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Behaviors Induced by Intrastriatal Dopamine Vary Independently Across the Estrous Cycle

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JOYCE, J. N. AND C. VAN HARTESVELDT. *Behaviors induced by intrastriatal dopamine vary independently across the estrous cycle.* PHARMACOL BIOCHEM BEHAV **20**(4) 551–557, 1984.—Unilateral intrastriatal injections of dopamine (DA; 25 μg/0.25 μl) or amphetamine (AMPHET; 25 μg/0.25 μl) induced contralateral postural deviation and contralateral rotation that varied systematically across the estrous cycle of Long-Evans hooded rats. Both the deviation and rotation elicited by either drug were suppressed during the early part of the day of proestrus (2–6 hours after lights on) and were enhanced on the day of estrus, compared to the other days of the estrous cycle. However, when the behaviors elicited by the two drugs were examined across the day of proestrus, it was found that postural deviation and rotation changed independently. Postural deviation elicited by intrastriatal DA and AMPHET was suppressed on the day of proestrus at 4 and 7 hours after lights on, but was enhanced to the level seen during estrus at 11 hours after lights on. In contrast, contralateral rotation induced by either drug was suppressed 4, 7 and 11 hours after lights on and was enhanced only by the morning of estrus. These data suggest that there are separate DA-modulated mechanisms within the striatum for postural deviation and contralateral rotation, and that these mechanisms are differentially affected across the estrous cycle.

Dopamine Amphetamine Estrous cycle Postural deviation Rotation Basal ganglia

RECENT research has focussed interest on the effects of gonadal hormones on the functional output of the basal ganglia. Several behaviors elicited by the systemic administration of dopamine (DA) agonists and antagonists, and thought to be mediated by the striatum, vary with gender [2, 22–25] and are affected by gonadal hormones [3, 4, 8, 10, 12, 13, 14, 15]. Estradiol given to both male and female rats results in an initial suppression and later enhancement of some behavioral responses to systemically administered DA agonists and antagonists [5,13]. The same results are found when the effects of estradiol are tested on contralateral deviation elicited by DA placed directly in one striatum [18]. However, these data do not enable one to conclude that variations in endogenous estradiol are sufficient to affect the behavioral output of DA mechanisms in the striatum.

We were interested in determining whether the variations in plasma estradiol over the estrous cycle would affect behaviors elicited by intrastriatal DA agonists according to the same pattern as that of exogenously administered estradiol. We therefore administered DA agonists unilaterally into the striatum and measured both postural deviation and rotation across the estrous cycle.

GENERAL METHOD

Animals

Female Long-Evans hooded rats weighed 180–220 g at the beginning of the experiment. They were housed individually and maintained on a 12:12 light:dark cycle (lights on, 0800–2000). Vaginal smears were taken twice daily to ensure clear determination of the onset of different parts of the cycle (1000 hr, 1600 hr) and each day of the estrous cycle was determined with reference to the day of estrus. Vaginal smears were taken for two weeks prior to surgery, and for two weeks prior to initiating behavioral testing. The rats were monitored for regularity of 4-day estrous cycles, and rats which cycled irregularly or over 5 days were not used.

Stereotaxic Surgery

The rats were implanted bilaterally with permanent cannulae under sodium pentobarbital (W. T. Butler Co.) anesthesia. Guide cannulae were constructed from 21 ga stainless steel tubing and the injection cannulae were constructed using 27 ga tubing. Since the injection cannulae terminated 3.0 mm below the guide cannulae, the guide cannulae were located stereotaxically such that the injection cannulae were aimed for the anterior dorsal striatum using the following coordinates derived from Pellegrino *et al.* [20]: +2.0 to 3.0 mm with respect to bregma; 2.0 to 4.0 mm lateral to bregma; and 3.5 to 5.0 mm below the surface of the brain. Stainless steel stylets, made from closed 27 ga tubing, kept the guide cannulae patent when the animals were not being injected intracerebrally.

