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Influence of the Estrous Cycle and Estradiol on the Behavioral Effects of Amphetamine and Apomorphine in Rats

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DÍAZ-VÉLIZ, G., R. BAEZA, F. BENAVENTE, N. DUSSAUBAT AND S. MORA. *Influence of the estrous cycle and estradiol on the behavioral effects of amphetamine and apomorphine in rats.* PHARMACOL BIOCHEM BEHAV **49**(4) 819–825, 1994. – This experiment was designed to investigate the influence of hormonal status of the rat on the effects of two doses of an indirect-acting dopamine agonist (amphetamine 0.25 and 1.0 mg/kg, IP) and a direct-acting dopamine agonist (apomorphine 62.5 and 250 μg/kg, SC) on the acquisition of conditioning avoidance responses (CARs) and the performance of some spontaneous behaviors. Active conditioned avoidance was improved by amphetamine in all the groups except in females at diestrus; apomorphine improved this response only in females at estrus and in ovariectomized rats after estradiol replacement, but the avoidance response was deteriorated in males and females at diestrus and after ovariectomy without estradiol replacement. Both dopaminergic drugs had contrasting effects on motor activity, number of rearings, and number of head shakes according to the hormonal status of the rat. Only the time spent in grooming behavior decreased after the treatment with both dopamine agonists in all of the five groups studied. These results provided behavioral evidence for the hypothesis that dopaminergic activity in the CNS is affected distinctively by modifications in the sexual hormone status (gender, estrous cycle, ovariectomy, and estradiol replacement). Relationships between ovarian hormones and dopaminergic system are discussed.

Dopaminergic systems Amphetamine Apomorphine Conditioned avoidance responses Estradiol Ovariectomy

REPORTS from our laboratory have demonstrated that the acquisition of conditioned avoidance responses is influenced by the sexual hormone changes that occur during the estrous cycle of the rat. This response is improved at diestrus but it is deteriorated at estrus and metestrus (7). Recently, we found that ovariectomy enhances the performance of avoidance and that systemic administration of a single dose of estradiol benzoate (EB 2 μg) reduces this behavior (8). Active avoidance conditioning has been related to the activity of central dopaminergic systems. Moreover, the inhibition of conditioned behavior, without affecting escape responding, is considered as a characteristic action of drugs that block dopaminergic transmission (1). This evidence led us to suggest that the changes in conditioning across the estrous cycle and the effects of the administration of estradiol are mediated, at least partially, by an interaction with the dopaminergic systems.

Several reports indicate that female sex hormones can have direct consequences for the action of drugs that influence dopaminergic transmission (20). Nevertheless, reports are somewhat controversial, and increases as well as decreases of dopaminergic function by estrogens have been reported. Whereas a stimulatory role for dopamine in the regulation of female sexual behavior has been proposed (14,17), other investigators have reported that amphetamine (22) and apomorphine (11) inhibit lordosis behavior in ovariectomized rats treated with estrogen. In addition, pimozide increases sexual receptivity in ovariectomized, estrogen-primed rats (13). Other studies have demostrated that estrogens increase apomorphine- and amphetamine-induced stereotypy in rats (5,18,19). In addition, ovariectomy decreases amphetamine- and apomorphine-induced stereotypes, whereas estradiol replacement reverses these effects in guinea pigs (28). On the contrary, other studies have shown that estradiol decreases apomorphine- and amphetamine-induced stereotypy (27,29), suggesting an antidopaminergic effect. The latter suggestion is supported by the observation that estrogen treatment of rats increases the num-

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ber of striatal dopamine receptors (10,18). In comparison with estradiol, haloperidol treatment also induces an increase in the number of estriatal dopamine receptors (9).

These various findings strongly suggest that estrogen may participate in the regulation of dopaminergic systems. The purpose of the present study was to investigate whether hormonal status (gender, estrous cycle, ovariectomy with and without EB replacement) might influence behavioral effects of dopamine agonists in the rat. We studied the behavioral effects of two moderate doses of amphetamine and of a small dose of apomorphine, acting presynaptically, and a moderate dose of apomorphine, acting postsynaptically (31).

METHOD

Animals

A total of 250 Sprague–Dawley rats (200 females and 50 males), weighing 180–200 g, were housed in groups of six per cage under a 12 L : 12 D cycle (lights were on from 0800 to 2000 h) with free access to food and tap water.

