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# THE INFLUENCE OF ESTROGEN ON NIGROSTRIATAL DOPAMINE ACTIVITY: BEHAVIORAL AND NEUROCHEMICAL EVIDENCE FOR BOTH PRE- AND POSTSYNAPTIC COMPONENTS

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The results of 3 experiments examining the influence of estrogen on the nigrostriatal dopamine (DA) system are reported. In two experiments the influence of hormonal manipulations on amphetamine (AMPH)-induced rotational behavior was investigated using rats with unilateral 6-hydroxydopamine lesions of the substantia nigra. It was found that: (1) female rats in estrus make more rotations than ovariectomized (OVX) rats; and (2) estrogen treatment (5 μg estradiol benzoate, daily for 4 days) in OVX rats enhances AMPH-induced rotational behavior 4 h and 4 days after estrogen treatment. During the intervening period, at 24 h after cessation of estrogen treatment, control and hormone-treated animals did not differ. In a third experiment, the effect of estrogen treatment on the release of endogenous DA from striatal tissue slices in superfusion was examined. Estrogen enhanced AMPH-stimulated striatal DA release 4 h after the last treatment relative to OVX controls. However, 24 h and 4 days after estrogen treatment DA release had returned to control levels. It is suggested that estrogen has an immediate potentiating effect on striatal DA release, and this may be responsible for the increased behavioral response to AMPH 4 h after estrogen treatment. The previously demonstrated increase in postsynaptic striatal DA receptors may be responsible for the second increase in AMPH-induced rotational behavior, that occurs 4 days after estrogen treatment.

## INTRODUCTION

Estrogen is known to influence neuronal activity in the hypothalamus and thereby exert feedback control over reproductive functions and sexual behavior[15,26,28]. However, many non-reproductive behaviors are also modulated by estrogen[3], suggesting that estrogen may influence neural activity in extrahypothalamic brain regions. For example, a number of researchers have suggested that estrogen influences activity in the nigrostriatal dopamine (DA) system[17,21].

We have previously reported that there are estrous cycle dependent variations in amphetamine (AMPH)-stimulated striatal DA release in vitro and rotational behavior[4,7,30]. On estrus, 6–12 h after the endogenous hormonal surges, rotational behavior and AMPH-stimulated striatal DA release both increase relative to other days of the estrous cycle. The removal of the endogenous source of gonadal steroids by ovariectomy (OVX) attenuates AMPH-stimulated striatal DA release and electrical stimulation-induced rotational behavior[4,30]. In addition, the treatment of OVX rats with estrogen plus progesterone results in an increase in striatal DA release stimulated by either AMPH or potassium[4,5]. However, estrogen treatment alone in OVX rats has no effect on AMPH-stimulated striatal DA release measured 24 h later[4].

Interestingly, the effect of estrogen on the nigrostriatal DA system appears to be closely asso-

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ciated with the interval between hormone treatment and the subsequent behavioral or neurochemical test[17,18,20]. In general, 24 h after estrogen, behavioral indices of striatal DA activity are attenuated, whereas 2–6 days later these same behaviors are potentiated. Therefore, it is possible that estrogen treatment influences striatal DA release at time points other than the one considered in our previous study[4]. In the series of experiments reported here, we examine the effect of OVX on AMPH-induced rotational behavior as well as the influence of estrogen on striatal DA release and rotational behavior at 3 time points: 4 h, 24 h and 4 days after estrogen treatment. We hypothesize that estrogen-induced changes in striatal DA release participate in the immediate effect of estrogen on the nigrostriatal DA system. Behavioral and neurochemical data in support of this idea are reported.

## MATERIALS AND METHODS

Adult female rats (Holtzman, Madison, WI) were maintained on a reversed light : dark cycle (14 : 10, lights off at 08.00 h) with food and water freely available. All treatments and procedures were conducted between 10.00 h and 14.00 h in order to minimize diurnal variation.

*Experiment 1*

*The influence of ovariectomy on AMPH-induced rotational behavior.* Animals were pretreated with desipramine (25 mg/kg) to protect noradrenergic neurons[9], then anesthetized with chloropent (2.4 ml/kg; Fort Dodge Laboratories, Fort Dodge, IA) supplemented by metofane (by inhalation; Pitman-Moore, Washington Crossing, NJ). Animals were positioned in a stereotaxic instrument and 8 μg 6-hydroxydopamine hydrobromide (6-OHDA) in 4 μl normal saline (also containing 0.1% ascorbic acid) was infused into the right substantia nigra at a rate of 1 μl/min. Two weeks later, half of the animals were ovariectomized (OVX, n = 21) under ether anesthesia. The other half of the animals received a sham operation (INTACT, n = 21). After an additional 2 weeks for recovery, OVX rats received daily injections of 0.1 ml peanut oil (s.c.) for 8 consecutive days. INTACT females were monitored for at least 2 consecutive estrous cycles (8–10 days) by daily examination of the vaginal epithelium and were tested on the day of estrus.