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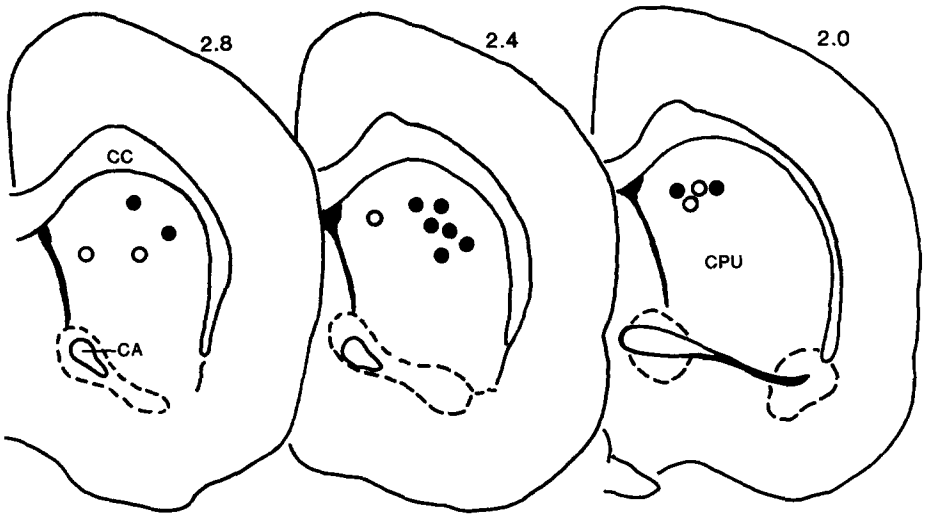

FIG. 1. Locations of cannula tips for intrastriatal injection of drugs (diagrams derived from Pellegrino *et al.* [20]). Filled circles indicate placements for rats in Experiment 1 (n=10); open circles, for Experiment 2 (n=5). CC=corpus callosum; CA=anterior commissure; CPU=caudate-putamen.

Drugs

The drugs d-amphetamine sulfate (AMPHET; Sigma) and dopamine hydrochloride (DA; Sigma) were dissolved in the phosphate buffer solution to a final pH of 7.4. The phosphate buffer solution was 140 mM sodium phosphate dibasic/7.0 mM sodium phosphate monobasic solution. DA and AMPHET solutions were made at a concentration of 25 μg/0.25 μl. The control drug (VH) was the phosphate buffer adjusted to a pH of 7.4 with glacial acetic acid.

Behavioral Testing

The intracerebral application of a drug was made by injecting the drug solution through the 27 ga cannula which was connected by polyethylene tubing to a Hamilton syringe mounted on a Sage syringe pump (Orion Research). Animals were injected with 0.25 μl of drug solution at a constant rate of 0.5 μl/min, and the injection cannula remained in place for an additional 30 sec after completion of the drug injection. After the drug administration the rats were placed into a circular clear Plexiglas observation chamber, 34 cm in diameter and 30.5 cm in height, and observed for 40 min. The duration of postural deviation and the number of 1/4 rotations that occurred both contralaterally and ipsilaterally to the side of intrastriatal injection were recorded. The amount of time the rats deviated contralateral and ipsilateral to the side of the intrastriatal injection was recorded continuously by the observer using a two pole switch connected in series to a time clock and a rack of cumulative counters. The cumulative durations of postural deviation and number of 1/4 rotations were recorded every 5 min for 40 min.

Histology

After behavioral testing, rats were administered an overdose of sodium pentobarbital and perfused intracardially with 0.9% saline followed by 10% formalin. The brains were placed in a 20% sucrose-10% formalin mixture for at least 24 hr. The brains were frozen, sectioned at 30 μm, stained with cresyl violet, and the locations of the cannula tips verified. Cannula tip placements for Experiment 1 and Experiment 2 are shown in Fig. 1.

