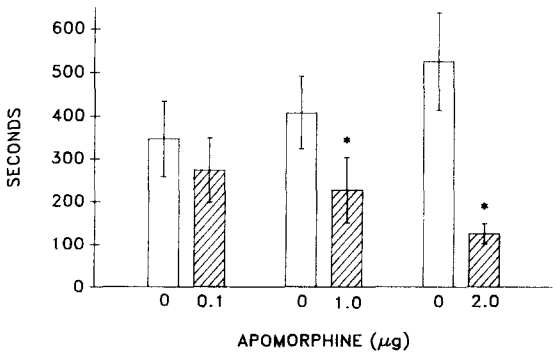

Fig. 1. Effects of microinjections of apomorphine into the medial preoptic area on the latency (s) to the first penile reflex (means ± S.E.M.). *$P < 0.02$ relative to 0 (vehicle).

TABLE II

The effects of apomorphine injections into the paraventricular nucleus on penile reflexes

Values are the means ± S.E.M. RL, latency to the first reflex (s); RT, total number of reflexes; CT, total number of clusters; ET, total number of erections; CUP, number of cups; FT, total number of flips.

	Vehicle	*0.1 μg*	*1.0 μg*
RL	139.78 ± 65.47	145.17 ± 68.00	42.44 ± 10.92
RT	38.78 ± 5.75	37.44 ± 3.83^{+}	49.44 ± 4.12*
CT	10.11 ± 1.14	11.50 ± 1.05	12.61 ± 0.96*
ET	26.89 ± 3.33	28.89 ± 2.46^{++}	38.94 ± 3.08**
CUP	0.44 ± 0.25	0.22 ± 0.13	0.17 ± 0.17
FT	11.89 ± 2.80	8.39 ± 1.79	10.50 ± 1.82

*$P < 0.05$ relative to vehicle, **$P < 0.01$ relative to vehicle, $^{+}P < 0.05$ relative to 1.0 μg, $^{++}P < 0.01$ relative to 1.0 μg.

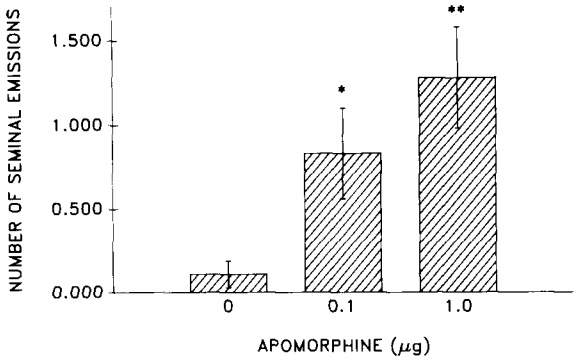

Fig. 2. Effects of microinjections of apomorphine into the paraventricular nucleus on the number of seminal emissions (means ± S.E.M.). $^{*}P < 0.05$; $^{**}P < 0.01$. Both relative to 0 (vehicle).

containing seminal emission) were excluded, the effect on erection number was diminished but still statistically significant (vehicle: 26.67; 0.1 μg: 27.06; 1.0 μg: 34.78; $F_{2,34} = 4.01$, $P < 0.05$). Intra-PVN APO administration did not affect the percentages of animals displaying penile reflexes.

DISCUSSION

The present results demonstrate that administration of the dopamine agonist APO into the MPOA facilitates several measures of penile reflex ability. Following APO injections, the latency to the first reflex was reduced and the numbers of erections, flips, and cups were increased. Thus, one site where moderate doses of systemically administered APO may act to facilitate penile reflexes is the MPOA. While seminal emission was not affected by intra-MPOA APO injections, this response was facilitated following APO administration into the PVN. Thus, systemically administered APO may act on the PVN to induce seminal emission.

Intra-PVN APO injections also increased the number of erections. It is not clear whether this represents a direct effect on erectile mechanisms, or an indirect effect resulting from a general facilitation of an ejaculatory pattern. During genital response tests in the supine rat, seminal emission is usually accompanied by numerous, extremely rapid erections. Thus, PVN APO injections could have induced an ejaculatory pattern consisting of seminal emission accompanied by erection. Consistent with this possibility is the recent description of the coital reflex in male rats by McKenna and colleagues[22]. This reflex, consisting of penile erection, perineal muscle contractions, and expulsion of urethral contents, was evoked by mechanical stimulation of the urethra in the spinally transected rat. These investigators hypothesized that this ejaculatory reflex is normally elicited when seminal fluids stimulate the urethra. Thus, it is possible that intra-PVN APO injections resulted in the movement of seminal fluids, which subsequently evoked a reflexive pattern including erection. When those erections temporally associated with seminal emission were omitted from data analyses, the effect on erection number was diminished but not abolished. Thus, while it is possible that at least some of the erections seen after PVN APO injections were secondary to an enhancement of ejaculatory mechanisms, it is also possible that such injections had a direct effect on erection per se.

