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Sex Differences in Stereotyped Behavior in The Rat[1]

WILLIAM W. BEATTY AND GERALD A. HOLZER

Department of Psychology, North Dakota State University, Fargo, ND 58105

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BEATTY, W. W. AND G. A. HOLZER. *Sex differences in stereotyped behavior in the rat.* PHARMAC. BIOCHEM. BEHAV. 9(6) 777–783, 1978.—Neurologically intact female rats exhibited more intense and more prolonged stereotyped behavior in response to 5 mg/kg doses of d-amphetamine than males. They also displayed greater stimulation of activity in response to 1.5 mg/kg doses of the drug. Prior treatment with intrastriatal injections of 6-hydroxydopamine (6HDA) eliminated the sex difference in response to 5 but not to 1.5 mg/kg amphetamine. Neither intact nor 6HDA treated rats differed in the amount of stereotyped behavior elicited by the dopamine agonist apomorphine suggesting that the sex difference in amphetamine-elicited stereotypy is not the result of differences in striatal receptor mechanisms. The present results could arise from sex differences in amphetamine uptake and metabolism which have been described recently although other explanations are possible.

Amphetamine Apomorphine Stereotypy Dopamine Striatum Caudate Nigrostriatal bundle Haloperidol Sex differences Activity

BECAUSE of its possible relevance to understanding the neurochemical pathology in human schizophrenia, much recent research has been concerned with the neuropharmacology of stereotyped behavior in animals. Profound increases in the frequency of stereotyped motor responses can be produced by drugs such as amphetamine which promote release and/or block reuptake of the catecholamine neurotransmitters dopamine (DA) and norepinephine (NE) [3, 4, 5, 14, 17, 18]. Since stereotypy is elicited by DA agonists and diminished by DA antagonists [4, 5, 17, 18, 23], a major role for DA in this behavior is indicated, especially since the effect of agents that alter NE activity on stereotypy is much less marked [14,23]. NE may, however, exert important influences on stereotypy and other DA-dependent behaviors by modulating the activity of DA pathways originating in the substantia nigra [1,3].

Studies of Iversen and her colleagues have implicated the nigrostriatal bundle in the stereotyped behavior produced by moderately high doses of amphetamine and apomorphine [4,5], although this point has been disputed [6, 7, 8]. Iversen's group has reported that intrastriatal injections of 6-hydroxydopamine (6HDA) block the appearance of stereotypy in response to 5 mg/kg doses of amphetamine but spare the stimulation of locomotor activity by 1.5 mg/kg doses of the same drug [4, 5, 18]. By contrast, 6HDA lesions of the mesolimbic DA pathway blocked stimulation of locomotor activity by low doses of amphetamine but did not prevent the appearance of stereotypy in response to higher doses of the drug [17,18].

Although injections of 6HDA into the brain may cause nonspecific destruction, especially around the injection site [10, 15, 21, 26], there is good reason to believe that the reduced stereotypy observed by Iversen's group resulted from specific damage to the nigrostriatal pathway, since the same rats that displayed little stereotypy after amphetamine showed enhanced stereotypy in response to treatment with apomorphine, a DA agonist. This exaggerated response to apomorphine presumably reflects denervation supersensitivity of striatal DA receptors, although other possibilities exist [22].

Recently, Meyer and his colleagues reported sex differences in the effect of amphetamine on locomotor activity, anorexia and hyperthermia [19,20]. On each of these measures the response of female rats was greater than that of males. The present experiment examined the possibility of sex differences in the magnitude of stereotypy elicited by amphetamine and apomorphine.

METHOD

Animals

The animals were 31 male and 36 female rats obtained from the Holtzman Co., Madison, WI; they were about 70 days of age at surgery. The rats were caged singly in an air-conditioned (22 ± 2° C) animal room with free access to food and water except at surgery. The room was illuminated from 0800–2000, and all behavioral tests occurred during the light portion of the day-night cycle.