EXPERIMENT 1

Procedure

All rats (n=10) were injected unilaterally into the striatum with the VH, DA or AMPHET on separate days. Animals in this study each received all drugs on each day of the estrous cycle with a minimum of 48 hours between drug injections, to allow within-animal comparisons. Thus all animals received 12 separate drug injections in the same striatum, in a random order. Animals were tested between 1000–1200 hr of the day of proestrus and between 1000–1500 hr on all other days of the estrous cycle.

Data Analysis

Only rats (n=10) which had regular 4 day estrous cycles during the entire experiment were used in the final analyses of the data. In order to obtain an index of the dominant direction of postural deviation, the time spent ipsilateral was subtracted from the time spent contralateral to the side of the intracerebral injection (difference score in 0.01 min units). A dominant direction index was also obtained for the number of 1/4 rotations by subtracting the number of 1/4 rotations ipsilateral from the number contralateral to the side of the intracerebral injection. The difference scores were used as the drug response (for each drug) to examine if there were differences due to the day of the estrous cycle (HORMONE); and were analyzed for the total 40 minute observation period (sum total) and across the eight 5-min blocks of the observation period (TIME). For the sum total scores, an analysis of variance was used to determine if the variables drug and day of the estrous cycle (HORMONE) had significant overall effects. Tests for simple main effects were then made using Scheffé's method for multiple comparisons (for equal sample size). An analysis of covariance was used to determine if the variables drug and day of the estrous cycle (HORMONE) had significant overall effects for the eight 5-min blocks of the observation period (TIME as the quantitative covariable). For each drug response, differences due to the day of estrous cycle (HORMONE) were tested for significance using least squares means estimation with quadratic function as the model. When testing for differences

