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SEX DIFFERENCES AND ESTROUS CYCLE DEPENDENT VARIATION IN ROTATIONAL BEHAVIOR ELICITED BY ELECTRICAL STIMULATION OF THE MESOSTRIATAL DOPAMINE SYSTEM

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SUMMARY

In this study electrical stimulation-induced rotational behavior was used as a behavioral index of mesostriatal dopamine (DA) activity to investigate gender and hormonal influences on the DA system. In female rats we found estrous cycle related variations in electrical stimulation-induced rotational behavior. A constant electrical stimulus produced significantly more turning on the day of estrus, than it did 24 h later, on diestrus 1. Gonadectomy attenuated contraversive rotational behavior in female, but not male rats. In contrast, ovariectomy had no effect on the ipsiversive rotational behavior produced by stimulation of the reticular formation. This evidence supports the idea that endogenous changes in gonadal hormone levels influence the functional activity of the mesostriatal DA system in a sexually dimorphic manner

INTRODUCTION

It is well established that gonadal steroid hormones modulate the activity of hypothalamic catecholamines (CA) [16,37]. It is less well known that gonadal

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hormones may also modulate extra-hypothalamic CA neurons, particularly mesostriatal dopamine (DA) neurons. A major approach in studying the effects of hormones on the mesostriatal DA system has been to examine hormonal influences on behaviors elicited by dopaminergic drugs. There have been a number of reports that gonadal steroids influence the stereotypy and/or locomotion elicited by dopaminergic drugs [9, 11, 18, 20, 25, 33]. Sex differences in the behavioral effects of dopaminergic drugs have also been found [30, 33, 34].

Gender and hormonal influences on behaviors elicited by dopaminergic drugs provide indirect evidence that gonadal hormones modulate the functional activity of the mesostriatal DA system. However, a major problem with using drug-induced behavioral models to study gender and hormonal influences on brain DA activity is in separating central from peripheral effects. The intensity and duration of many dopaminergic drug effects are very dependent on the rate the drug is metabolized by liver microsomal enzymes [12]. Unfortunately, gonadal steroid hormones may alter the rate of drug metabolism by either inducing or suppressing liver microsomal enzyme production [12]. In rats there are also large sex differences in the rate at which many drugs are metabolized [22], including amphetamine [8, 19, 24]. Therefore, if one observes drug-induced behavioral differences between male and female rats, or between rats of the same sex but in different hormonal conditions, one cannot be sure if the behavioral differences are due to differences in brain organization or in drug metabolism. It is also possible that behavioral differences observed between groups are not due to hormones modulating neuronal activity, but due to a unique interaction between hormones and the test drug.

One solution to these problems would be to use a behavioral model of mesostriatal DA activity which does not require the use of drugs. Electrical stimulation-induced rotational behavior provides such a model [3]. Contraversive rotational behavior is produced by electrical stimulation of ascending DA fibers, which originate in the substantia nigra and ventral tegmental area and course through the posterior-lateral hypothalamus. This rotational behavior is thought to result from the release of DA in the striatum, and perhap the nucleus accumbens [1–3]. We have used this behavioral model of mesostriatal DA activity to investigate gender and hormonal influences on ascending brain DA systems.

METHODS

Electrical stimulation paradigm

After pilot studies to establish coordinates, a total of 65 Holtzman (Madison, WI) rats were bilaterally implanted with bipolar electrodes aimed at the ascending DA fibers as they course through the posterior-lateral hypothalamus. With the skull flat [15] the electrodes were placed 3.0–3.5 mm posterior to

bregma, 1.8 mm lateral to the sagittal suture and 8.0–8.4 mm ventral from the skull surface. The electrodes consisted of 2 twisted strands of Teflon insulated 254 μm diameter stainless steel wire (Plastic Products).