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Surgery and Histology

Surgery was performed under Chloropent anesthesia (Fort Dodge Labs; 3 cc /kg males, 2 cc/kg females) with atropine sulfate (0.1 mg) to inhibit mucus secretion. Animals in the experimental condition (16 males, 18 females) received bilateral intrastriatal injections of 6-hydroxydopamine HBr (Regis Chemical Co.; 20 μg in 2 μl expressed as the free base). 6HDA was dissolved in physiological saline containing 1 mg/ml ascorbic acid to retard oxidation. Approximately 2 hr before 6HDA treatment, the rats were given protryptiline HCl (Merck, Sharpe and Dohme; 15 mg/kg, IP) to minimize damage to NE neurons [12]. Injections were delivered from a 5 μl Hamilton syringe, that was stereotaxically placed, at the rate of approximately 0.5 μl/min. With the rat's head held horizontally between bregma and lambda the target coordinates in mm with respect to bregma were: 0.0 mm anterior, 3.6 mm lateral and 5.5 mm below the surface of the cortex. Approximately half of the 18 female and 15 male controls received identical treatment to that of animals in the experimental groups except that they were given intrastriatal injections of the ascorbic acid-saline vehicle. The remaining controls were not surgically treated, but they received injections of Chlorpent, atropine and protryptiline.

Following completion of testing, animals with 6HDA injections were sacrificed with an overdose of Chloropent and perfused intracardially with saline and 10% Formalin. Brains were removed, sectioned serially at 40 μm with a cryostat and stained with formol-thionin [11].

Postoperative Recovery

Following surgery all animals that received 6HDA treatment were at least temporarily aphagic and adipsic. If the rat had not recovered feeding and drinking of lab chow pellets and water by the third postoperative day, it was fed 5 ml of chocolate Nutrament (Mead Johnson) intragastrically and given approximately 30 ml of Nutrament in a small dish in the home cage. On subsequent days females were intubated with 7 ml of Nutrament while males received 10 ml. Most experimental animals also were given dishes of wet mash. Despite these measures 7 of the 16 males and 11 of the 18 females given intrastriatal 6HDA perished. Death occurred 9–14 days postoperatively, evidently from inanition. All of the male survivors eventually recovered feeding and drinking and gained weight when maintained on lab chow and tap water. Six of the seven female survivors ate lab chow but did not drink water from drinking spouts. They continued to receive Nutrament throughout the experiment. All of the controls recovered feeding and drinking rapidly without special assistance, although two males developed chronic respiratory disease and were discarded. To achieve equal sample size in the control groups, 5 females were discarded at random before stereotypy measurements. All of the animals received tests of open field behavior and 1 and 2-way avoidance conditioning 65–75 days postoperatively using procedures described elsewhere [24]. The results of these tests were inconclusive and will not be reported here.

Behavioral Measures

Stereotyped behavior was measured using a slight modification of the 7 point scale developed by Iversen and her colleagues [17]. Our version of that scale is shown in Table 1.

We did not attempt to employ blind raters because a pilot study suggested that it was impossible to keep the raters unaware of the animal's treatment. In that study, conducted as part of a psychopharmacology class, undergraduate students rated the behavior of male rats given 0, 1.5, 4 or 7.5 mg/kg doses of d-amphetamine sulfate. Despite the fact that these students had never rated stereotyped behavior before (they had heard a verbal description in a class lecture), they correctly guessed the dose received on 67% of the occasions, an accuracy rate well in excess of chance (see [2]). Since the raters in the present study were considerably more experienced, it seemed unlikely that they could be kept "blind," so we did not attempt to do so.

TABLE 1
STEREOTYPY RATING SCALE

0	Asleep or stationary
1	Active
2	Active with bursts of stereotyped rearing or sniffing
3	Stereotyped sniffing or rearing over a *wide area*
4	Stereotyped sniffing or head bobbing *in one place*
5	Stereotyped behavior in one location with *bursts of gnawing or licking*
6	*Continuous* gnawing or licking *in one place* including self destructive behavior (e.g., gnawing the paw or tail)

Locomotor activity was also measured as the number of shuttling responses made when the rat was placed in a BRS-LVE shuttlebox (Model 146-04).