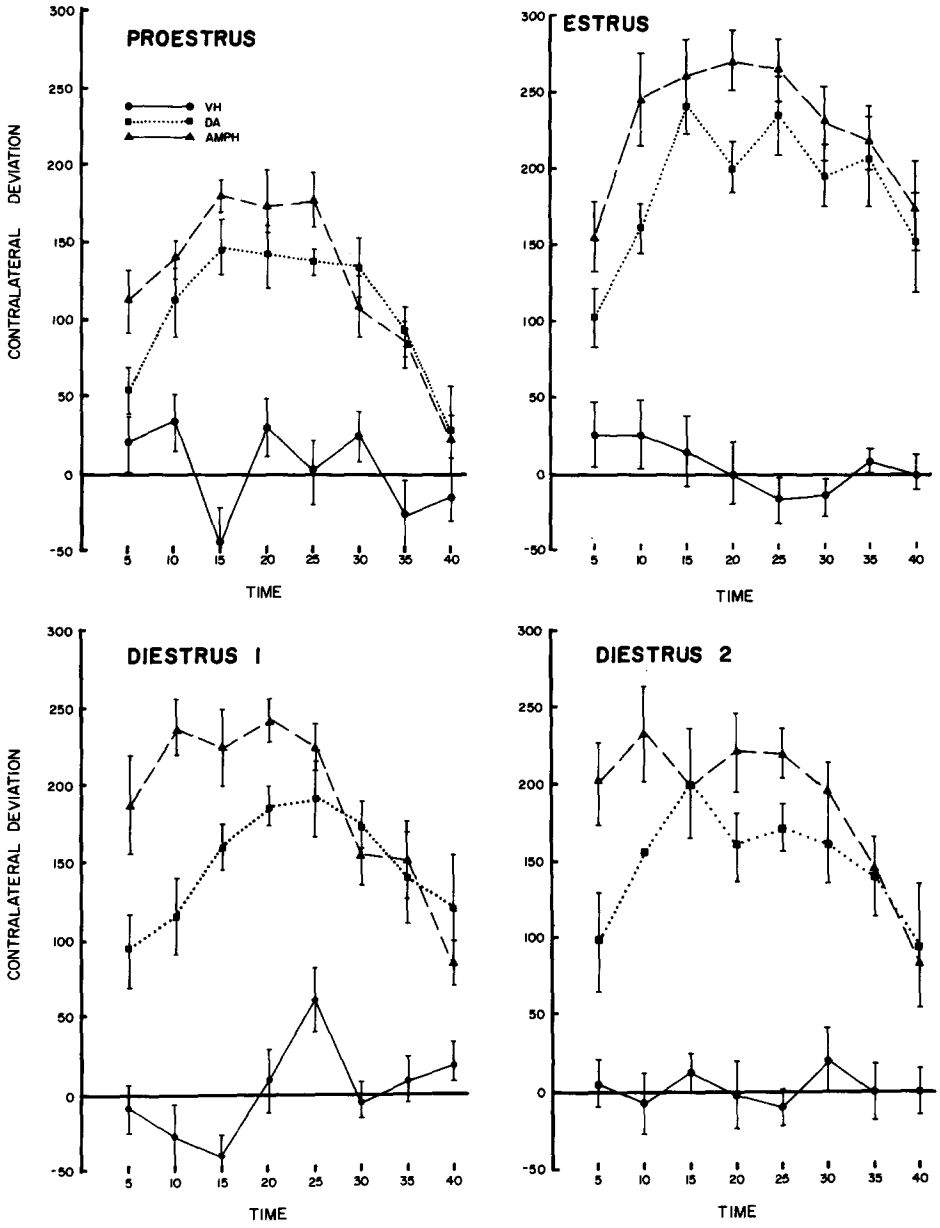

FIG. 2. Postural deviation scores for Experiment 1. The ordinate represents the average difference score for postural deviation expressed in 0.01 min. Ipsilateral deviation was subtracted from contralateral deviation for each animal to obtain an absolute difference score. Positive scores represent a predominantly contralateral deviation, and negative scores, an ipsilateral deviation. The graph represents the mean time +/− S.D. for each sequential 5-min block of the 40 min observation period; the abscissa represents each 5 min time block. The response to the intrastriatal injection of dopamine (DA, 25 μg in a volume of 0.25 μl), amphetamine (AMPHET, 25 μg in a volume of 0.25 μl) and vehicle (VH, 0.25 μl) are shown for each day of the estrous cycle (PROESTRUS, ESTRUS, DIESTRUS 1, DIESTRUS 2).

using drug response across the eight 5-min blocks of the observation period, it was assumed that the lines were parallel. Only the preplanned comparisons for each day of the estrous cycle (HORMONE) by drug were tested.

RESULTS

In order to measure the degree of dopaminergic activity following injection of DA, AMPHET, or VH into one striatum, the absolute difference (in 0.01 min units) between ipsilateral and contralateral postural deviation was determined. Thus, for any 5-min block, a score of 500 would indicate that the animal was deviated contralaterally for the entire 5-min period. The difference scores for postural deviation for each drug by day of estrous cycle are shown in Fig. 2. The data are presented for the entire 40-minute observation period by each 5-min block. The response to the unilateral intrastriatal injection of the VH was not significantly different from zero for any day of the estrous cycle.

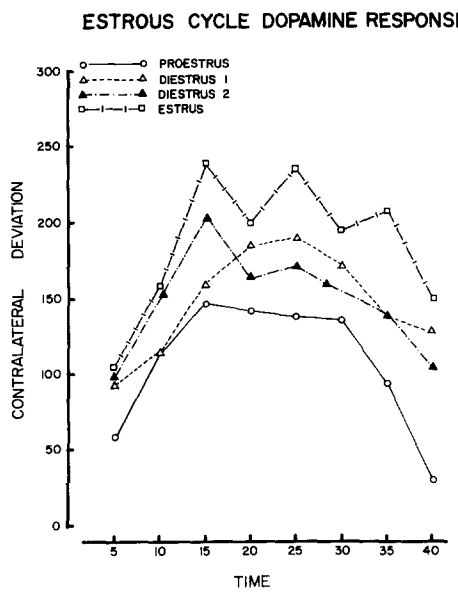

FIG. 3. Postural deviation scores for intrastriatal injection of DA at each day of the estrous cycle (Experiment 1); PROESTRUS, DIESTRUS, DIESTRUS 1, DIESTRUS 2, ESTRUS. All other details as in Fig. 2.