Vaginal smears were taken daily from 100 intact female rats to determine the different stages of the estrous cycle. Only rats exhibiting three or more consistent 4-day cycles were utilized. Because a previous report (7) showed great differences in the acquisition of a conditioned avoidance response between diestrous and estrous females, only these phases were considered for the pharmacological treatments.

Another group of 100 female rats was bilaterally ovariectomized under light ether anesthesia. Fourteen days after surgical removal of the ovaries, rats were randomly divided into two groups that received either estradiol benzoate (EB 2 μg/rat) or corn oil vehicle (0.2 ml/rat), injected SC in the dorsal region of the neck 48 h prior to the administration of the dopaminergic drugs.

Drugs

Rats were injected with either *d*-amphetamine sulphate (AMPH) (0.25 or 1.0 mg/kg, IP) or apomorphine hydrochloride (APO) (62.5 or 250 μg/kg, SC), 30 or 5 min before the behavioral experiments, respectively. All doses were expressed in terms of total salts. Drugs were dissolved in 0.9% saline and injected in a volume of 1 ml/kg. Control animals were injected with an equal volume of physiological saline. Although separate control groups were run for both doses of AMPH and APO, they were considered as a homogeneous group ($N = 20$) because statistical analysis of the behavioral data revealed no significant differences between them. Each animal was injected only once to avoid complications associated with multiple injections of dopaminergic drugs, and they were tested between 1000 and 1400 h.

Spontaneous Motor Activity

The animals were individually placed in a Plexiglas cage (30 × 30 × 30 cm), inside a sound-proof room. The floor of the cage was an activity platform (Lafayette Instrument Co.) connected to an electromechanical counter. Spontaneous motor activity was monitored for 30 min and, simultaneously, the following responses were recorded: number of times each animal reared, number of head shakes, and the time (in seconds) spent in grooming behavior. Each animal was observed continuously via a Sony video camera connected to a VHS tape recorder. Scores were generated from live observations, and video sequences were used for subsequent reanalysis.

Active Avoidance Conditioning

The conditioning experiments were carried out with a two-way shuttle box (Lafayette Instrument Co.) composed of two stainless steel modular testing units, which were equipped with an 18-bar insulated shock grid floor, two 28-V DC lights, and a tone generator (Mallory Sonalert 2800 Hz). Electric shocks were provided to the grid floor by a Master shock supply (Lafayette Instrument Co.). The rats were individually placed in the shuttle box and were trained over 50 trials. Each trial consisted of the presentation of a tone that after 5 s was overlapped with a 0.20-mA foot shock until the animal escaped to the opposite chamber, with a maximum shock duration of 10 s. A conditioned avoidance response (CAR) was defined as a crossing within the first 5 s (tone).

Statistical Analysis

All data were analyzed by the two-way analysis of variance (ANOVA) followed by the post hoc Newman-Keuls' multiple comparison test. A probability of 0.05 was accepted as statistically significant.

RESULTS

Conditioned Avoidance Responses (CARs)

In saline control animals (Figs. 1 and 2), the avoidance performance was similar in rats at diestrus, ovariectomized (OVX), and males. At estrus and after a single injection of EB to OVX rats, the acquisition of CARs was seriously deteriorated ($p < 0.001$ in both cases).

