

Sex Differences in Amphetamine-Elicited Rotational Behavior and the Lateralization of Striatal Dopamine in Rats¹

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Sex differences	Amphetamine	Asymmetry	Dopamine	Striatum	Rotational behavior
Lateralization	Gonadal steroids	Catecholamines			

SEX differences in a wide variety of behaviors have been documented in a great many species [2, 3, 9, 27, 28, 37, 42, 43, 46, 52, 53, 57, 59]. Many of these sex differences in behavior have been attributed to either the early organizational effects of gonadal steroid hormones on the central nervous system, or to their activational role in the adult animal [3, 27, 28, 55]. An obvious question which arises from these observations is, with what brain structures do gonadal steroids interact to result in behavioral sex differences? Considerable progress has been made towards answering this question with respect to sex differences in reproductive behaviors. For example, sex differences have been described in hypothalamic-preoptic area anatomy and function [18, 26, 27, 30, 54] that are believed to underlie sex differences in gonadotrophin release and reproductive behaviors. However, there is very little evidence available as to whether gonadal steroids interact with extra-hypothalamic neural systems to result in sexually dimorphic non-reproductive behaviors.

In the initial attempt to study sex differences in non-

reproductive behaviors reported here, we first identified a neural system outside the hypothalamo-pituitary axis which may be sexually dimorphic. There is considerable evidence to suggest that gonadal steroids interact with hypothalamic catecholamine (CA) systems [22]. Therefore, one logical place to suspect sexual dimorphism would be in other brain CA systems. Indeed, a review of the literature shows that the nigrostriatal dopamine (DA) system may be sexually dimorphic. In recent studies Becker and Ramirez [5] demonstrated that the *in vivo* presence or absence of gonadal steroids modulates the amphetamine-stimulated *in vitro* release of DA from striatal tissue fragments obtained from female, but not male, rats. Sex differences have been reported in striatal DA content [14], and in female rats or mice the concentration and turnover of striatal DA fluctuates across the estrous cycle [15,34]. Also gonadal steroid modulation of striatal activity is suggested by reports that estrogen influences circling (rotational) and stereotyped behaviors induced by dopaminergic agonists ([7, 11, 33, 39, 50, 51]; see below).

We hypothesized that if sex differences exist in the *in*

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vitro release of striatal DA [5], such differences should be evident in behaviors thought to involve nigrostriatal activity. There is a good deal of evidence that amphetamine (AMPH)-induced rotational behavior in both unilaterally lesioned and intact rodents involves the asymmetric release of DA from nigrostriatal neurons [24, 49, 58]. In the experiments reported here we looked for sex differences in AMPH-elicited rotational behavior in intact (non-lesioned) rats because: (1) The evidence that rotational behavior in intact rats is a reasonably sensitive 'behavioral assay' of nigrostriatal DA activity seems quite strong [24]; (2) It is an easily quantifiable behavior; and (3) we thought that CA/hypothalamo-pituitary interactions may be altered in unknown ways by use of a model involving unilateral lesions of ascending DA systems.

As predicted, we found sex differences in AMPH-elicited rotational behavior. Therefore, this behavior may be added to the list of non-reproductive behaviors which are sexually dimorphic. More interestingly, we found that these behavioral sex differences may be related to sex differences in the lateralization of striatal DA.

METHOD

Subjects

The experimental subjects were 26 female and 17 male adult Sprague-Dawley (Holtzman) rats (200–325 g) housed in a temperature (23°C) and light controlled room (14:10 hr light:dark cycle, lights off at 19:00 hr). The female group consisted of 14 rats which were in estrus and 12 rats which were in proestrus at the time of the experiment. Estrous cycle condition was determined by daily vaginal smear examinations for at least 8 days prior to the experiment, and only regularly cycling females were used. To control for the effects of handling the females, male rats were also handled daily prior to testing. The reason for examining females at known stages of their estrous cycle was to determine if this variable influenced rotational behavior. The effects of the estrous cycle on rotation will be discussed in a later publication.

Apparatus

The rats were tested in a spherical rotometer which consisted of 2 white hemispherical bowls with a diameter of 30.5 cm, one inverted on the other. The top bowl had a 10 cm diameter hole in its top, which was covered with a wire grid through which the animal could be observed. The rotometer was divided into quadrants by lines on the outside of the top bowl.