After 2 weeks of recovery the animals were screened by applying current to each electrode in turn to determine if electrical stimulation would produce rotational behavior. The current was supplied by a Grass S8 stimulator and consisted of monophasic rectangular pulses of 0.1 msec duration presented at a frequency of 50 pulses/sec. The electrode which produced the most vigorous rotational behavior at the lowest current intensity was used for the remainder of the experiment. This electrode was tested using a variety of current levels (50–300 μA). The lowest current intensity which produced vigorous turning (5–8 full turns/10 sec) was used thereafter when testing that electrode. The maximum current intensity ever used was 300 μA. Not all the implanted animals showed contraversive rotational behavior. The data presented below were obtained from the 40 rats which did show consistent contraversive rotational behavior. The remaining animals are discussed briefly in the section on electrode placement.

Approximately one week after this screening procedure formal testing began. The leads were connected to each rat and it was placed in a 18.5 × 25 × 45 cm high plexiglass chamber with a solid stainless steel floor. The current level used for each individual animal was set by recording the voltage drop across a 100 Ω resistor in series with the rat and adjusting the output of the stimulator appropriately. At least 2 min after setting the current level the animal was stimulated for 10 sec and the number of $\frac{1}{4}$ turns (90°) it made was observed by the experimenter and manually recorded. Each animal was given 3 stimulation trials per day, with at least 2 min between each trial. The average number of $\frac{1}{4}$ turns made over the 3 trials constituted the number of $\frac{1}{4}$ turns recorded for that day. Each animal was tested in the same chamber every day for 21 days.

All testing was conducted between 09.00 and 12.00 h. However, the animals were housed on a reversed light–dark cycle (14 : 10), with the lights going off at 06.30 h. The testing room was dimly illuminated with red light and the animals were transported from the dark colony room (equipped with red lights) to the testing room in a covered box. Therefore, the animals were tested 2.5–5.5 h after lights out.

After testing on Day 21 half of the females were ovariectomized (OVX) and half the males castrated (CAST) under ether anesthesia (n = 10/gp). The remaining animals received a sham operation in which the gonads were externalized and then replaced without being damaged (n = 10/gp). After one day of recovery the animals were subjected to the same daily testing paradigm as described above for an additional 30 days. To monitor the estrous cycle vaginal smears were taken for at least the last 8 days of baseline testing prior to gonadectomy (GDX) or the sham operation, and for at least 8 days afterwards.

Reticular sites

An additional group of 12 female rats were implanted with stimulating electrodes aimed at the nucleus reticularis pontis caudalis [15]. Earlier studies [29] have shown that stimulation of this site also produces vigorous rotational behavior, but ipsilateral to the stimulating electrode. These animals were tested in the same manner as described above, except they were only tested for 10 consecutive days prior to OVX or a sham-op. After testing on the 10th day, 7 rats were OVX and 5 received a sham-operation. Following this the animals were not tested every day for rotational behavior, but only on Days 15, 25 and 40.

Time sample of behavior

On Day 21 PRE-OP (prior to GDX or the sham operation) and Days 15 and 30 POST-OP (after GDX or sham-op), the general behavior of each animal was monitored using a time sampling procedure. Approximately 2 h after being tested for rotational behavior, each rat was returned to its usual testing chamber (under red light conditions). It was left there to habituate for 5 min, although the animals were already quite familiar with the test chamber. The incidence of each of the following behaviors was then recorded every 5 sec for 5 min (60 samples): walking (all 4 legs in motion); rearing (2 front paws off the floor); head movements (including postural adjustments); sniffing (while otherwise immobile); chewing (usually on the small pieces of wood shavings on the floor); grooming (face-washing and body grooming); and immobility.

Histology and electrode placements

At the completion of the experiment each rat was perfused through the heart, first with 0.9% saline followed by 10% formal saline. The brains were cut into 40 μm sections using a frozen technique, mounted on gel-coated slides and stained with cresyl violet. The location of each electrode tip was determined, and plotted on drawings adapted from the atlas of Fifková and Maršala [15].