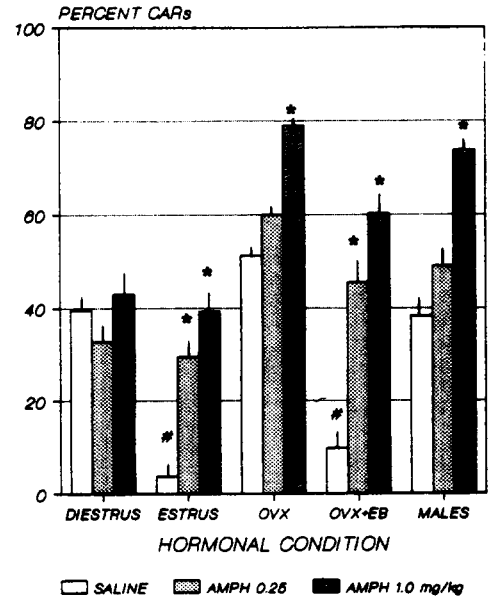

FIG. 1. Influence of hormonal condition (females at diestrus = DI, estrus = E, ovariectomized = OVX, ovariectomized with estradiol replacement = OVX + EB, and male rats) on the effects of amphetamine (AMPH) on the acquisition of conditioned avoidance responses (CARs). Each bar represents the mean ± SEM of the percentages of CARs out of 50 trials. Comparisons were made by using two-way ANOVA followed by post hoc Newman-Keuls test: $*p < 0.001$ when compared with its saline control group and $\#p < 0.001$ comparing diestrus vs. estrus or OVX vs. OVX + EB rats. The number of rats in the control group was 20 and in each drug group was 10.

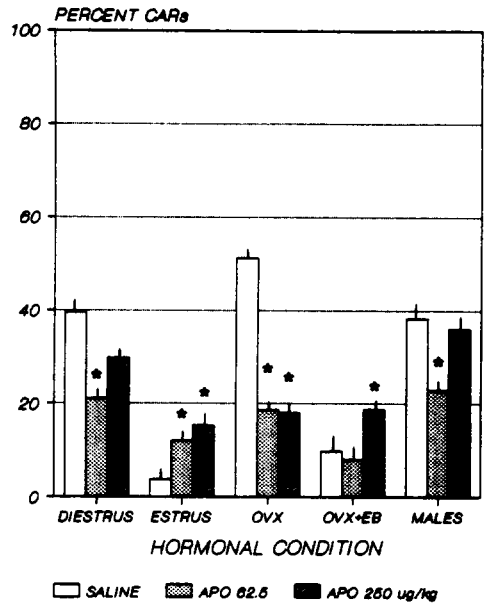

FIG. 2. Influence of hormonal condition (females at diestrus = DI, estrus = E, ovariectomized = OVX, ovariectomized with estradiol replacement = OVX + EB, and male rats) on the effects of apomorphine (APO) on the acquisition of conditioned avoidance responses (CARs). Each bar represents the mean ± SEM of the percentages of CARs out of 50 trials. Comparisons were made by using two-way ANOVA followed by post hoc Newman-Keuls test: $*p < 0.025$ when compared with its saline control group. The number of rats in the control group was 20 and in each drug group was 10.

Amphetamine

The data illustrated in Fig. 1 revealed that both doses of AMPH induced significant effects on the acquisition of CARs, $F(2, 135) = 60.02$, $p < 0.001$, and that these effects change with the hormonal condition, $F(4, 135) = 35.32$, $p < 0.01$. The interaction between these two factors was also significant, $F(8, 135) = 5.20$, $p < 0.01$. Post hoc analysis indicated that both doses of AMPH significantly enhanced the acquisition of CARs at estrus and in OVX rats with EB replacement ($p < 0.001$ in all cases). In OVX rats without EB treatment and in male rats, only AMPH 1 mg/kg significantly improved this performance ($p < 0.001$ in both cases). Both doses of AMPH failed to induce significant changes on the acquisition of CARs in the diestrus group.

Apomorphine

Figure 2 shows the effects of two doses of APO on the acquisition of CARs of female and male rats. A two-way ANOVA revealed a significant effect of APO dose on this behavior, $F(2, 135) = 10.11$, $p < 0.01$. The hormonal condition, $F(4, 135) = 26.17$, $p < 0.01$, and the interaction of dose and hormonal status, $F(8, 135) = 8.66$, $p < 0.01$, were also significant. Post hoc comparisons showed that both doses of APO significantly enhanced the acquisition of CARs during the estrous stage ($p < 0.025$) and APO 250 μg/kg improved this behavior in OVX rats treated with EB ($p < 0.025$). APO 62.5 μg/kg significantly impaired the response in diestrus and male rats ($p < 0.025$, respectively). Both doses of APO significantly decreased the CAR performance in OVX rats without EB replacement ($p < 0.001$).

Spontaneous Motor Behaviors

As in previous reports, in saline control groups significant changes in some motor responses according to their hormonal condition (Tables 1 and 2) were observed. Motor activity was lower at estrus than at diestrus ($p < 0.05$). The effect of ovariectomy in motor activity was reversed by EB treatment ($p < 0.05$). Male motor activity was similar to that observed at estrus. The number of head shakes was also lower at estrus than at diestrus ($p < 0.05$) and EB treatment increased this response in OVX rats ($p < 0.05$). In males rats the head shakes were fewer than in all the female groups. Finally, ovariectomy significantly enhanced the time spent in grooming behavior, and this effect was reversed by EB treatment ($p < 0.05$).