Procedure

Testing occurred between 900 and 1200 hours. Each rat was individually placed in the rotometer and observed directly for 15 min. A record was kept of every 1/4 turn made to the right and left. A rat was considered to make a 1/4 turn whenever an imaginary point located midway between its front shoulders passed from one quadrant to another. The animal was then removed from the rotometer and injected with either 0.9% saline or d-amphetamine sulfate (20 mg/kg, IP) dissolved in saline (20 mg/ml). The animal was then immediately replaced in the rotometer and the above procedure repeated.

From the data on 1/4 turns the following variables were

calculated: (1) *Total 1/4 turns* (1/4 turns to the left and right summed); (2) *Total rotations* (rotations to the left and right summed). One rotation equals 4 consecutive 1/4 turns in the same direction; and (3) *Net rotations* (rotations in the dominant direction minus those to the other). This procedure was designed to produce data comparable to that obtained with the automatic rotometer described by Greenstein and Glick [31].

At the end of this second 15 min period, the animal was killed by decapitation and the brain placed on an ice-chilled tray. The striatum and medial frontal cortex [41] was then dissected from the brain by an experimenter (J. B. B.) who was unaware of the behavioral results. In all animals the order of dissection was (1) right striatum, (2) left striatum, (3) right medial frontal cortex, (4) left medial frontal cortex. The tissue pieces were weighed and placed in collection tubes on ice as each dissection was completed. After all pieces had been dissected, perchloric acid (0.1 N) was added to the collection tubes.

Catecholamine Assay

Tissue was homogenized in ice cold 0.1 N HClO₄ (weight:volume, cortex 1:10; striatum 1:40) and centrifuged (Beckman J-21B centrifuge, JCF-2 swinging bucket rotor) at 5,000 RPM for 45 min at 4°C. The supernatant was frozen at -20°C until the day of the assay. Samples were assayed using a microradioenzymatic assay with a sensitivity of 32 pg per tube [6]. In this assay, partially purified catechol-O-methyl-transferase (COMT) prepared from rat liver is used to transfer the methyl group of S-adenosyl-L-[methyl]³H-methionine to norepinephrine and dopamine. After extraction of the methylated products, the O-methylated [³H]-normetanephrine and [³H]-methoxytyramine are separated on Dowex-50-W-X-4 cation exchange columns and radioactivity in the appropriate effluent fractions determined by liquid scintillation [6].

RESULTS

Behavior

(A) *Pre-Drug*. In the initial 15 min period (prior to injection) female rats made significantly more total 1/4 turns ($p < 0.01$) and total rotations ($p < 0.02$) than did males (Fig. 1A and 1B, left). Unless otherwise noted, all comparisons were made with two-tailed t-tests.

Net rotations consist of total rotations in one direction minus total rotations in the other direction. An animal may be rotating very vigorously but if these rotations are distributed equally to the right and left, net rotations would equal zero. Thus, net rotations provide one index of behavioral lateralization. In the 15 min period prior to AMPH treatment females made a mean of 5.73 ± 0.81 (SE) and males 3.90 ± 0.76 net rotations (pre-drug in Fig. 1C). This difference was not statistically significant.

(B) *Post-Drug*. The effect of AMPH-treatment on total 1/4 turns and total rotations is plotted on Figs. 1A and B (right). AMPH treatment greatly enhanced the number of 1/4 turns (mean percent change \pm SE: males-417 \pm 102%; females-475 \pm 69%) and total rotations (males-694 \pm 217%; females-872 \pm 190%) made by both males and females. After AMPH, females made significantly more total 1/4 turns ($p < 0.01$) and total rotations ($p < 0.05$) than males. A saline injection produced no effect on rotational behavior, and activity decreased to very low levels as the animal further habituated to the apparatus.