RESULTS

Estrous cycle dependent variations in contraversive rotational behavior

Those rats (n = 15) which showed clear 4 day estrous cycles during Days 14 to 21 PRE-OP were identified by a post hoc analysis of their vaginal smear records. Using the last estrous period closest to Day 21 as a reference point, and working backward in time, the days of proestrus (P), diestrus 2 (D2), diestrus 1 (D1) and the preceding estrus (E) were determined. Following this, the number of $\frac{1}{4}$ turns produced on each day of the identified estrous cycle was determined

from the behavioral records, and expressed as a percent change from baseline. The baseline score for each animal consisted of the average number of $\frac{1}{4}$ turns produced over the last 5 days of baseline testing (Days 17–21). Thus, the number of $\frac{1}{4}$ turns produced on any one day are expressed as a percent of this baseline. It was necessary to convert the raw data to percent values because of the considerable variation in the number of $\frac{1}{4}$ turns produced from electrode site to electrode site. Some sites produced 5–10 $\frac{1}{4}$ turns per 10 sec, while others produced 40–50 $\frac{1}{4}$ turns per 10 sec. Most sites produced between 20 and 40 $\frac{1}{4}$ turns per 10 sec (see below).

Fig. 1 shows that the number of $\frac{1}{4}$ turns (percent of baseline) produced by a constant electrical stimulus varies across the estrous cycle (one-way analysis of variance for repeated measures, $F = 3.63$, $P < 0.01$). The greatest amount of rotational behavior was elicited during E, and dropped 24 h later, on D1 (paired t-test, $t = 2.49$, $P < 0.026$; all two-tailed tests). The drop on D1 was followed by a gradual rise in the number of $\frac{1}{4}$ turns, which peaked during the second estrous period. The number of $\frac{1}{4}$ turns produced on the second day of E was significantly greater than the number of $\frac{1}{4}$ turns produced on D1 or D2 ($P < 0.028$). An analysis of the number of $\frac{1}{4}$ turns (percent of baseline) produced by males over a comparable 5 day period (Days 17–21 PRE-OP) yielded no such differences.

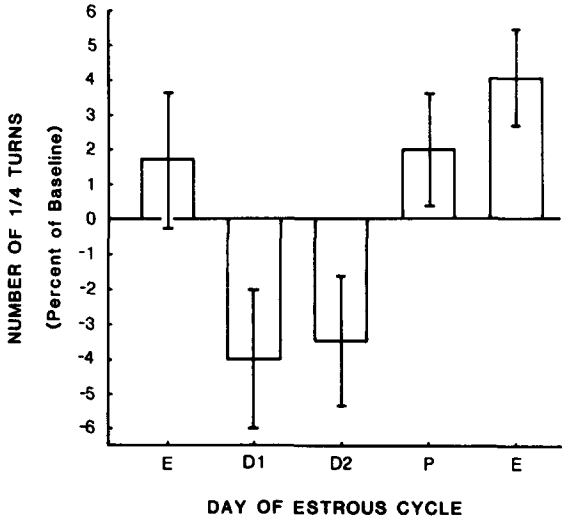

Fig. 1. Estrous cycle dependent variations in electrical stimulation-induced rotational behavior. The bars represent the mean (±S.E.) number of $\frac{1}{4}$ (90°) turns made in a 10 sec trial plotted as a percent change from baseline. E = day of estrus; D1 = diestrus 1; D2 = diestrus 2; P = proestrus. A constant electrical stimulus elicited significantly more rotational behavior on the first day of E than on D1. The number of $\frac{1}{4}$ turns elicited on the second day of E was significantly greater than on D1 or D2. See text for a complete description.