Amphetamine

The overall effects of AMPH on motor behaviors are summarized in Table 1. There were significant dose effects on motor activity, $F(2, 135) = 8.56$, $p < 0.01$, and rearing behavior, $F(2, 135) = 53.23$, $p < 0.001$. Post hoc comparisons showed that both doses of AMPH did not induce any significant change in spontaneous motor activity or number of rearings in females at diestrus. However, AMPH 1 mg/kg significantly increased both behaviors in rats from all other groups.

AMPH induced significant effects on head shakes, $F(2, 135) = 27.14$, $p < 0.01$, and this effect changed with the hormonal condition, $F(4, 135) = 26.35$, $p < 0.01$. A significant interaction between these two factors was also observed, $F(8, 135) = 4.79$, $p < 0.01$. AMPH 1 mg/kg significantly enhanced this behavior in females at estrus and diestrus ($p < 0.05$), whereas both doses of AMPH significantly increased head shaking in OVX rats, with and without EB pretreatment ($p < 0.001$ in both cases). Only the lowest dose of AMPH increased this behavior in males rats.

Significant effects of the dose, $F(2, 135) = 27.79$, $p < 0.01$, and the hormonal condition, $F(4, 135) = 5.19$, $p < 0.01$, were observed on grooming behavior. AMPH 1 mg/kg decreased the time spent in grooming behavior in all female groups ($p < 0.025$ in all cases), whereas AMPH 0.25 mg/kg decreased this behavior in OVX rats ($p < 0.05$ in both cases). Males were not sensitive to this inhibitory effect of AMPH.

Apomorphine

The spontaneous motor responses induced by APO are shown in Table 2. Two-way ANOVA revealed significant effects of the dose, $F(2, 135) = 56.19$, $p < 0.001$, and hormonal conditions, $F(4, 135) = 7.56$, $p < 0.01$, on motor activity. APO 62.5 μg/kg significantly diminished motor activity in all the groups studied ($p < 0.05$ in all cases); a fourfold greater dose (250 μg/kg) was unable to increase motor activity in intact female and OVX rats compared with the saline controls. In male rats this behavior was significantly increased ($p < 0.001$).

Other spontaneus motor activities (rearing, grooming, and head shaking) were depressed in all the groups injected with APO. The stimulant drug produced a dose-dependent decrease in the number of rears, $F(2, 135) = 35.58$, $p < 0.01$, and in the time spent in grooming behavior, $F(2, 135) = 145.50$, $p < 0.001$. There was a significant effect of the dose on the number of head shakes, $F(2, 135) = 18.10$, $p < 0.01$. APO 250 μg/kg induced an important decrease of head shakes in all the groups ($p < 0.01$ in all cases), but APO 62.5 μg/kg only modifies this behavior in OVX rats, with or without EB treatment.