Approximately 5 weeks after the 6-OHDA lesions, INTACT females in estrus and OVX animals were tested for AMPH-induced rotational behavior in automated rotometers[31]. After a 15-min habituation period, the animals were given an i.p. injection of D-AMPH sulfate. Testing occurred under standard white light illumination. Some animals from each group (OVX, n = 9; INTACT, n = 8) received 0.65 mg/kg AMPH and rotational behavior was recorded for 90 min. The other animals in each group (OVX, n = 12; Intact, n = 13) received 2.5 mg/kg AMPH and rotational behavior was recorded for 120 min. Rotations were cumulated over 5 min intervals and a rotation was defined as 4 consecutive 90° in the same direction. Three weeks later the animals were tested a second time, either on the day of estrus or after treatments with oil. Rotational behavior was measured as just described, except that all animals received 2.5 mg/kg and rotational behavior was recorded for 120 min. Statistical evaluation of the differences between groups were conducted by two-way analysis of variance (group × time).

At the conclusion of the experiment, the animals were killed by decapitation and striatal DA concentrations were determined by high performance liquid chromatography with electrochemical detection (HPLC-EC) after extraction of catecholamines with alumina adsorbent[31]. Only the results from animals with >90% DA depletion were included in the analysis so as to reduce variability in AMPH-induced rotational behavior that is associated with partial lesions.

*Experiment 2*

*The influence of estrogen treatment on AMPH-induced rotational behavior in OVX rats.* Animals received 6-OHDA lesions of the right substantia nigra and were OVX 2 weeks later as described in Expt. 1. After an additional 2-week recovery period, a hormone treatment regimen began in which each animal received 8 s.c. injections. The hormone treatment groups received estradiol

benzoate (EB; 5 μg in 0.1 ml peanut oil) on 4 consecutive days and vehicle (0.1 ml peanut oil) on the other 4 days. The protocol for hormone administration was designed to approximate the 4-day estrous cycle of the female rat. The length of the time after EB was varied. The EB : 4D group (n = 16) received EB for 4 days and was tested 4 days later (oil for 4 days). The EB : 24H group (n = 15) was tested 24 h after EB. The EB : 4H group was tested 4 h after EB (n = 14). A control group (OVX(OIL), n = 12) received injections of oil on 8 consecutive days. This group also served as one of the OVX(OIL) groups in Expt. 1. Four h after the last oil or EB treatment, animals were given 2.5 mg/kg AMPH and rotational behavior was measured for 120 min as described in Expt. 1. At the conclusion of the experiment, DA concentrations in the striatum were determined by HPLC-EC; only the results from animals with >90% DA depletion were included in the statistical analysis.

*Experiment 3*

*The influence of estrogen on AMPH-stimulated release of endogenous DA in vitro.* Female rats were ovarectomized under ether anesthesia and allowed to recover for two weeks. Animals were then assigned to 1 of 4 treatment groups (n = 5/group). The groups were: EB : 4D, EB : 24H, EB : 4H, and OVX(OIL), as just described for Expt. 2. Four h after the last oil or hormone treatment, the animals were killed by decapitation. The striata were rapidly dissected, and 1-mm$^3$ tissue fragments were placed in superfusion chambers with a volume of 200 μl containing a Krebs–Ringer phosphate medium, pH 7.4, maintained at 37 °C in a water-bath[6]. Medium continuously flowed through the chamber at a rate of 100 μl/min.

Following a 75-min stabilization period, effluent samples were collected at 5-min intervals. The amount of endogenous DA released into the medium was measured in the effluent samples by HPLC-EC[6]. The first sample was collected to determine basal DA efflux, the medium containing 10 μM D-AMPH was infused for 2.5 min and 4 additional samples were collected to determine AMPH-stimulated DA release. This dose of AMPH was determined to produce consistant, but less than the maximum, DA release in dose-response studies[6]. The amount of DA in each effluent sample was expressed as pg DA/mg tissue/min.