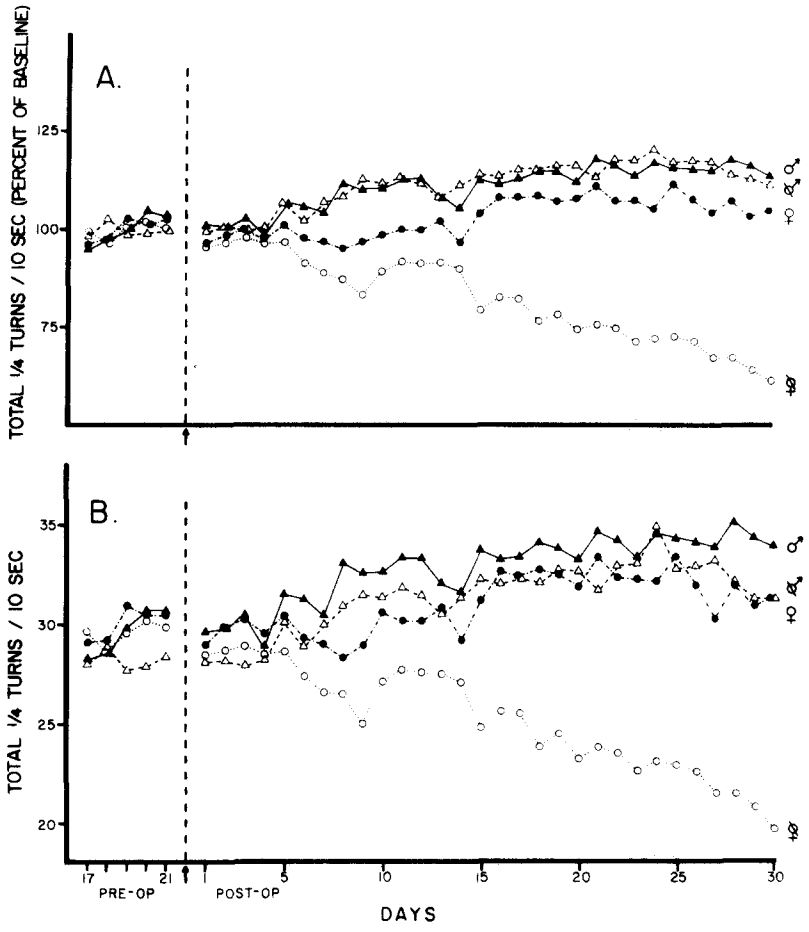

Fig. 2. The effects of gonadectomy (GDX) in male and female rats on electrical stimulation-induced rotational behavior. A: each symbol represents the mean number of $\frac{1}{4}$ turns made in a 10 sec trial on one day plotted as a percent change from baseline. B: each symbol represents the actual number of $\frac{1}{4}$ turns made in a 10 sec trial on one day. All animals were tested daily for 21 days prior to GDX or a sham-operation (PRE-OP), although only the last 5 days PRE-OP (days 17–21) are plotted. The average number of $\frac{1}{4}$ turns made over these 5 days for each animal constitutes baseline for that animal. At the vertical dashed line half the animals were GDX and half received a sham-operation, and daily testing resumed for an additional 30 days (POST-OP). GDX attenuated rotational behavior in female but not male rats (see text). Symbols: open circles, GDX females; closed circles, sham-operated females; open triangles, GDX males; closed triangles, sham-operated males.

*Effects of gonadectomy on contraversive rotational behavior**

Fig. 2 shows the effects of gonadectomy (GDX) or a sham-operation on electrical stimulation-induced rotational behavior in male and female rats. In Fig. 2A rotational behavior is expressed as a percent of baseline turning (as

* A preliminary version of these data was published in an earlier report [31].

described above). The actual number of $\frac{1}{4}$ turns made during 10 sec of stimulation is plotted in Fig. 2B for comparison purposes. Statistical analyses were conducted on the percent of baseline turning data. Prior to GDX or a sham-operation, there were no differences between the 4 groups (analysis of variance on Days 17 and 21 PRE-OP). However, following surgery, the number of $\frac{1}{4}$ turns produced by OVX females slowly declined. An analysis of variance on Days 1, 5, 10, 15, 20, 25 and 30 POST-OP revealed that the groups differed in the number of $\frac{1}{4}$ turns (percent baseline) by Day 10 ($F = 3.9$, $P < 0.02$). On Day 10 OVX females made significantly fewer $\frac{1}{4}$ turns (percent baseline) than either male group ($P < 0.05$, Tukey A test [38]), but did not differ from sham-operated females. By Day 15 POST-OP the OVX females differed from the sham-operated females ($P < 0.05$) and both male groups ($P < 0.01$), although these latter 3 groups did not differ from each other at any time. The magnitude of the differences between the OVX females and the other 3 groups steadily increased between Days 15 and 30 POST-OP. Thus, OVX of female rats attenuated electrical stimulation-induced rotational behavior, but castration of male rats had no effect on this behavior.