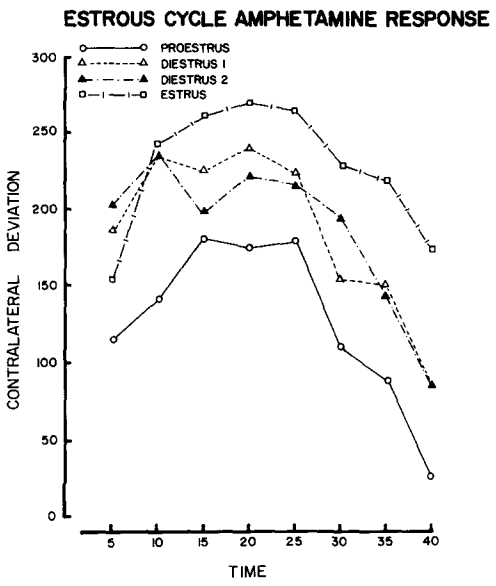

FIG. 4. Postural deviation scores for intrastriatal injection of AMPHET at each day of the estrous cycle (Experiment 1); PROESTRUS, DIESTRUS 1, DIESTRUS 2, ESTRUS. All other details as in Fig. 2.

The response to both DA and AMPHET was significantly different from the VH for each day of the estrous cycle ($p<0.01$). Unilateral injections of DA or AMPHET produced contralateral postural deviation, as indicated by the positive difference scores across each of the eight 5-min blocks of the 40 min observation period (Fig. 2). The results shown in Fig. 2 also indicate that the response to DA and AMPHET injections varied in magnitude across the estrous cycle. The difference score for postural deviation for the intrastriatal injection of DA for each day of the estrous cycle is shown in Fig. 3. The response to DA was least on the morning of proestrus and greatest on the morning of estrus ($p<0.01$). Diestrus day 1 and diestrus day 2 were not different from one another, but were different from proestrus and estrus ($p<0.01$). The difference score for postural deviation for the intrastriatal injection of AMPHET for each day of the estrous cycle is shown in Fig. 4. The response to AMPHET was least on the morning of proestrus and greatest on the morning of estrus ($p<0.01$). Diestrus day 1 and day 2 were not different from one another, but were different from proestrus and estrus ($p<0.01$).

In addition to postural deviation, the number of 1/4 rotations elicited by intrastriatal injection of DA, AMPHET, and VH were measured across the estrous cycle. Unilateral intrastriatal injections of DA and AMPHET produced contralateral 1/4 rotations greater in number than that produced by the VH (Table 1, $p<0.01$). Similar to the postural deviation response to DA and AMPHET, the number of 1/4 rotations varied across the estrous cycle (Table 1). The rotational response to DA was least on the morning of proestrus, and increased significantly by the morning of estrus ($p<0.01$). The rotational response to AMPHET was least on the morning of proestrus, and had increased significantly by the morning of estrus ($p<0.01$).

EXPERIMENT 2

The results of Experiment 1 indicate that behaviors induced by intrastriatal injections of DA and AMPHET vary in magnitude across the estrous cycle. Furthermore, consistent with the hypothesis that estrogen suppresses the behavioral responses to intrastriatal dopaminergic stimulation [18] the responses were least on the morning of proestrus. Serum estradiol levels are highest at this time [7,26]. Within 24 hours of the proestrus suppression, there was a significant enhancement in the behavioral responses to intrastriatal DA and AMPHET. The surge in serum concentration of estradiol is known to be over by the afternoon of proestrus [7,26], and so the behavioral changes are apparently related to the estrogen levels. This postulated correlation between levels of estrogen and the behavioral response to intrastriatal DA and AMPHET can be better examined by testing at various times during the day of proestrus, since the most rapid changes in serum levels of estradiol occur then.