It should be noted that although intra-PVN APO administration increased the total number of reflexes similar to MPOA injections, this increase reflected an increased number of erections in the case of the PVN but an increase in erections, flips, and cups in the MPOA. Thus, in actuality, the only similarity between MPOA and PVN APO administration was that both treatments increased the number of erections.

One must consider whether APO's effects in the present study are anatomically specific to either the MPOA or PVN since both structures are in close proximity to the third ventricle. In general, a different pattern of results was obtained when APO was administered into the MPOA, as compared to the PVN. This finding suggests that the drug did not exert its effects by diffusing into the cerebrospinal fluid circulatory system and thereby acting on other sites that presumably would be affected by either MPOA or PVN administration. Furthermore, Melis, Argiolas, and Gessa[23] found that erection was not affected following APO injections into the ventromedial or dorsomedial hypothalamic nuclei, the preoptic area, the caudate nucleus, the nucleus accumbens, or the substantia nigra. Their lack of effect of preoptic area injections does not conflict with the present results since the preoptic area is lateral (stereotaxic coordinates = 1.5 mm lateral to bregma) to the medial preoptic area (coordinates =

0.2 mm lateral). Indeed, it suggests considerable anatomical specificity of these effects. In addition, we have recently found that intrathecal APO administration inhibited erection but did not affect seminal emission[26]. Thus, the evidence suggests that the observed results are localized to the MPOA and the PVN. It is possible that dopamine receptors in other, as of yet unexplored, brain areas may also contribute to the CNS regulation of genital responses.

Another consideration is whether the present findings are pharmacologically specific to the dopamine receptor. Melis et al.[23] found that the effect on erection produced by APO injections into the PVN was blocked by pretreatment with the dopamine antagonists haloperidol and sulpiride. This result suggests that APO affected genital responses by acting on the DA receptor, rather than acting non-specifically. As noted, we have shown previously that the facilitation of male copulatory performance (in tests with a female) produced by intra-MPOA APO injections was blocked by *cis*-flupenthixol administration[26]. Recent unpublished findings in our laboratory indicate that injections of *cis*-flupenthixol into the MPOA impair penile reflexes in the restrained, supine rat, providing further evidence that MPOA DA receptors regulate both in and ex copula performance.

Sachs has provided data indicating that flips and cups, as well as erections, are utilized during copulation in the rat[33]. His studies also demonstrated that different peripheral mechanisms may subserve these different reflexes. Removal of the ischiocavernosus perineal muscle prevented the display of flips ex copula and severely impaired the ability to intromit in copula. Excision of the bulbocavernosus muscle eliminated cups and prevented the impregnation of females, perhaps because a properly formed seminal plug could not be deposited around the cervix. Thus, flips and cups appear to be induced primarily by activity in the striated perineal muscles. Erection was not affected by excision of the perineal muscles, suggesting that erection is primarily a function of autonomic input to the penile vasculature.

The studies by Sachs utilizing the rat support the findings of others demonstrating that erection results primarily from vascular changes induced by parasympathetic activity (reviewed in Benson[2]). Since previous reports have indicated a role for the MPOA in the control of parasympathetic processes (including erection)[11,12,18,31], and since erection was enhanced in the present study following MPOA APO injections, MPOA DA receptors may regulate the activity of the parasympathetic fibers that induce erection. Furthermore, since flips and cups were also affected by such injections, MPOA DA receptors may affect the activity of the somatic neurons that innervate the perineal muscles. While MPOA efferents do not appear to project directly to spinal autonomic nuclei, they do innervate other brain areas implicated in the control of autonomic function, including brainstem autonomic nuclei[5,13,36]. PVN DA receptors may influence the activity of sympathetic fibers regulating seminal emission, possibly by regulating the activity of neurons that project directly from the PVN to the sympathetic dorsal commissural nucleus[37].

Previous research indicates that the neural mechanisms regulating male copulatory performance are relatively independent from those regulating sexual arousal[32]. Our previous results have shown that MPOA DA receptors primarily regulate male copulatory performance, rather than arousal[14,26a]. For example, the rate of copulation (a measure of copulatory performance) was enhanced following MPOA APO injections, while the latency to the first mount (a measure of sexual arousal) was not affected[14]. The present findings demonstrate that another aspect of copulatory performance, the ability to display reflexive penile responses, was enhanced following MPOA APO administration.

The present results demonstrate differential effects of intracranial APO administration on penile reflexes and seminal emission as a function of the injection site. Previous studies employing systemically administered APO found different dose–response curves for these two responses[25]. Thus, the CNS DA receptors subserving penile reflexes and seminal emission are experimentally separable and may be located in different brain areas, namely the MPOA and the PVN, respectively. This hypothesized dissociation of the regulation of penile reflexes and seminal emission is consistent with previous pharmacological studies demonstrating that these two responses are usually not affected in

parallel, and, in fact, are often inversely related[6,20,21,35]. Through their reciprocal connections[5,36] and their connections to other brain areas, the MPOA and PVN may interact both with each other and with other structures during copulation to coordinate genital responses with other aspects of male sexual behavior.

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