It should be mentioned that not all of the OVX females showed a reduction in rotational behavior. Of the 10 OVX animals tested 3 failed to show any decline. The average percent change from baseline for all 10 OVX animals was $-38.3\% \pm 11.5$ (S.E.). If the 3 rats which did not drop are omitted the average percent change was $-56.1\% \pm 9.4$. Why some rats did not drop is unknown. For example, there were no obvious differences in electrode placement.

Reticular stimulation

We studied the effects of GDX on rotational behavior elicited by reticular stimulation to determine if the drop we observed following OVX of mesostriatal stimulated animals was a relatively specific effect. In contrast to the difference observed between OVX and sham-operated animals given mesostriatal stimulation there was no difference between sham-op and OVX females given reticular stimulation at any point in time after surgery (Table I).

Time sample of behavior

To determine if a generalized hypokinesia could account for the decline in contraversive rotational behavior shown by OVX females we divided the behaviors observed during the 5 min time sample of behavior into two behavioral categories. Table II shows the incidence of the most 'active' behaviors (walking and rearing) and the incidence of 'immobile' behaviors (immobility and sniffing while otherwise immobile) for each of the 4 groups on Day 21 PRE-OP and Days 15 and 30 POST-OP. A 3×4 analysis of variance yielded no significant effects of group or time when performed on either the 'active' or 'immobile' scores.

TABLE I

The number of $\frac{1}{4}$ turns/10 sec produced by electrical stimulation of the reticular formation before and after ovariectomy or a sham-operation in female rats

Each value represents the mean ± S.E.M. The ovariectomized (OVX) and sham-operated animals did not differ statistically at any point in time.

	Pre-operative Days			*Post-operative Days*		
	1	5	10	5	15	30
Sham-op females	28.6 ± 5.2	28.0 ± 3.5	24.7 ± 3.1	21.3 ± 1.9	21.3 ± 2.2	21.9 ± 3.5
OVX females	27.3 ± 3.0	24.4 ± 2.6	25.5 ± 4.5	22.8 ± 4.5	19.7 ± 3.7	22.7 ± 5.6

TABLE II

The mean (± S.E.) incidence of 'active' behaviors (walking and rearing) and immobility during a 5 min time sample of behavior

Each animal was tested on Day 21 pre-op and Days 15 and 30 after gonadectomy (GDX) or sham-operation (sham-op). There are no significant differences between groups or across time.

	Active behaviors			*Immobility*		
	PRE-OP (Day 21)	*POST-OP (Day 15)*	*POST-OP (Day 30)*	*PRE-OP (Day 21)*	*POST-OP (Day 15)*	*POST-OP (Day 30)*
Sham-op females	24.9 ± 3.1	20.7 ± 2.2	19.0 ± 1.8	5.9 ± 1.8	4.0 ± 1.4	3.3 ± 0.9
GDX females	20.3 ± 1.2	16.5 ± 3.2	15.0 ± 1.6	2.2 ± 0.8	1.0 ± 0.5	1.7 ± 0.5
Sham-op males	18.3 ± 1.7	17.1 ± 1.6	17.9 ± 2.3	3.3 ± 1.0	2.9 ± 1.0	1.8 ± 0.7
GDX males	19.3 ± 1.6	21.6 ± 1.9	20.6 ± 1.6	2.9 ± 0.5	3.6 ± 0.9	3.3 ± 0.8

Therefore, although OVX of female rats produced a decline in electrical stimulation-induced rotational behavior it is unlikely that this is due to a generalized decline in motor activity as measured in an open-field situation (see ref. 5 for review).