Procedure

Rats (n=5) were given unilateral intrastriatal injections of DA and AMPHET at various times on the day of proestrus and the morning of estrus. Injections of the drugs were made on separate days, but all animals received each drug at 4, 7 and 11 hours after lights on and again at 4 hours after lights on at estrus. The drugs were administered in a counterbalanced order. All rats were monitored for their estrous cycles for two weeks prior to the initiation of behavioral testing.

Data Analysis

Only rats with regular 4 day estrous cycles throughout the entire experiment were used in the final analyses. The difference scores for the behavioral responses postural deviation and 1/4 rotations were analyzed for differences due to drug and time of day (HORMONE) using the sum total for the 40 min observation period. An analysis of variance was used to determine if the variables drug and time of day on proestrus and estrus (HORMONE) had significant overall effects.

TABLE 1

INTRASTRIATAL DA- AND AMPHET-INDUCED DEVIATION AND ROTATION ACROSS THE ESTROUS CYCLE

		Proestrus	Estrus	Diestrus I	Diestrus 2
VH	DEV*	33.8 [27]	35.0 [40]	10.8 [28]	10.8 [28]
	ROT†	1.3 [0.7]	0.2 [0.2]	−1.4 [1.2]	−1.1 [2.2]
DA	DEV	848.9 [65]‡§	1496.0 [121]‡§	1177.0 [72]‡	1189.0 [77]‡
	ROT	18.6 [4.4]¶	69.1 [14]‡	65.5 [11]‡	94.0 [19]‡
AMPHET	DEV	1017.8 [34]‡§	1822.0 [117]‡§	1508.0 [51]‡	1507.0 [77]‡
	ROT	127.4 [33]†‡¶	331.8 [51]‡	222.0 [69]‡	198.0 [52]‡

*Postural deviation score, contralateral minus ipsilateral (0.01 min units) for 40 min total.
†Rotation score, contralateral minus ipsilateral (1/4 rotations) for 40 min total.
‡Different from VH for that hormone condition.
§Proestrus different from estrus for that drug.
¶Proestrus different from all others.
[ ]=Standard Deviation.

TABLE 2

INTRASTRIATAL DA- AND AMPHET-INDUCED DEVIATION AND ROTATION AT VARIOUS TIMES OF PROESTRUS AND ESTRUS

		Proestrus			Estrus
		4 hours	7 hours	11 hours	4 hours
DA	DEV*	391 [68]‡	372 [96]‡	1075 [162]	1092 [159]
	ROT†	54 [16]	40 [14]	43 [26]	153 [37]§
AMPHET	DEV	753 [135]‡	699 [153]‡	1671 [113]+	1572 [150]
	ROT	308 [52]	278 [72]	258 [73]	681 [88]§

*Postural deviation score, contralateral minus ipsilateral (0.01 min units) for 40 min total.
†Rotation score, contralateral minus ipsilateral (1/4 rotations) for 40 min total.
+4=DA different from AMPHET.
‡Different from Proestrus −11 hours and Estrus −4 hours.
§Different from all other hormone conditions for that response.
[ ]=Standard Deviation.

Tests for simple main effects were then made using Scheffé's method for multiple comparisons (equal sample size).

RESULTS

The behavioral responses deviation and rotations, induced by the unilateral intrastriatal injections of DA and AMPHET, varied across the day of proestrus. The postural deviation response to DA and AMPHET was suppressed at 4 and 7 hours after lights on at proestrus, but was enhanced by 11 hours after lights on (Table 2; $p<0.01$). The rotational response to DA and AMPHET was suppressed at 4, 7, and 11 hours after lights on at proestrus, but enhanced by the morning of estrus (Table 2; $p<0.01$).

GENERAL DISCUSSION

In previous work we have shown that exogenous administration of estradiol benzoate initially suppresses and later enhances intrastriatal DA-induced contralateral postural deviation [18]. The results of the present study support the hypothesis that estradiol released during the estrous cycle also suppresses striatal DA-elicited behaviors; enhancement occurs as plasma estradiol declines. Both behaviors measured here, contralateral postural deviation and rotation, were relatively suppressed when plasma estradiol should be high, on the morning of proestrus [7,26] and enhanced when it is low on the day of estrus as well as on the other days of the estrous cycle. It is of interest that, when measured during the lights on portion of the light-dark cycle, striatal DA levels are highest, and DA turnover lowest, on the day of proestrus, and that DA turnover significantly increases by 12–24 hours after the proestrus surge of estrogen [1, 9, 16, 17].