Drug Treatments

Eighty-five–95 days after surgery stereotyped behavior and locomotor activity were studied in response to amphetamine injections. The animals received 0, 1.5, 5.0 or 7.5 mg/kg d-amphetamine sulfate (Smith, Kline and French) IP presented in a counterbalanced order with 2–4 days intervening between treatments. Twenty minutes after the injection stereotyped behavior was rated in the rat's home cage, and shuttling activity was measured for 5 min. Such measurements were taken at 1 hr intervals for the next 5 hr. Because in a pilot study 2 females with 6HDA lesions died when given high doses of amphetamine, we did not test females at the 7.5 mg/kg dose.

Next stereotypy and activity in response to IP injections of 0, 1, 2 or 4 mg/kg doses of apomorphine HCl (Eli Lilly and Co.) dissolved in physiological saline were studied. These tests occurred 110–120 days after surgery; 4–7 days intervened between tests. During the apomorphine tests stereotypy was first rated 5 min after injection. Next the rat was placed in the shuttlebox, and activity was measured for the next 60 min (40 min for the 1 mg/kg dose). Concurrently, stereotyped behavior was rated every 10 min while the rat remained in the shuttlebox.

Approximately 2 months after the end of the apomorphine tests, shuttling activity was measured during 2 hr tests for the control animals of both sexes in response to injections of haloperidol (McNeil Laboratories). Rats received 0, 0.025, 0.05, 0.10 or 0.20 mg/kg haloperidol (IP) prepared by diluting the stock solution with physiological saline. Measurements began 40 min after injection and the order of doses was counterbalanced with 4–7 days between treatments.

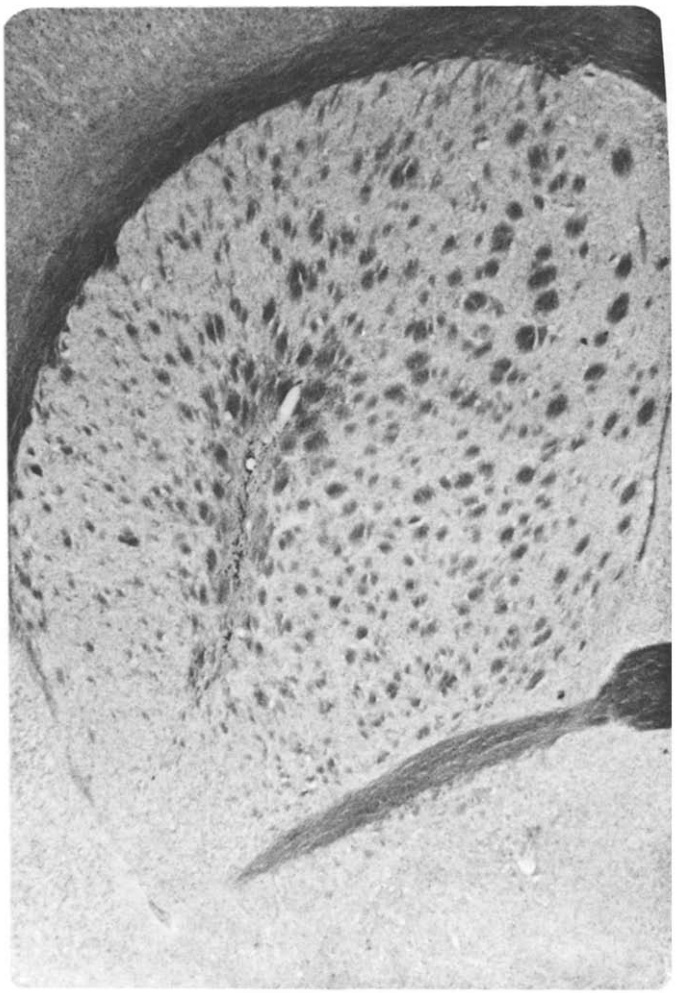

FIG. 1. Photomicrograph of a representative section from 6HDA-treated rat at the point of maximum destruction caused by the cannula and drug. Formol-thionin stain (see [11]).

RESULTS

Histology

Figure 1 shows a photomicrograph of the injection track of an animal given 6HDA. Note that the region of non-specific damage is restricted to the area immediately adjacent to the track. This was the appearance of the brains in all experimental animals. Inspection of the histology indicated that all tracks terminated in the ventral caudate, sometimes encroaching on the anterolateral globus pallidus. There was variation in the placements with respect to the anterior-posterior dimension, but these differences were not systematically related to the sex of the animal.