TABLE 1

EFFECTS OF AMPHETAMINE (AMPH) ON SPONTANEOUS MOTOR RESPONSES UNDER DIFFERENT HORMONAL CONDITIONS

Hormonal Condition	N	Motor Activity (counts)	Rearing (No.)	Head Shaking (No.)	Grooming (s)
Diestrus					
Saline	20	608.7 ± 67.6*	32.1 ± 3.7	10.7 ± 1.3*	351.4 ± 24.4
AMPH 0.25 mg/kg	10	398.0 ± 29.7	24.1 ± 1.3	10.0 ± 1.9	283.8 ± 43.3
AMPH 1.0 mg/kg	10	434.3 ± 55.4	37.8 ± 5.6	17.9 ± 4.3†	127.3 ± 11.9†
Estrus					
Saline	20	449.7 ± 58.5	22.3 ± 3.6	6.3 ± 0.8	315.7 ± 52.5
AMPH 0.25 mg/kg	10	550.0 ± 98.9	38.5 ± 8.3	12.0 ± 3.5	243.1 ± 43.2
AMPH 1.0 mg/kg	10	675.9 ± 87.8†	57.6 ± 9.7†	13.0 ± 3.5†	146.6 ± 18.1†
OVX					
Saline	20	516.6 ± 9.7*	27.9 ± 2.9	8.9 ± 1.3*	554.3 ± 64.7*
AMPH 0.25 mg/kg	10	612.0 ± 92.3	41.1 ± 5.4	36.1 ± 6.9†	352.8 ± 49.3†
AMPH 1.0 mg/kg	10	742.3 ± 89.0†	61.4 ± 4.5†	46.6 ± 4.5†	152.8 ± 19.3†
OVX + EB 2 μg					
Saline	20	460.1 ± 35.8	37.6 ± 3.7	18.6 ± 3.6	375.1 ± 22.9
AMPH 0.25 mg/kg	10	425.5 ± 45.4	37.8 ± 3.8	29.0 ± 5.8†	239.0 ± 41.5†
AMPH 1.0 mg/kg	10	681.3 ± 51.8†	62.9 ± 6.2†	35.0 ± 3.6†	237.0 ± 24.5†
Males					
Saline	20	493.0 ± 44.8	20.7 ± 1.9	3.9 ± 0.9	442.4 ± 40.8
AMPH 0.25 mg/kg	10	461.9 ± 88.2	12.5 ± 2.3	17.0 ± 3.7†	355.9 ± 47.0
AMPH 1.0 mg/kg	10	809.3 ± 73.1†	71.6 ± 9.8†	9.5 ± 3.0	308.5 ± 92.2

Values are expressed as mean ± SEM. Comparisons were made by using two-way ANOVA followed by post hoc Newman-Keuls test: *$p < 0.05$ comparing diestrus with estrus or OVX with OVX + EB. †$p < 0.001$ when compared with its saline control group.

TABLE 2

EFFECTS OF APOMORPHINE (APO) ON SPONTANEOUS MOTOR RESPONSES UNDER DIFFERENT HORMONAL CONDITION

Hormonal Condition	N	Motor Activity (counts)	Rearing (No.)	Head Shaking (No.)	Grooming (s)
Diestrus					
Saline	20	608.7 ± 67.6	32.1 ± 3.7	10.7 ± 1.3	351.4 ± 24.4
APO 62.5 μg/kg	10	287.9 ± 38.1*	11.1 ± 2.1*	12.9 ± 4.4	184.9 ± 45.9*
APO 250 μg/kg	10	671.3 ± 43.5	9.8 ± 2.6*	3.6 ± 1.3*	20.6 ± 5.9*
Estrus					
Saline	20	449.7 ± 58.5	22.3 ± 3.6	6.3 ± 0.8	315.7 ± 52.5
APO 62.5 μg/kg	10	212.9 ± 33.7*	11.4 ± 1.7*	6.9 ± 2.7	168.5 ± 45.6*
APO 250 μg/kg	10	460.5 ± 28.3	7.5 ± 0.7*	2.3 ± 0.8*	49.0 ± 15.8*
OVX					
Saline	20	516.6 ± 9.7	27.9 ± 2.9	8.9 ± 1.3	554.3 ± 64.7
APO 62.5 μg/kg	10	345.0 ± 41.0*	15.2 ± 2.1*	4.8 ± 1.1*	183.0 ± 29.1*
APO 250 μg/kg	10	533.7 ± 79.3	9.5 ± 1.5*	2.1 ± 0.9*	59.0 ± 21.5*
OVX + EB 2 μg					
Saline	20	460.1 ± 35.8	37.6 ± 3.7	18.6 ± 3.6	375.1 ± 22.9
APO 62.5 μg/kg	10	277.3 ± 18.3*	12.9 ± 1.3*	3.4 ± 0.8*	131.3 ± 25.8*
APO 250 μg/kg	10	416.7 ± 37.4	15.8 ± 1.6*	2.6 ± 0.9*	63.3 ± 13.4*
Males					
Saline	20	493.0 ± 44.8	20.7 ± 1.9	3.9 ± 0.9	442.4 ± 40.8
APO 62.5 μg/kg	10	249.7 ± 38.6*	6.3 ± 1.0*	3.2 ± 0.9	119.9 ± 18.0*
APO 250 μg/kg	10	902.4 ± 79.7*	2.8 ± 0.9*	0.4 ± 0.3*	15.8 ± 4.7*

Values are expressed as mean ± SEM. Comparisons were made by using two-way ANOVA followed by post hoc Newman-Keuls test: *$p < 0.001$ when compared with its saline control group.