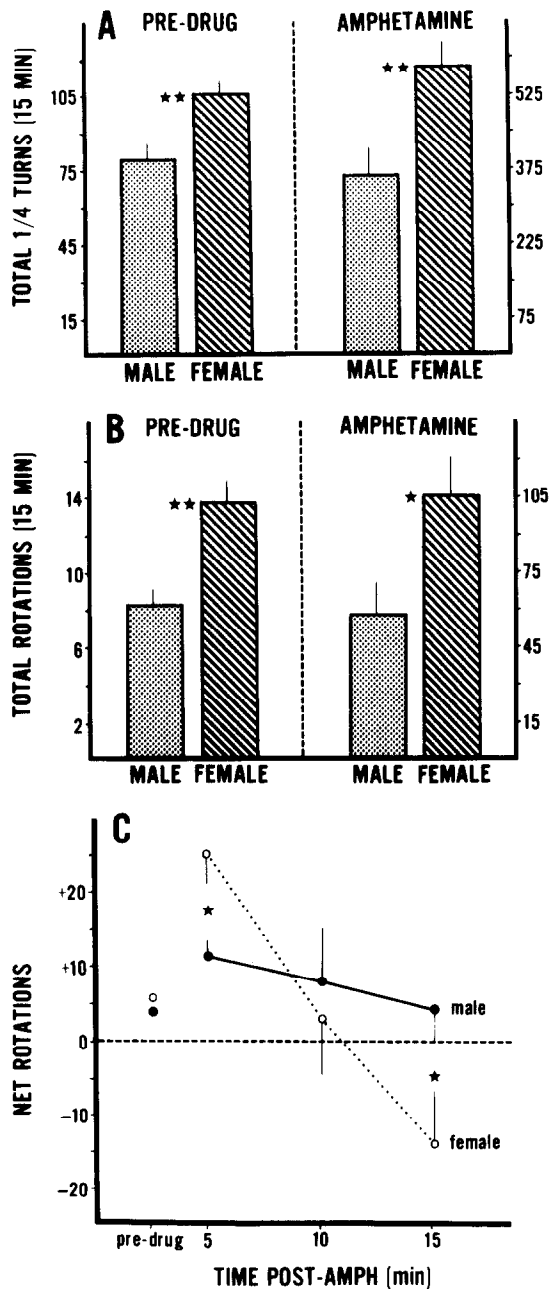


FIG. 1. Sex differences in rotational behavior prior to and after an injection of d-amphetamine (AMPH; 20 mg/kg). (A) Total 1/4 turns made by male and female rats during the 15 min period prior to AMPH (left), and during the 15 min period after AMPH treatment (right). Note the different scales pre- and post-AMPH. (B) Total rotations before (left) and after (right) AMPH treatment. (C) Net rotations. (i) The 2 pre-drug points represent total net rotations over the 15 min period prior to AMPH treatment. Pre-drug, net rotations to either the left or right are plotted as positive scores. (ii) During the first 5 min interval following AMPH some animals rotated predominantly left and others predominantly right. Whatever the dominant direction for an individual animal during the first 5 min interval, these net rotations were scored as a positive value. The net rotations plotted during the second and third 5 min intervals (10 and 15) were then scored relative to the first 5 min interval. Therefore, a negative value means that the animals were rotating in the opposite direction to which they rotated during the first 5 min interval. Bars (A and B) and circles (C) represent mean values, and lines the standard error of the mean. (* $p < 0.05$; ** $p < 0.01$).

The sex differences in net rotations made during the three 5 min intervals following AMPH were particularly striking (Fig. 1C). An analysis of variance revealed a significant main effect for time ($F=8.11$, $p < 0.01$) and a significant sex \times time interaction ($F=3.98$, $p < 0.05$), justifying pairwise comparisons (Duncan's procedure [61]). During the first 5 min interval following AMPH females made significantly more net rotations than the males did during any 5 min period ($p < 0.05$). Following the first 5 min interval sex differences in the pattern of rotations over time emerged. After exhibiting a significantly greater number of net rotations than males during the first 5 min interval the rotational behavior of the females declined significantly ($p < 0.05$), and during the second 5 min period they did not differ from males. This decline in net rotations was not due to a general decline in activity because the number of total rotations made by females actually increased from an average of 32.8 ± 2.7 (SE) during the first 5 min period to 43.1 ± 8.9 in the second 5 min period. During the third 5 min interval females significantly increased their net rotations again, and made more net rotations than males ($p < 0.05$). It is important to note, however, that the females reversed their direction of rotation between the first and third 5 min intervals. Thus, relative to males the net rotational behavior of the 'average' female was significantly elevated during the first 5 min interval following AMPH, it declined during the second 5 min period, and then was significantly elevated, but in the opposite direction, during the third 5 min interval.