Amphetamine

Omnibus analyses of variance on the stereotypy and activity data during the amphetamine phase of the study were performed including the between-animals variables Sex and 6HDA treatment and the repeated measures variables Dose and Time Blocks. These analyses revealed highly significant main effects of all variables as well as numerous interactions. To facilitate exposition the results at each dose will be presented separately. In every analysis the main effect of Time Blocks was significant, reflecting the general decline in stereotypy and concurrent changes in activity during testing sessions.

The results of the saline tests are shown in Fig. 2. Female rats were generally more active than males, $F(1,24)=8.91$, $p<0.01$ for controls; $F(1,14)=4.92$, $p<0.10$ for 6HDA animals, and attained higher stereotypy scores, $F(1,24)=8.45$ for controls; $F(1,14)=5.16$, $p<0.05$ for 6HDA animals. This latter effect arose mainly because males in both brain treatment conditions were more likely to be asleep during the later observation periods; in fact no animal displayed behavior that could be labelled highly stereotyped. During the saline tests, intrastriatal 6HDA treatment affected neither activity nor stereotypy in either sex (all $F<1$); interactions between Sex and Time and 6HDA and Time were not reliable.

Figure 3 describes the results on the stereotypy and activity measures at the 1.5 mg/kg dose. Again females were more active, $F(1,24)=10.84$, $p<0.005$ for controls; $F(1,14)=11.57$, $p<0.005$ for 6HDA animals, and attained higher stereotypy scores, $F(1,24)=8.83$, $p<0.01$ for controls; $F(1,14)=16.91$, $p<0.001$ for 6HDA groups. The higher

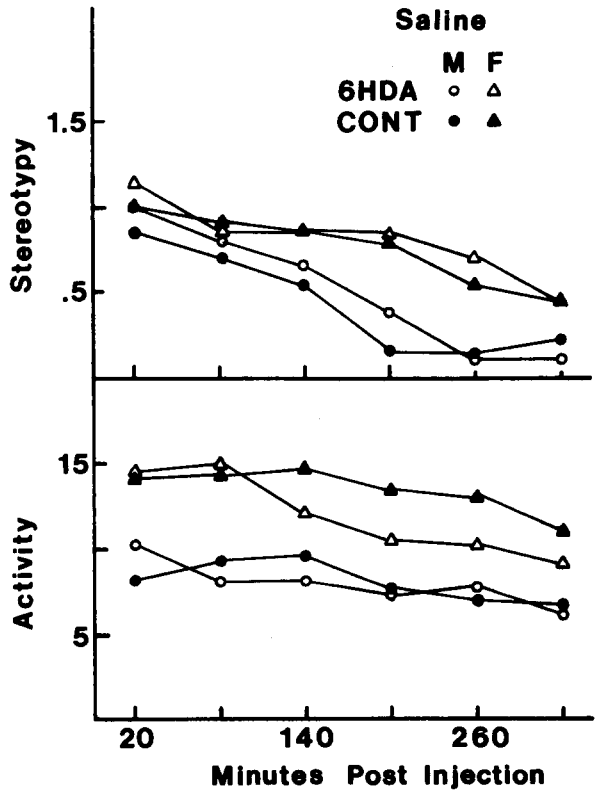

FIG. 2. Mean stereotypy ratings and activity scores for all groups during the saline tests.

stereotypy scores of females consisted mainly of more frequent bursts of sniffing directed toward all parts of the home cage; highly stereotyped behavior was not seen at this dose. Hence sex differences in stereotypy scores at this dose may simply reflect greater activity in the females.

Consistent with this view is the fact that relative to saline, the 1.5 mg/kg dose of amphetamine stimulated locomotor activity in control females, $F(1,12)=13.30$, $p<0.005$, but this effect was not significant in control males. Activity scores were enhanced by 1.5 mg/kg amphetamine in the 6HDA groups of both sexes (both $p<0.025$), and this dose of amphetamine increased stereotypy scores relative to saline in controls and 6HDA subjects of both sexes (all $p<0.01$).