Electrode placements

Fig. 3 illustrates the locations of the electrode tips in the hypothalamus plotted as a function of their efficacy in producing rotational behavior. Those sites which produced rotational behavior away from the side stimulated (contraversive) were subdivided into 4 groups based on the number of baseline $\frac{1}{4}$ turns (Days 17–21 PRE-OP) produced per μCoulomb of electricity passed. Those sites which were most effective in producing contraversive turning were closest to the ascending dopamine fibers. Less efficacious sites were located further away from the dopamine fibers. In addition, the most effective sites were located rostrally. Sites which failed to elicit rotational behavior fell outside the cluster of positive sites, and these tended to be ventral to the ascending DA fibers. These latter sites typically produced general hyperactivity (rearing, walking, sniffing) or forced movements, depending on their location. Lastly, some sites in the hypothalamus produced rotational behavior towards the side stimulated (ipsiversive). These sites were located in or near the fibers of the crus cerebri. Sites which produced ipsiversive turning did not overlap with sites which produced contraversive turning. This analysis provides further support for the assumption that contraversive rotational behavior results from stimulation of ascending dopamine fibers.

There were no significant differences in the location of the electrodes in intact or GDX males or females. For example, using the number of $\frac{1}{4}$ turns/μCoulomb as an index of electrode position relative to the mesostriatal bundle the average number of $\frac{1}{4}$ turns/μCoulomb produced by each group was calculated. OVX females produced an average of 2.71 ± 0.42 (S.E.) $\frac{1}{4}$ turns/μCoulomb, sham-op females 2.14 ± 0.14, CAST males 2.90 ± 0.64 and sham-op males 2.21 ± 0.32.

Lastly, the electrodes aimed at the reticular formation were all found within nucleus reticularis pontis caudalis, as described by Fifková and Maršala [15].

DISCUSSION

In the present study we found that the amount of rotational behavior elicited by a constant electrical stimulus varies with the estrous cycle in female rats. Electrical stimulation-induced rotational behavior was most vigorous on the day of E, and least vigorous on the day of D1. Although the magnitude of the change was small, it was reliable, and the pattern is the same as that seen for amphetamine (AMPH)-induced rotational behavior [8]. Becker et al. [8] reported that AMPH-induced rotational behavior is also highest on the day of E, and declines dramatically 24 h later, on the day of D1. Estrous cycle dependent variations are seen in other behaviors, including running wheel activity, feeding (see ref. 5 for review), and self-stimulation from electrodes implanted in the substantia nigra [36]. As with rotational behavior the highest levels of activity in these behaviors are seen