Both contralateral postural deviation and rotation were elicited by DA from the dorsal striatum in the present study. In the past it has been presumed that rotation is mediated by the simultaneous activation of two DA systems, one terminating in the ventral striatum and the other in the dorsal striatum [19,21]. The DA system terminating in the dorsal striatum is thought to mediate the deviation component of rotation, while the DA system terminating in the ventral striatum is thought to mediate the activity component of rotation. However, in the present study as well as in others, rotation is mediated by the dorsal striatum itself. For example, Brown and Wolfson [6,29] have shown that rats with

unilateral DA injection into the dorsal striatum rotate contralaterally, and do so without spread of the DA into the ventral striatum. In addition, rotation induced by AMPHET or apomorphine in unilaterally DA-denervated rats is suppressed by substantia nigra pars compacta implants which innervate the dorsal striatum [11].

While both rotation and postural deviation were elicited from the dorsal striatum, and while both behaviors were suppressed on the morning of proestrus and enhanced at estrus, they did not covary simultaneously. By eleven hours after the beginning of the light period, intrastriatal DA- and AMPHET-induced postural deviation peaked, while rotation was still suppressed. In addition, rotation and postural deviation did not covary within the test sessions. Since these behaviors are differentially affected by changes in gonadal hormones, they are probably mediated by different underlying neural systems. In addition, injections of DA or AMPHET into the medio-dorsal striatum tended to induce greater contralateral rotation and less contralateral postural deviation than injections did into more lateral sites. Thus, there is functional heterogeneity within the dorsal striatum with respect to these behaviors.

The finding that two behaviors mediated by DA mechanisms in the dorsal striatum are affected by hormones on a different time course is consistent with the literature on the relationship between changes in other behaviors across the estrous cycle. With respect to rotation, authors studying amphetamine-induced rotation in intact rats [2] or rotation induced by electrical stimulation of the nigrostriatal bundle [24] also find that it peaks during estrus, although they have not found a suppression during proestrus. In the present experiment, postural deviation peaked late in the day of proestrus. Other behaviors, including self-stimulation elicited from the substantia nigra pars compacta, wheel running, and sexual receptivity, which may also relate to DA mechanisms, peak during proestrus [27,28].

There are several possibilities why the various behaviors mediated by DA in the nigrostriatal system peak at different times in the estrous cycle. First, it is reasonable to consider the hypothesis that behaviors mediated by DA-sensitive neural systems in the basal ganglia are differentially sensitive to estrogen itself. This proposition would be supported by the findings of Bédard *et al.* [5] in monkeys, who reported that the DA-related behaviors tremor and lingual dyskinesia, induced by a midbrain lesion involving the substantia nigra pars compacta, are differentially affected by estradiol benzoate. Lingual dyskinesia is enhanced by DA agonists; this enhancement is suppressed by the systemic administration of estradiol benzoate. In contrast, tremor is suppressed by DA agonists, a suppression which is unaffected by estradiol benzoate. Second, these separate behaviors mediated by DA-sensitive systems of the basal ganglia may be differentially affected by other releasing factors or hormones which change during the estrous cycle. For example, progesterone reaches its peak after estrogen; changes in DA-mediated behaviors occurring during the estrous cycle may relate to progesterone levels. Third, unless behavioral measures are taken continuously or are timed fortuitously, rapidly-occurring behavioral changes may be missed. For example, other authors have not measured rotational behavior on the morning of proestrus [2, 23, 24]. Finally, the various methods used to induce dopaminergic stimulation of the striatum may be differentially sensitive to the effects of estrogen, and consequently lead to different behavioral results.

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