No significant main effects of 6HDA treatment were observed for either sex on either the stereotypy or activity measures. For female subjects a reliable 6HDA×Time Blocks interaction was present on the activity measure, $F(5,90)=5.73$, $p<0.001$, reflecting the greater stimulation of activity of the 1.5 mg/kg dose in 6HDA-treated females.

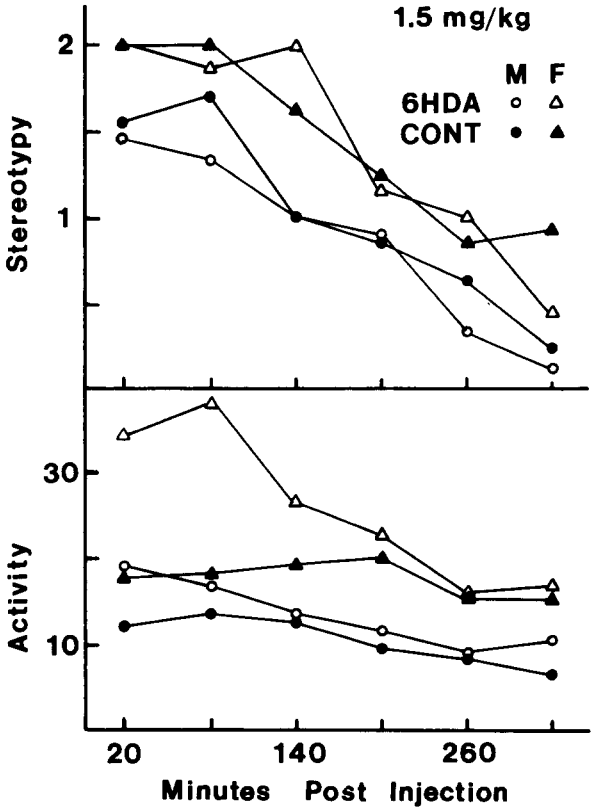

FIG. 3. Mean stereotypy ratings and activity scores for all groups when treated with 1.5 mg/kg d-amphetamine.

Performance at the 5 mg/kg dose is shown in Fig. 4. Relative to the saline and 1.5 mg/kg conditions, stereotypy scores were higher in all groups. In controls of both sexes locomotor activity was almost completely suppressed during the first 1–2 hr and then recovered; the magnitude of recovery was greater for females although it occurred somewhat more slowly (Sex×Time: $F(5,120)=6.77$, $p<0.001$). By contrast, this higher dose of amphetamine did not suppress activity in 6HDA-treated animals; in fact, activity was mildly stimulated.

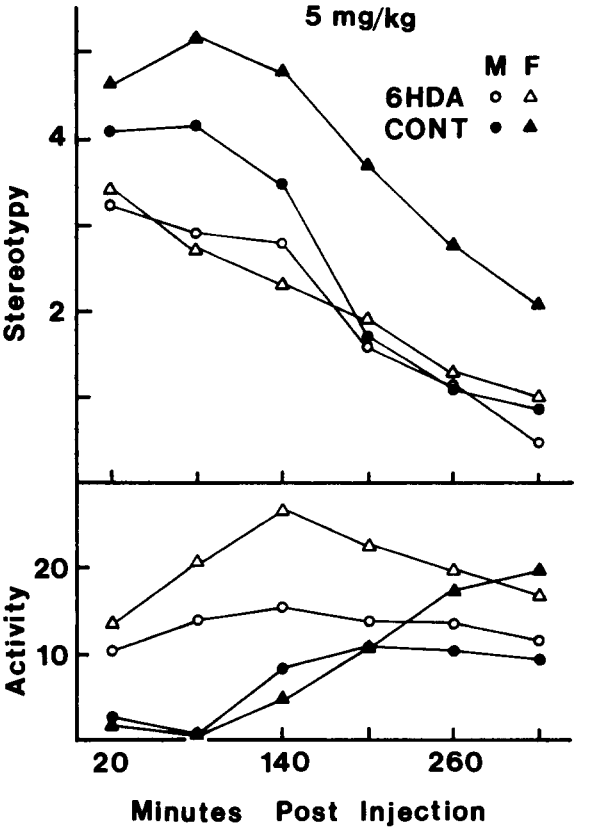

FIG. 4. Mean stereotypy ratings and activity scores for all groups when treated with 5.0 mg/kg d-amphetamine.