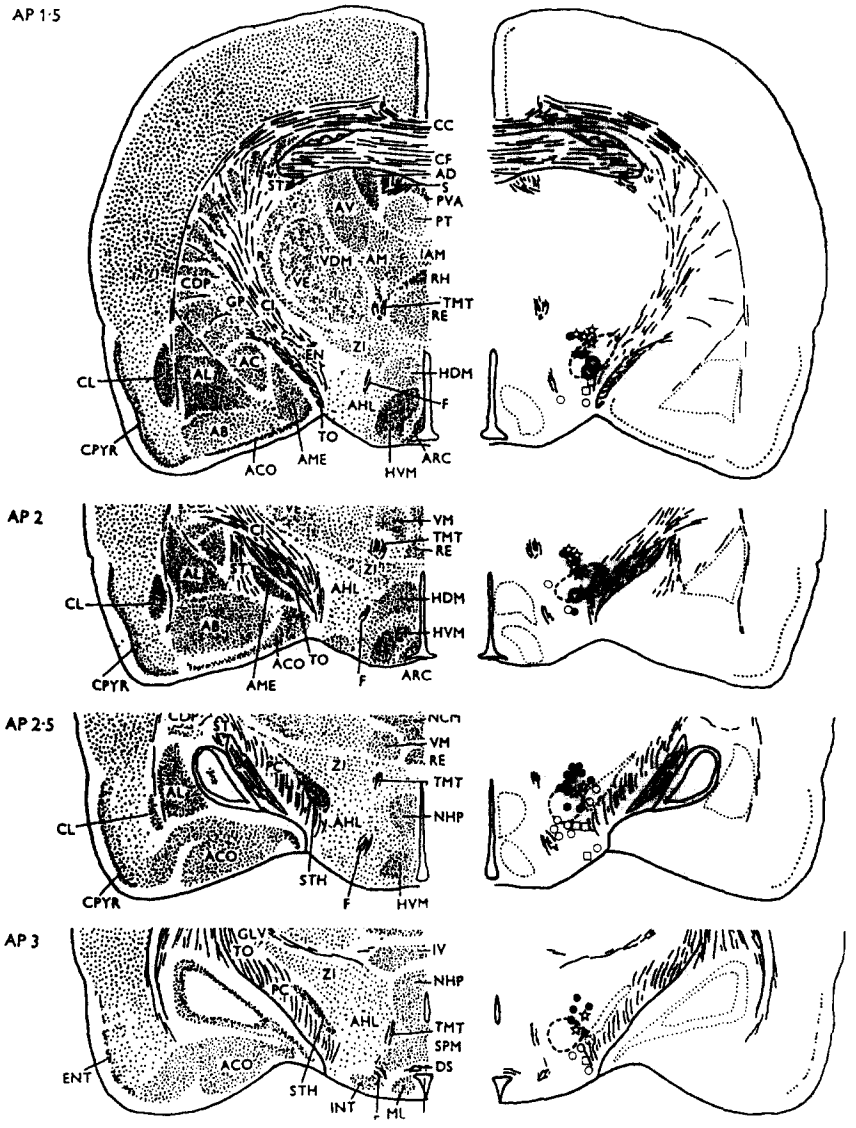

Fig. 3. The location of the electrode tips plotted as a function of their efficacy in producing rotational behavior. The sections are adapted from the atlas of Fifková and Maršala [15]. Those electrodes which produced contraversive rotational behavior were divided into one of 4 groups based on the number of baseline $\frac{1}{4}$ turns (mean of days 17–21 PRE-OP) produced per μCoulomb of electricity passed during one trial. Symbols: white star in black circle, $> 5\frac{1}{4}$ turns/μCoulomb; filled star, 3–5 $\frac{1}{4}$ turns/μCoulomb; open star, 2–3 $\frac{1}{4}$ turns/μCoulomb; filled circle, 1–2 $\frac{1}{4}$ turns/μCoulomb. The sites indicated by open squares produced ipsiversive rotational behavior, and those indicated by open circles did not produce any rotational behavior. These latter sites typically produced general hyperactivity (walking, rearing, sniffing) or forced movements. The heavy dashed oval represents the approximate location of the ascending dopamine fibers.

on the day of E. All of the above behaviors are thought to involve the mesostriatal DA system to some extent, and therefore it seems reasonable to suggest that estrous cycle related changes in brain DA activity contribute to these variations in behavior.

There is more direct evidence that mesostriatal DA activity changes with the estrous cycle. On the day of E there is increased striatal DA turnover and AMPH-stimulated DA release, concomitant with low striatal DA concentrations [7, 14, 21]. According to these measures, striatal DA activity remains elevated throughout D1. Relative to E and D1, AMPH-stimulated DA release from striatal tissue is depressed, DA turnover is low, and levels elevated during P. It is interesting that by these neurochemical measures one would predict the greatest striatal activity on E and D1, followed by a decline on P. In contrast, rotational behavior was highest on E, and declined on D1 (also see ref. 8).

One difference between the studies using rotational behavior as an index of mesostriatal activity and the neurochemical experiments is that behavioral testing was done during the night portion of the day/night cycle (see Methods). The neurochemical studies were conducted during the day. There are strong changes in brain DA activity across the day/night cycle [10, 23, 35], and this may account for the apparent discrepancy between the behavioral and neurochemical findings. For example, Becker and Ramirez [7] found that when rats were killed approximately 4 h after lights on AMPH-stimulated DA release from striatal tissue was elevated on E and D1, and depressed on P. However, preliminary data from this laboratory indicate that when rats are killed about 4 h after lights off AMPH-stimulated DA release from striatal tissue is significantly lower on D1 than on E (unpublished studies by J.B. Becker). Thus, when the neurochemical and behavioral measures are taken at the same time of day we found a strong correlation between estrous cycle dependent changes in AMPH-stimulated DA release, and both electrical stimulation and AMPH-induced rotational behavior [8]. It may be that striatal DA activity is in fact highly modulated by gonadal hormones and this variable also interacts with circadian changes in DA activity. Obviously more work is needed to precisely follow the changes in striatal DA activity across the estrous cycle. Of course, we cannot rule out the possibility that gonadal hormones actually modulate a non-dopaminergic system, which in turn influences DA activity.