In contrast to the females, neither the number nor direction of net rotations produced by the males differed significantly between the first, second or third 5 min intervals.

Finally, the extent of the change in the number of net rotations produced by AMPH appears to be greater in females than males. The average percent change in the number of net rotations when the last 5 min interval pre-AMPH is compared with the first 5 min interval post-AMPH is $1,795 \pm 421\%$ (SE) for females and $850 \pm 189\%$ for males ($t=1.87$, $df=23$, $p < 0.072$ two tailed, $p < 0.036$ one-tailed).

In summary, during the 15 min pre-drug period females made significantly more 1/4 turns and total rotations than did males, but the sexes did not differ in the number of net rotations. AMPH greatly increased the number of total 1/4 turns and total rotations made by both males and females, but the pre-drug sex difference persisted. In the first 5 min interval following AMPH the number of net rotations made by females increased to a greater extent than in males. Finally, the pattern of rotational behavior over time differed between females and males. During the last 5 min interval females rotated significantly more than males, but they reversed their direction of rotation relative to that in the first 5 min interval.

Catecholamine Levels; Striatum

Amphetamine-treated animals. Earlier studies have reported that following AMPH treatment, DA concentrations are higher in the striatum contralateral to the dominant direction of rotation [23]. However, in all the published experiments which have reported his asymmetry, of which we are aware, female rats were used. Therefore, we were anxious to compare the lateralization of striatal DA in relation to the differences in rotational behavior of male and female rats.

The calculation of CA levels in relation to the dominant

TABLE 1
THE RELATIONSHIP OF STRIATAL AND NEOCORTICAL CATECHOLAMINE
CONTENT TO ROTATIONAL BEHAVIOR IN AMPHETAMINE-TREATED MALE AND
FEMALE RATS*

	CONTRA.	IPSI.	Right	Left
Striatal dopamine				
Male (n=10)	11.77 ± 1.38	12.31 ± 1.26	13.19 ± 1.14‡	10.24 ± 1.10
Female (n=14)	14.17 ± 1.02†	12.42 ± 1.27	14.12 ± 1.12§	12.47 ± 1.18
Medial frontal cortex dopamine				
Male (n=10)	0.057 ± 0.009	0.064 ± 0.012	0.064 ± 0.01	0.056 ± 0.009
Female (n=12)	0.074 ± 0.010	0.064 ± 0.011	0.062 ± 0.008	0.073 ± 0.011
Medial frontal cortex norepinephrine				
Male (n=9)	0.132 ± 0.019	0.191 ± 0.059	0.139 ± 0.018	0.186 ± 0.054
Female (n=14)	0.122 ± 0.015	0.116 ± 0.014	0.116 ± 0.014	0.122 ± 0.015

*Values represent mean levels (ng/mg wet tissue weight) ± standard error. Abbreviations: CONTRA. and IPSI. (contralateral and ipsilateral to the dominant direction of rotation observed during the first 5 min interval, respectively).

†Differs from female IPSI. DA ($t=2.19$; $p<0.05$; paired t -test; all tests two-tailed).

‡Differs from left male DA ($t=3.85$; $p<0.01$).

§Differs from left female DA ($t=2.29$; $p<0.05$).

direction of rotation was somewhat complicated by the fact that female rats changed their preferred direction of rotation over the three 5 min intervals, while the males did not (Fig. 1). However, previous studies by Glick *et al.* [24] suggest that with the dose of AMPH we used the direction of rotation observed in the first 5 min interval is the 'dominant direction of rotation.' In extensive AMPH dose-response studies Glick *et al.* [24] noted that after 20 mg/kg of AMPH peak rotational behavior occurs during the first 5 min interval. After lower doses of AMPH (e.g. 1.0 mg/kg) peak rotational behavior is not observed until 30–40 min post-AMPH. Furthermore, the preferred direction of rotation seen during the first 5 min interval following 20 mg/kg AMPH is the same as the preferred direction observed if the same animal is given a low dose of AMPH at a different time [24]. Finally, following the first 5 min interval the direction of rotation becomes quite variable after large doses of AMPH [24]. Therefore, the dominant direction of rotation used in determining the relation of CA levels to behavior was that observed in the first 5 min interval following AMPH treatment.