Of particular importance was the sex difference in stereotypy ratings observed in control subjects. Overall females attained higher stereotypy scores, $F(1,24)=21.81$, $p<0.001$. This difference reflected higher ratings during the first two measurements (20 and 80 min post injection) when stereotypy was greatest in both sexes, $F(1,24)=6.30$, $p<0.025$ as well as slower recovery over the last 4 measurement periods, $F(1,24)=22.40$, $p<0.001$.

By contrast, there was no sex difference on the stereotypy measure in rats given intrastriatal treatment with 6HDA ($F<1$). Significantly lower stereotypy scores were obtained by animals given 6HDA treatment, $F(1,20)=6.44$, $p<0.025$ for males; $F(1,18)=24.93$, $p<0.001$ for females. But intrastriatal 6HDA led to reliably greater activity in both

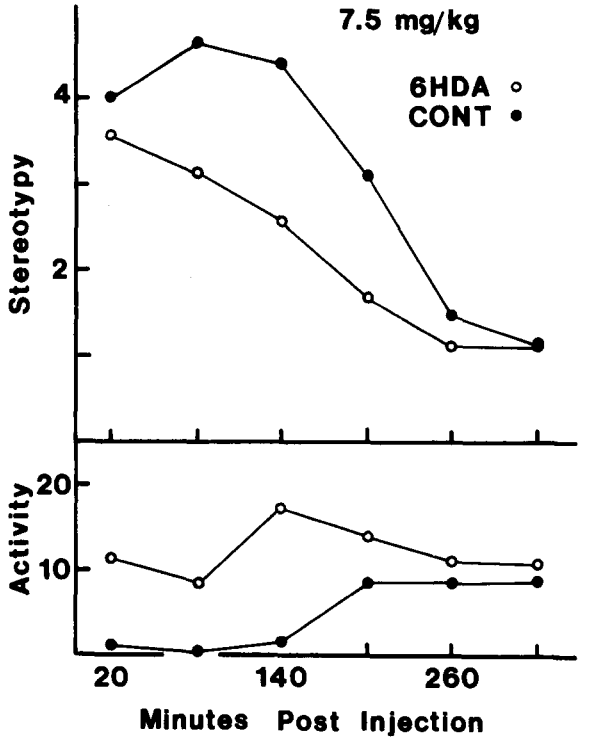

FIG. 5. Mean stereotypy ratings and activity scores for male groups treated with 7.5 mg/kg d-amphetamine.

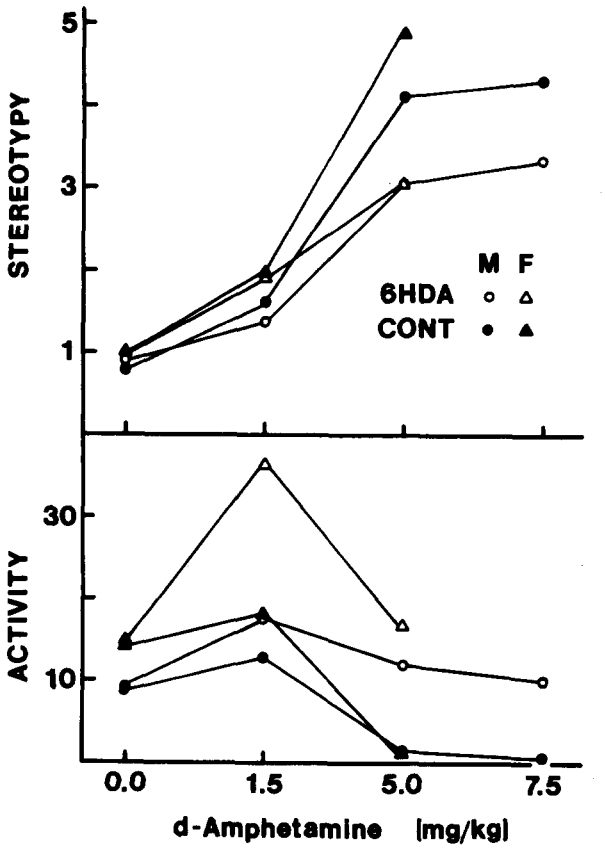

FIG. 6. Dose-response curves for stereotypy and activity scores averaged over the first 80 min post injection for all groups given d-amphetamine.

sexes, $F(1,20)=10.28$, $p<0.005$ for males; $F(1,18)=15.85$, $p<0.001$ for females.