APO 62.5 μg/kg (a dose thought to act presynaptically) was able to induce the appearance of repeated episodes of yawning behavior in all groups studied. The number of yawns was registered during 30 min starting 5 min after APO administration. A one-way ANOVA revealed a significant effect of hormonal condition, $F(4, 45) = 19.56$, $p < 0.01$, on this behavior. Table 3 shows that APO was less effective in eliciting yawning over females compared to male rats. The number of yawns was significantly lower in intact female rats compared to males ($p < 0.025$ in both cases);ovariectomy significantly inhibited the yawning elicited by APO ($p < 0.01$), and the occurrence of yawns did not change with EB treatment.

The data in Table 3 demonstrate that APO, in a dose of 250 μg/kg (a dose that has postsynaptic actions), induced stereotypy characterized by continuous sniffing restricted to the periphery of the chamber. The stereotyped sniffing of each animal was scored at 5-min intervals during a 30-min period and was rated according to the following scale: 0 = absent; 1 = sniffing with other motoric behaviors; 2 = continual sniffing over a large area; 3 = continual sniffing in one location. One-way ANOVA revealed a significant effect of hormonal condition on stereotyped sniffing, $F(4, 45) = 124.21$, $p < 0.001$. This behavior was significantly depressed in intact female rats compared with male rats ($p < 0.01$ in both cases), and was almost completely suppressed after ovariectomy ($p < 0.001$ compared with intact female rats, and $p < 0.001$ compared with males). EB treatment decreased partially, but significantly ($p < 0.025$), the effect of ovariectomy.

DISCUSSION

Our results demonstrate that the effects of drugs influencing dopaminergic transmission upon rat avoidance conditioning and spontaneous motor activity are influenced by the gender and hormonal changes that occur in female rats during the estrous cycle or after ovariectomy with or without EB administration.

Previous reports from our laboratory have shown that the acquisition of conditioned avoidance responses (CARs) is facilitated during diestrus and almost suppressed at estrus (7). We demonstrated that the administration of EB to OVX rats induces effects on acquisition of CARs, which are dose dependent and time dependent (8). EB (0.2, 2, or 20 μg/kg) was injected 3, 24, 48, and 72 h before the behavioral test. A severe disruption of the avoidance response, similar to that observed in the intact rat at estrus, was evident 48 h after EB 2 μg/rat. We postulated that the increase in estradiol levels could trigger behavioral changes through the interaction with neurotransmitters such as dopamine. The present study supports this suggestion and, in addition, it demontrates that the impairment of CARs performance during estrus and in OVX rats treated with EB can be completely reversed through the systemic administration of AMPH and partially by APO. However, neither AMPH nor APO improved this behavior in rats at diestrus, suggesting that the effects of these dopaminergic agonists could be facilitated by the decay of estradiol levels, because their stimulating effects were observed late after the peak concentration of the ovarian hormone, that is, during estrus and 48 h after a single injection of EB to OVX rats.

Active avoidance conditioning has been associated with the activity of central dopaminergic systems, and the impairment of this behavior is considered as a characteristic effect of antidopaminergic drugs (1). Several but not conclusive reports have demonstrated a direct interaction of estrogen and dopaminergic systems (20,34). The effects, sometimes contradictory, seem to depend on dosage and duration of estradiol treatment and may vary in relation to species, sex, and age of the animals. For example, although some reports demonstrate that steroids with estrogenic properties are able to exert an antidopaminergic activity at the striatal level (12), others show that estrogen treatment increases the number of striatal dopamine receptors (10,18). Although it is difficult to evaluate the numerous factors that may influence the action of dopaminergic drugs, it is conceivable that estrogens could be interfering with dopamine receptor sensitivity. It is known that conditioned avoidance performance can vary according to the foot shock intensity. However, in our experimental conditions, no significant differences were observed between the foot shock thresholds applied to the different groups. Therefore, the results cannot be explain by changes in pain sensitivity.