The idea that changes in gonadal hormone levels are responsible for estrous cycle dependent differences in rotational behavior is supported by our observation that OVX of female rats attenuates rotational behavior elicited by electrical stimulation of the mesostriatal bundle. OVX has also been reported to attenuate the stereotyped behaviors produced by AMPH or apomorphine [26], although this is not always found [18, 33]. Castration of male rats or a sham-operation in males or females did not alter electrical stimulation-induced rotational behavior. These effects of OVX seem relatively specific since OVX females did not differ

from sham-operated females when rotational behavior was elicited by stimulation of the reticular formation. Also, a time sample of spontaneous behavior in the testing chambers did not reveal any generalized hypokinesia in OVX rats [5]. This sex difference in the effect of gonadectomy on rotational behavior was predicted by the report of Becker and Ramirez [7], who found that OVX of females attenuates the AMPH-stimulated release of DA from striatal tissue, while CAST of males is without effect.

For an electrode placed in the hypothalamus to produce rotational behavior it had to be either in, or very near the axons of ascending DA neurons. Electrode placements even slightly more medial or ventral in the lateral hypothalamus did not produce rotational behavior. The anatomical area where rotational behavior was induced seems considerably more circumscribed than the area where electrical stimulation produces stimulus-bound consummatory behaviors or self-stimulation [13, 17, 39]. It has been suggested that these latter behaviors are also due to stimulation of ascending DA systems (e.g. refs 17, 27, 28 and 39). The differences in the location of effective sites for producing contraversive rotational behavior vs self-stimulation or evoked behaviors suggest that these latter behaviors are not due solely to the stimulation of ascending DA neurons.

Lastly, a recent report suggested that the contraversive rotational behavior elicited by electrical stimulation of the substantia nigra is not due to activation of ascending DA neurons [32]. We cannot comment directly on the effects of stimulation of the substantia nigra, since we stimulated the DA fibers as they pass through the hypothalamus. The rotational behavior produced by stimulation in the hypothalamus is much more vigorous than that produced by stimulation of the substantia nigra. Our animals averaged around 7–8 full turns/10 sec, while Saranak and Goldfarb [32] report that substantia nigra stimulation produced approximately 2 turns/10 sec in a 'good rotator'. Our best animals made up to 15 full turns in 10 sec. As discussed above, the anatomical distribution of effective sites supports the idea that the contraversive rotational behavior reported here is due to activation of ascending DA neurons. In addition, Bandler et al. [4] have reported that stimulation of the hypothalamus only produces contraversive turning behavior when the electrode is within axons ascending from the zona compacta of the substantia nigra. We are currently examining the effects of 6-hydroxydopamine lesions of the substantia nigra on turning elicited by stimulation in the lateral hypothalamus (E. Castaneda, unpublished experiments). Rotational behavior is attenuated by the depletion of striatal DA. However, for a 6-hydroxydopamine lesion to be effective in attenuating electrical stimulation-induced rotational behavior it must produce nearly total depletion of striatal DA. Smaller depletions have little effect. Therefore, we agree with previous researchers [1–4] that turning behavior produced by stimulation of ascending DA fibers is caused by the release of DA in the striatum.

In summary, we suggest that: (1) the sex differences and estrous cycle

variations observed in behaviors elicited by dopaminergic drugs are not necessarily due solely to peripheral factors, such as differences in drug metabolism; (2) physiological changes in the levels of gonadal steroid hormones modulate the activity of mesostriatal DA neurons, at least in female rats; and (3) there are sex differences in the hormonal modulation of striatal DA activity. Exactly which gonadal hormone(s) plays the major role, where in the nervous system it acts, and whether it acts directly or indirectly are not yet known.

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