Behavior of the males at the 7.5 mg/kg dose was quite similar to their performance at the lower 5 mg/kg dose, except that the drug effects were somewhat longer lasting, as seen in Fig. 5. Again 6HDA treatment reduced stereotyped behavior, $F(1,20)=12.11$, $p<0.005$, and resulted in greater activity, $F(1,20)=15.64$, $p<0.001$.

Figure 6 depicts average performance during the first two measurement periods (20 and 80 min after injection) for all of the amphetamine doses. Note that during the first hour and 20 min after injection, when the most highly stereotyped behavior was observed in all groups, increasing the dose of amphetamine from 5 to 7.5 mg/kg did not increase stereotyped behavior in control males ($F<1$). The higher dose did prolong the display of fairly high levels of stereotypy in these animals during the last 4 measurement periods, $F(1,12)=39.96$, $p<0.001$; cf., Figs. 4 and 5).

Apomorphine

Average stereotypy ratings over the test sessions are shown for various doses of apomorphine in Fig. 7. All animals achieved ratings of "1" on all observations during saline tests so these results are not shown on the figure. Because the test sessions were not equally long, the data were analyzed separately for each dose.

Two major points are apparent from these data. First, apomorphine led to increased stereotypy in the 6HDA groups of both sexes. Analyses of variance including Sex and 6HDA treatment as between animals variables revealed significant effects of 6HDA treatment at both the 1 mg/kg,

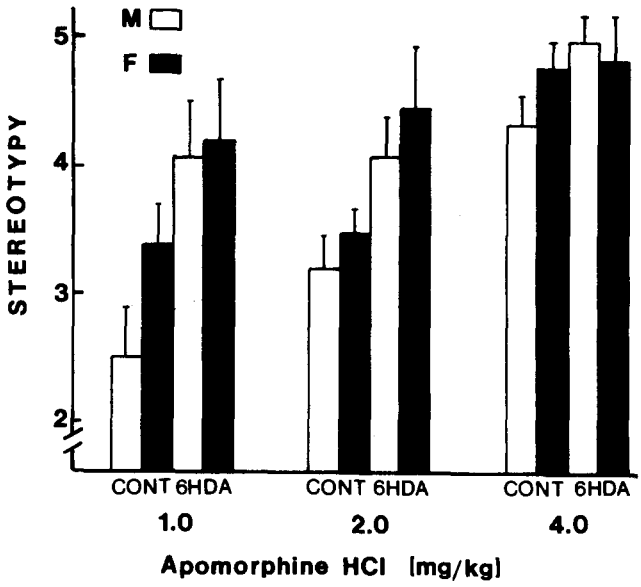

FIG. 7. Mean stereotypy ratings for varying doses of apomorphine HCl for all groups. Data have been averaged over the test session. Bars at the top of the histogram depict standard errors of the mean.

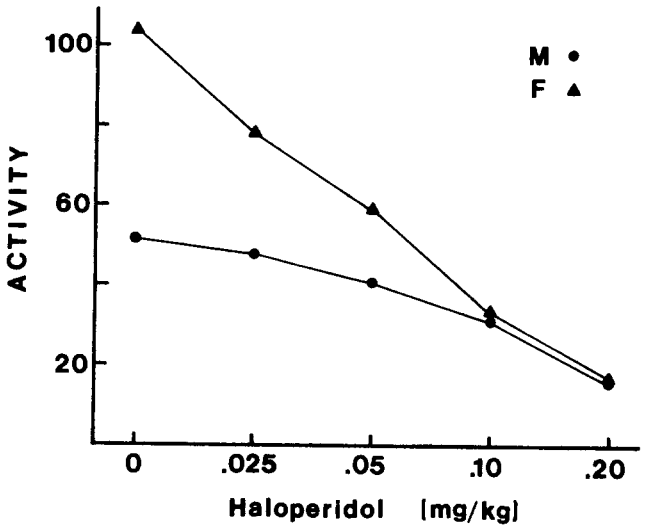

FIG. 8. Mean activity scores over the 2 hr-long session for neurologically intact males and females treated with varying doses of haloperidol.