The effects of AMPH on motor behaviors were clearly different from those of APO according to the hormonal condition of the rats. In fact, AMPH was not able to stimulate motility and rearing behavior in females during estrus, whereas APO stimulated motor activity only in males. It is known that AMPH acts indirectly by liberating endogenous dopamine onto receptors and also stimulating the release of norepinephrine (15) and serotonin (16). Apomorphine, a direct-acting dopamine agonist, mimics dopamine at the receptors. The hypomotility induced by small doses of APO (4) is probably due to the stimulation of presynaptic dopamine receptors in the CNS (3). By activation of postsynaptic dopamine receptors, higher doses of APO produce huperactivity and stereotyped behaviors (31). The improvement in the acquisition of CARs induced by AMPH in intact rats at estrus and in OVX rats treated with EB cannot be merely explained

TABLE 3

YAWNING AND STEREOTYPED SNIFFING INDUCED BY APOMORPHINE UNDER DIFFERENT HORMONAL CONDITIONS

	Diestrus	Estrus	OVX	OVX + EB	Males
Yawning (number/30 min)					
APO 62.5 μg/kg	11.3 ± 0.6	13.6 ± 1.2	6.7 ± 1.0*	6.4 ± 1.0*	17.7 ± 1.4†
Sniffing (score/30 min)					
APO 250 μg/kg	10.5 ± 0.3	11.0 ± 0.3	0.1 ± 0.1*	2.0 ± 0.6‡	13.1 ± 0.8†

Values are expressed as mean ± SEM. Comparisons were made by using one-way ANOVA followed by post hoc Newman-Keuls test. The number of animals on each group was 10.

*$p < 0.001$ when compared with intact female and male rats.

†$p < 0.001$ when compared with intact female rats.

‡$p < 0.025$ comparing OVX with OVX + EB.

by the increase in motor activity, considering that the lower dose of AMPH used in this study (0.25 mg/kg) significantly enhanced conditioning without modifying motor activity. Moreover, APO in a dose that exerts a depressant effect on motility significantly increases acquisition of CARs in rats at estrus.

In the present study, the number of head shakes was also distinctively affected by AMPH and APO. AMPH increased this behavior and APO depressed it in all experimental groups; however, OVX rats were more sensitive than intact female rats to both drugs. There are evidences that this behavior is evoked through the stimulation of serotonin receptors in rodents (2,21) and that a dopaminergic stimulation markedly decreased the serotonin-induced head shakes response (6). Our results show that AMPH and APO decreased grooming behavior and that the effect of AMPH was modified by the hormonal condition. Ovariectomy increased the sensitivity to this drug, and male rats were refractory to both doses of AMPH. Nevertheless, the effect of APO on grooming behavior was not influenced by hormonal status. There are reports that consider the posibility that dopamine receptors could be involved in the expression of grooming behavior. Some evidence shows that grooming is potentiated by D_1 agents, whereas D_2 agonists had the opposite effect (23,33).

As expected from previous experiments (26), APO at a dose of 62.5 μg/kg elicited yawning in rats. Hormonal condition modified this effect; intact female rats yawn fewer times than male rats, and ovariectomy attenuated the yawning behavior induced by APO, with or without EB replacement. In agreement with these results, previous reports have demonstrated that APO is less effective when inducing yawning in female than in male rats (32).

Stereotypy induced by APO 250 μg/kg was affected by sex, ovariectomy, and EB replacement. This effect was greater in male than in female rats. Ovariectomy annuled the response but EB treatment slightly increased it. These findings are compatible with studies indicating that stereotypy induced by APO is reduced by ovariectomy (30) and it is enhanced by treatment with EB (5,18,19). However, there are also studies reporting that systemic administration of estrogen reduces stereotypy induced by APO (27,29). Procedural differences may be responsible for these different results.

In conclusion, the gonadal hormonal status appears to be able to modulate behavioral responses to central dopaminergic stimulation in animal models, but the precise mechanism of action of this effect remains unknown. It is possible that female sex hormones may act directly, modifying dopamine receptor sensitivity or influencing other neurotransmitter systems that, in turn, may modulate dopaminergic activity. Another mechanism could be secondary to the effects of sex hormones at a hypothalamic level. In fact, these steroids induce synthesis and release of hypothalamic peptides, like LHRH (20). We have previously postulated that the behavioral effects of LHRH could be a consequence of its interaction with dopaminergic systems in the brain (24,25). Alteration of the metabolism of drugs by various hormonal conditions has not been ruled out as a possible mechanism. Female sex hormone fluctuations may be valuable in the understanding and therapy of human psychomotor disorders that are pressumed to rely on central dopaminergic activity.

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