## RESULTS

*Experiment 1*

*Ovariectomy attenuates AMPH-induced rotational behavior.* Table I shows that OVX rats made significantly fewer rotations than intact female rats with either dose of AMPH. This was true during both the first and the second test sessions. Both groups made more rotations during the second test session than during the first, as previously reported[31].

*Experiment 2*

*Time course of the effect of estrogen on AMPH-induced rotational behavior.* Estrogen treatment had both immediate and long-term effects on AMPH-induced rotational behavior. In a two-way analysis of variance (group × time), there was a significant effect of treatment group on the number of rotations produced during the 2-h test period ($F_{3,53} = 2.81$, $P < 0.05$). The EB : 4H group made significantly more rotations

TABLE I

*The influence of ovariectomy on AMPH-induced rotational behavior*

| *Group* | *(n)* | *Dose of AMPH*[1] | *Total rotations*[2] |
|---|---|---|---|
| INTACT | (8) | 0.65[3] | 220 ± 26* |
| OVX | (9) | 0.65[3] | 137 ± 16 |
| INTACT | (13) | 2.5[3] | 628 ± 93** |
| OVX | (12) | 2.5[3] | 422 ± 78 |
| INTACT | (21) | 2.5[4] | 1041 ± 90*** |
| OVX | (21) | 2.5[4] | 729 ± 85 |

[1] Dose of AMPH in mg/kg. Rotational behavior was recorded for 90 min after a dose of 0.65 mg/kg and 2 h after 2.5 mg/kg; [2] mean ± S.E.M.; [3] first AMPH treatment; [4] second AMPH treatment; * INTACT > OVX: $F_{1,15} = 7.98$, $P = 0.012$; ** INTACT females exhibit a more rapid onset of rotational behavior than do OVX females, resulting in a significant interaction between groups: $F_{11,253} = 2.0$, $P < 0.03$; *** INTACT > OVX: $F_{1,49} = 5.41$, $P < 0.025$.

throughout the 2-h test period than did OVX(OIL) controls ($P < 0.05$, Fig. 1A). There were no differences between control and EB-treated animals 24 h after hormone treatment. However, 4 days after EB treatment animals exhibited enhanced AMPH-induced rotational behavior once again ($P < 0.05$, Fig. 1B).

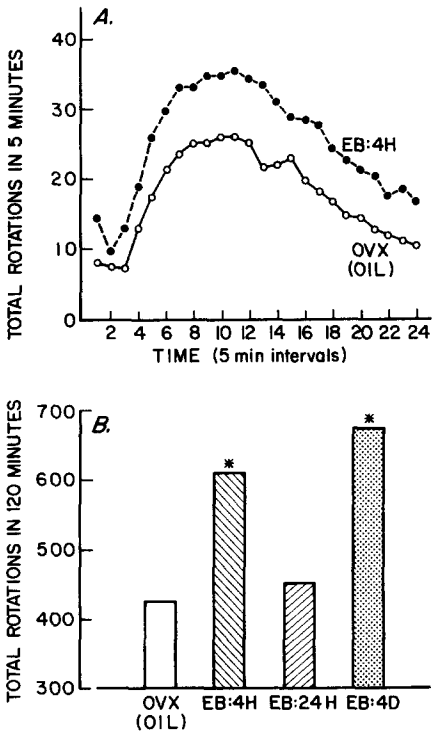


Fig. 1. The influence of estrogen treatment on AMPH-induced rotational behavior. OVX rats with unilateral 6-OHDA lesions of the substantia nigra were treated with 5 μg EB for 4 days and tested for 4 h (EB : 4H), 24 h (EB : 24H) or 4 days (EB : 4D) later. Control animals received oil injections (OVX(OIL)). Rotational behavior was measured for 2 h following the administration of 2.5 mg/kg AMPH. A: time course of the behavioral response. Total rotations were cumulated over 5-min intervals for the OVX(OIL) group (n = 12, solid line) and the EB : 4H group (n = 14, dashed line). There was a significant effect of hormone treatment on rotational behavior throughout the 2-h testing session ($F_{3,53} = 2.808, P = 0.047$). In subsequent pairwise comparisons the EB : 4H group made significantly more net rotations than did the OVX(OIL) control group ($P < 0.05$). The profile of the time course of the behavioral response to AMPH in the EB : 4D group was comparable to that seen in the EB : 4H group. B: total rotations cumulated over 120 min. There was a significant effect of hormone treatment on the total number of rotations made during the behavioral testing session ($F_{3,53} = 2.834, P = 0.046$). Total rotations for each group (mean ± S.E.M.): OVX, 422 ± 78; EB : 4H, 609 ± 93; EB : 24H, 432 ± 42; and EB : 4D, 672 ± 77. *AMPH-induced rotational behavior was significantly greater at 4 h and 4 days after estrogen treatment than in OVX(OIL) animals ($P < 0.05$).