Table 1 gives striatal DA levels in relation to the dominant direction of rotation. AMPH-treated female rats had significantly higher levels of DA in the striatum contralateral to the dominant direction of rotation, than in the ipsilateral striatum, as reported earlier by Glick and his colleagues [23]. However, to our surprise, males showed no significant relation between striatal DA levels and direction of rotation (Table 1). Of the 14 females tested, 12 had higher contralateral than ipsilateral striatal DA levels. Of the 11 males tested, 4 had higher contralateral levels, 5 had higher ipsilateral levels, 1 had equal contralateral/ipsilateral levels, and 1 did not show any net rotations.

Figure 2 shows the DA content of the striatum contralateral to the dominant direction of rotation, and the ipsilateral DA content expressed as a ratio (contralateral/ipsilateral or C/I ratio). Thus, a C/I ratio >1 indicates that DA levels were highest in the striatum contralateral to the dominant direction of rotation. Females treated with AMPH had more striatal C/I ratios >1 than would be expected either by chance ($\chi^2=7.14$, $p<0.01$), or than did AMPH-treated males

(Fisher test, $p<0.05$). In contrast, the C/I ratios of AMPH treated males did not differ from chance in either direction.

Of the 14 females tested, 10 rotated preferentially to the left. This seeming preference for the left is probably due to chance since Glick and his colleagues have tested many females and report that preferences for the left and right are evenly distributed in a large sample [24]. However, the distribution of rotational preferences in our sample of animals resulted in 10/14 females having the striatum on the right side contralateral to the preferred direction of rotation. This probably explains why the right striatum of females had significantly higher DA levels than the left striatum (Table 1). Of the 4 females which rotated preferentially to the right, 3 of these had higher left than right striatal DA levels, and one higher right DA.

A totally unexpected finding shown in Table 1 is that although AMPH treated males showed no relationship between direction of rotation and striatal DA they nevertheless had an asymmetry in striatal DA levels which was unrelated to behavior. In AMPH treated males the levels of DA in the right striatum were significantly higher than those in the left. The distribution of rotational preferences cannot account for this latter finding since 5 of the males rotated predominantly right, 5 predominantly left, and 1 showed no net rotations. The possibility that this asymmetry was due to a bias in the dissection procedure, which resulted in more tissue being excised on the right than the left was examined, but the average wet tissue weights showed no left-right differences. Moreover, if this asymmetry were due to the order of dissection similar asymmetries might be expected in the saline-treated animals or in cortical CA levels, but none were found. Since this is the first report of a left-right asymmetry in striatal DA these observations need to be replicated.

Saline-treated animals and medial frontal cortex CA levels. As noted above, no asymmetry was found in striatal DA levels in relation to rotational behavior or between the left and right striatum, in either males or females treated with saline (Fig. 2). Glick *et al.* [23,24] have reported similar results for females. However, interesting differences emerged when striatal DA levels were compared between saline and