*Experiment 3*

*Time course of the effect of estrogen on AMPH-stimulated striatal DA release.* There was also a significant effect of estrogen treatment on the AMPH-stimulated release of endogenous DA from striatal tissue fragments in vitro (two-way ANOVA, group × time (i.e. 5 collection intervals), significant interaction: $F_{12,64} = 2.362, P = 0.013$; Fig. 2). The AMPH-stimulated increase in DA release was significantly greater 4 h after EB than was found with striatal tissue obtained from any of the other 3 groups ($P < 0.05$). With striatal tissue from the EB : 24H, EB : 4D or the OVX(OIL) groups, the AMPH-stimulated release of DA had already begun to decline by the time of the third collection interval. In contrast, the AMPH-stimulated release of DA was sustained through the third interval with striatal tissue from the EB : 4H group (Fig. 2B).

## DISCUSSION

The experiments reported here demonstrate that OVX attenuates AMPH-induced rotational behavior in the female rat. This result was predicted, since OVX has been shown to attenuate AMPH-stimulated striatal DA release as well as rotational behavior induced by electrical stimulation of the nigrostriatal bundle[4,30]. Estrogen treatment restored the behavioral response to AMPH at two time points, immediately following (4 h) the cessation of estrogen treatment and again 4 days later. Interposed between these 2 periods of heightened behavioral responsiveness to AMPH, is a period 24 h after estrogen treatment, when control and hormone-treated animals did not differ in rotational behavior. We found no evidence for an attenuation of striatal DA release or AMPH-induced rotational behavior 24 h after hormone treatment as might be expected from previous reports[8,17]. In addition, the AMPH-stimulated release of DA from striatal tissue was potentiated relative to OVX(OIL) 4 h after estro-

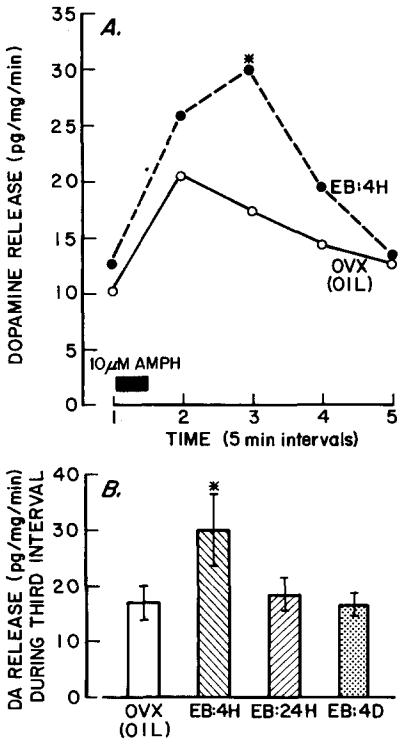


Fig. 2. The influence of estrogen on AMPH-stimulated striatal DA release. The release of endogenous DA from striatal tissue slices in a superfusion system was examined following hormonal manipulations. Female rats were OVX and then treated with EB as described in the legend to Fig. 1 and the text. After the first 5 min effluent sample was collected, 10 $\mu$m AMPH (in medium) was infused for 2.5 min and samples were collected at 5-min intervals for an additional 20 min (intervals 2–5). A: time course of AMPH-stimulated striatal DA release. There was significantly more ($P < 0.05$) AMPH-stimulated DA release from striatal tissue obtained 4 h after estrogen withdrawal (EB : 4H, dashed line) than from control animals (OVX(OIL), solid line). This difference is due to a more sustained release of DA in the EB : 4H group. The bar marks the interval when AMPH was introduced into the superfusion chamber; *interval depicted for all groups in Fig. 2B. B: the influence of estrogen on AMPH-stimulated striatal DA release. There was significantly more AMPH-stimulated DA release from striatal tissue obtained from the EB : 4H group, during the third interval (second post-AMPH interval, marked with * in Fig. 2A) than for any other group ($P < 0.05$). Bars indicated ± S.E.M.

gen treatment, but not at any other time point tested.