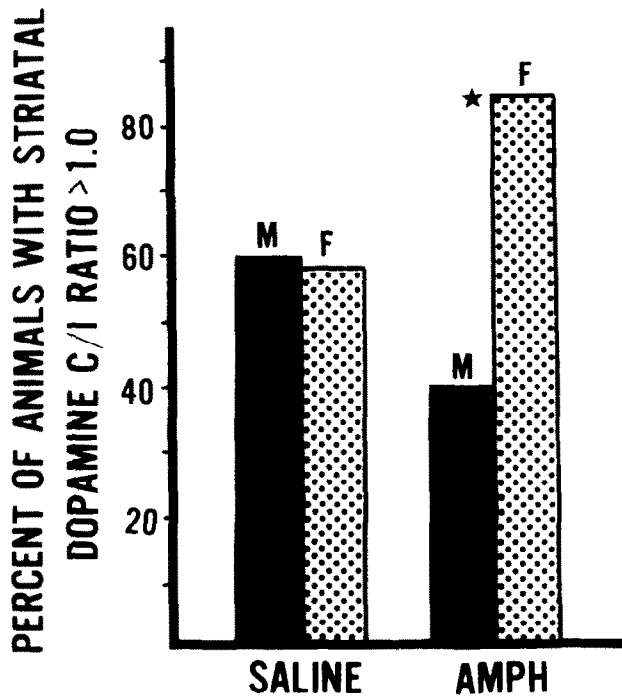


FIG. 2. The relationship of striatal dopamine (DA) content to rotational behavior in amphetamine (AMPH) or saline-treated male and female rats. For this analysis the DA content of the striatum located contralateral to the dominant direction of rotation, and the DA content of the striatum located ipsilateral to the dominant direction of rotation were expressed as a ratio (C/I ratio). A C/I ratio > 1 indicates that DA levels were highest in the striatum contralateral to the dominant direction of rotation. For saline-treated animals the dominant direction of rotation was calculated over the first 15 min. A little over half of the male and female saline-treated rats had C/I ratios > 1, and this was not significantly above what would be expected by chance for either group. For AMPH treated animals, C/I striatal DA ratios were calculated relative to the dominant direction of rotation during the first 5 min interval post-AMPH (see text). After AMPH, males did not show any significant relationship between direction of rotation and striatal DA. Females had significantly more C/I striatal DA ratios > 1 than males, or would be expected by chance.

AMPH-treated animals. Relative to levels in saline-treated female animals, AMPH treated female rats had elevated DA levels in the striatum contralateral to the dominant direction of rotation ($p < 0.01$). This was not true for males. Since the majority of females rotated predominantly to the left, it would be expected that elevated DA levels would also be found in the right striatum of AMPH treated females, relative to saline controls, and indeed they were ($p < 0.05$). The higher DA levels found in the right striatum of males, relative to the left, were also accompanied by a significant elevation of right striatal DA in AMPH-treated males, relative to saline-treated males ($p < 0.05$).

Examination of medial frontal cortex DA and NE levels did not reveal any striking asymmetries, such as those seen in striatal DA (Table 1). There were no significant differences in CA levels when contralateral-ipsilateral or right-left values were compared, regardless of sex or treatment.

DISCUSSION

Glick and his colleagues originally reported that AMPH

produces rotational behavior in unlesioned female rats [35], and that the striatum with the highest DA content is usually contralateral to the dominant direction of rotation [23]. The experiments reported here support these contentions, but in addition, we report sex differences both in rotational behavior and in the lateralization of striatal DA. After AMPH, female rats showed significantly greater rotational behavior than males. Biochemical analyses showed that in AMPH treated females the preferred direction of rotation was contralateral to the striatum with the highest DA content. This asymmetry appears to be confined to striatal DA as no relationship was found between rotational behavior and medial frontal cortex DA or NE. In addition, Glick *et al.* [24] reported no relationship between rotational behavior and striatal acetylcholine (ACh) or telencephalic ACh or NE in female rats. Male rats differed from females in that, (1) they rotated less than females, and (2) no relationship was found between the preferred direction of rotation and the lateralization of striatal DA in males. However, AMPH treated male rats did have significantly higher DA in the right than in the left striatum, irrespective of rotational behavior. This surprising finding needs to be replicated. Thus, the evidence suggests that the striatum of both males and females are asymmetrically organized, but in different ways. The female striatum may be organized asymmetrically in relation to rotational behavior, while the male striatum is not. This suggestion is supported by Glick's comment [25] that female gerbils show greater net rotations and percent dominance scores than males.

Males and females also differed in the pattern of rotations over time. In the last 5 min interval, females, but not males, rotated in the opposite direction to the first 5 min interval. Glick *et al.* [24] previously noted that during the last 30 min of a test session female rats given a large dose of AMPH tend to reverse their usual rotational preference. One possible explanation for this reversal may be that AMPH elicits a massive release of DA, which initially is greater in the striatum contralateral to the direction of rotation in females. This greater release may then result in the feedback inhibition of release and/or DA synthesis, perhaps mediated by pre-synaptic DA receptors [10,56]. Greater inhibition of the side contralateral to the initial direction of rotation would result in predominant release ipsilateral and therefore a reversal in the direction of rotation. The decline in net rotations during the second 5 min interval may reflect a period of transition.

It is possible that the results reported here are due to sex differences or asymmetries in the metabolism of AMPH. However, AMPH is reported to reach each striatum in equal quantities when injected systemically [24]. Therefore, the asymmetries in striatal DA content induced by AMPH are probably not due to the asymmetric uptake of AMPH. Sex differences have been described in AMPH metabolism [32,47], and this factor needs to be examined more closely. Although Meyer and Lytle [47] reported that female rats accumulate more AMPH in the brain than males at 30 min to several hours post-injection, they found no sex difference at 5 min, which is when we see the largest behavioral differences. In addition, sex differences have been reported in AMPH-stimulated DA release from striatal tissue fragments *in vitro* [5]. It is very unlikely that this *in vitro* response of striatal tissue fragments could be due to sex differences in the metabolism of AMPH.

Another possibility is that the sex differences in AMPH-induced rotational behavior reported here are due to sex

differences in the modulation of striatal DA activity by gonadal steroid hormones. In female rats ovariectomy (OVX) severely attenuates the AMPH-stimulated release of DA from striatal tissue fragments *in vitro* [5]. The *in vivo* administration of estrogen plus progesterone reinstates the *in vitro* release of DA in OVX females (J. B. Becker, unpublished data). In contrast, castration has no effect on the *in vitro* release of DA from striatal tissue fragments obtained from male rats [5].

There appears to be growing support for the idea that gonadal steroids modulate striatal activity. However, the nature of the interaction is far from clear. It has been suggested that some female gonadal steroids may have an *antidopaminergic* effect on striatal activity [7]. This is supported by reports that estrogen treatment decreases circling behavior induced by apomorphine (APO) in unilaterally-lesioned rats [7]. Reports that estradiol or progesterone attenuate stereotyped behaviors induced by AMPH or β -phenylethylamine (PEA) [50], that ovariectomy (OVX) enhances PEA-elicited stereotyped behaviors [50], that estrogen prolongs spiperone-induced catalepsy [11], and that estrogen reduces the increases in striatal ACh normally induced by DA agonists [19], all support this idea. Female rats have also been reported to show a higher incidence of chlorpromazine-induced catalepsy than males, and this sex difference is abolished by OVX [48].

In contrast, there is evidence which suggests that female gonadal steroids may *enhance* striatal dopaminergic activity. In addition to the results reported here, others have reported that estrogen prolongs the duration and increases the intensity of AMPH or APO elicited rotational and stereotyped behaviors [33,39]. In female guinea pigs, OVX decreases the responsiveness to AMPH or APO [51]. Also, females are reported to show longer and more intense stereotyped behavior after AMPH than males [4,20]. These findings may

relate to reports that estrogen increases the amount of [³H]-spiperidol binding in striatum [16,33], and that OVX reduces DA-stimulated adenylate cyclase activity in the striatum and nucleus accumbens [38]. Further research may reveal that many of these discrepancies are due to species, sex and drug dosage level differences between the various studies.

The idea of sex differences in striatal function does have clinical relevance and may relate to reports that human females show a greater incidence of extra-pyramidal side effects following treatment with neuroleptic drugs than do males ([1, 12, 21, 40]; however, also see [13]). In addition, choreiform disorders are sometimes associated with pregnancy (chorea gravidarum) [17,62], and as a complication of oral contraceptives [17]. Gonadal steroid modulation of striatal activity may have therapeutic relevance since it is reported that estrogen may precipitate Parkinsonian symptoms in males or females receiving neuroleptics [29], but improves the symptoms of tardive dyskinesia [8].

Lastly, the greater amount of lateralized behavior in female rats reported here may relate to reports that female children show greater motor asymmetries than males [36,46]. Girls are reported to show greater preferences for their right hand than boys. However, this latter sex difference may not persist into adulthood [46]. In contrast, adult human females are reported to be less lateralized than males both anatomically [60], and in verbal and visuo-spatial abilities [44, 45, 46]. Regardless of the direction, sex differences in brain lateralization in humans and rats may have a common developmental basis. The sex differences may result from anatomical differences which occur during early sexual differentiation and/or the hormonal changes of puberty. Whatever the answers to these questions, it seems apparent that there may be greater differences between the brains of males and females than previously thought.

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