The finding that rotational behavior is increased at both 4 h and 4 days after estrogen treatment, while AMPH-stimulated DA release is greater only 4 h after estrogen, suggests that there is more than one component contributing to the effect of estrogen on nigrostriatal DA activity. The results presented here suggest that the initial effect of estrogen is to potentiate the stimulated release of striatal DA. How estrogen enhances AMPH-stimulated striatal DA release and rotational behavior is not known, but the available evidence suggests the following possibility. AMPH is thought to release DA from a nonvesicular, storage pool by exchange diffusion, a process mediated by the DA reuptake carrier[16]. Activity of the reuptake carrier is sensitive to $Na^+$ and $K^+$ concentrations and may be further regulated by membrane polarity[16,24]. The AMPH-stimulated release of DA should be similarly regulated. (The transport of glutamate and serotonin in brain and catecholamines in adrenal chromaffin cells have been shown to be electrogenic[24]. Whether DA transport in the striatum is similarly modulated by membrane polarity has not been tested directly.) Low-frequency stimulation of the nigrostriatal pathway results in decreased terminal excitability and presumably hyperpolarization[33]. AMPH-stimulated [$^3$H]DA release is greater during low-frequency stimulation of the nigrostriatal pathway than the sum of release induced by either AMPH or electrical stimuation alone[34]. Therefore, one possible mechanism of estrogen's action in the nigrostriatal DA system is to enhance AMPH-stimulated DA release by hyperpolarizing striatal DA terminals.

Evidence to support the idea that estrogen treatment is associated with hyperpolarization in nigrostriatal DA neurons comes from electrophysiological studies. Estrogen treatment is followed by a decrease in spontaneous activity in nigral DA neurons[10,11] and an increase in spontaneous activity in striatal DA-sensitive neurons[2]. The effect of estrogen in the nigra occurs within minutes following estrogen administration (i.v.)[11].

Interestingly, the effect of estrogen in the nigra is similar to the effect of DA agonists and is reversed by treatment with the DA antagonist haloperidol[11]. DA agonists are known to decrease spontaneous activity both in nigral DA cell bodies and in DA terminals in the caudate by hyperpolarizing DA neurons[1,11,19,32]. Therefore, hyper-

polarization in DA neurons occurs in association with the DA agonist-induced increase in activity in the nigrostriatal DA system. The finding that estrogen has an effect similar to DA agonists on electrical activity in both the nigra and striatum suggests that estrogen also potentiates activity in the nigrostriatal DA system.

The estrogen-induced potentiation of striatal DA activity may mediate both the increase in AMPH-stimulated DA release at 4 h (by the mechanism proposed above) and the increase in AMPH-stimulated rotational behavior that occurs 4 days after EB. For example, potentiation of the striatal DA system by DA agonists has been shown to induce changes in DA receptors. The sensitivity of DA autoreceptors is decreased 24 h after AMPH[35] and there is a behavioral hyposensitivity to APO after prior APO pretreatment[25]. In addition, 3–5 days after pretreatment with APO or AMPH, APO-induced stereotypy and rotational behavior are enhanced and there is an increase in the number of striatal DA receptors[12–14]. The effect of estrogen on striatal DA neurons may be analagous to the effect of DA agonists and it may also trigger compensatory postsynaptic responses including: (1) a decrease in the behavioral response to DA receptor agonists, 24 h after estrogen treatment[11,17,18,22,29]; and (2) an increase in dopamine mediated behaviors and in the number of striatal DA receptors 2–6 days later[18,21].

Whether there is a direct effect of estrogen on nigrostriatal DA neurons is yet to be conclusively determined. However, direct effects of 17-$\beta$-estradiol in the striatum on APO-induced postural deviation has been reported[23]. Unilateral implants of crystalline estradiol result in postural deviation ipsilateral to the implant when low doses (0.07 or 0.75 mg/kg) of APO are administered, but not with a higher dose (3 mg/kg). Since low doses of APO are thought to act selectively at inhibitory DA autoreceptors and higher doses are thought to stimulate postsynaptic DA receptors[1], this finding suggests that there is a direct effect of estrogen on presynaptic DA activity and a complex interaction between the presynaptic effects of APO and estrogen.

An effect of estrogen on nigrostriatal DA activity may be responsible for some of the estrous cycle-dependent variation in non-reproductive behaviors in the female rodent as well. For example, there is an increase in locomotor activity, exploratory behavior, running wheel activity and sensory responsiveness on estrus or following estrogen treatment[3]. In summary, the data presented here indicate that the immediate effect of estrogen on the striatum is to enhance striatal DA release, thereby enhancing sensori-motor responsiveness.

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