$F(1,38)=9.49$, $p<0.005$, and 2 mg/kg doses, $F(1,38)=9.26$, $p<0.005$. The same trend was observed at the 4 mg/kg dose, but this difference was not significant, probably because of ceiling effects imposed by the rating scale. Second, apomorphine treatment did not cause sex differences in the amount of stereotyped behavior regardless of whether the animals were neurologically intact or had received intrastriatal 6HDA. Neither the main effect of Sex nor the Sex×6HDA interaction approached significance at any apomorphine dose level (all $F<1.75$).

Apomorphine led to reduced locomotor activity relative to saline in all groups (Main Effect of Dose: $F(3,114)=10.58$, $p<0.001$ followed by subsequent t tests), but there was no reliable difference in activity among the 3 doses of apomorphine tested.

Haloperidol

Figure 8 illustrates average shuttling activity for control animals at various doses of haloperidol. Analysis of these data revealed significant main effects of Sex, $F(1,24)=6.61$, $p<0.025$, and Dose, $F(4,96)=18.26$, $p<0.001$, as well as a Sex×Dose interaction, $F(4,96)=3.53$, $p<0.025$. Subsequent analyses of the interaction revealed that haloperidol at doses of 0.05, 0.10 and 0.20 mg/kg reduced activity of females below the saline baseline (all $p<0.025$). By contrast, only the 0.20 mg/kg dose significantly depressed activity in males.

DISCUSSION

The results of the present studies confirm earlier observations regarding the effects of intrastriatal 6HDA treatment on amphetamine and apomorphine-induced responses in male rats and extend these findings to females. Consistent with the earlier work, intrastriatal 6HDA treatment reduced stereotypy and activity suppression caused by 5–7.5 mg/kg doses of amphetamine. By contrast, the same subjects displayed exaggerated stereotypy to apomorphine, which has been attributed to denervation supersensitivity of striatal DA receptors [5,18]. Finally, the effectiveness of 1.5 mg/kg amphetamine in stimulating locomotor activity was not impaired by intrastriatal 6HDA treatment in either sex; in fact, this response was somewhat enhanced in 6HDA-treated females. Taken together these observations support the view that the integrity of the nigrostriatal DA pathway is critical to the display of strongly stereotyped behavior in both male and female rats.

At the same time the data demonstrated that the 5 mg/kg dose of amphetamine elicited more intense and longer lasting episodes of stereotyped behavior in females than in males. Several possible explanations of this sex difference merit consideration. First, sex differences in the accumulation and excretion of amphetamine in the brain and in its metabolism may account for the differences in stereotyped behavior. Meyer and his associates [19,20] have reported that amphetamine produces greater stimulation of motor activity in female rats, an effect we have replicated, and also causes longer lasting anorexia and hyperthermia. They have related these differences to a longer half-life of amphetamine in the brain and to slower metabolism in females. A similar explanation may be offered for the sex differences in stereotyped behavior we observed.

A second possibility is that amphetamine may release greater amounts of dopamine from nigrostriatal terminals in females than in males. This explanation is suggested by the report [13] of higher DA levels in the striatum of female rats, but recently Crowley, O'Donohue and Jacobowitz [9] observed just the opposite result. Obviously, more work is needed to resolve this controversy and moreover, no information is available on possible sex differences in the size of the recently synthesized pool of catecholamines which is thought to be primarily responsible for the behavioral effects of amphetamine [23].

The present finding that apomorphine elicited comparable levels of stereotypy in both sexes suggests that differences in postsynaptic receptor mechanisms are probably not a major factor in the sex difference in stereotypy elicited by amphetamine. Such an inference is necessarily quite tentative in the absence of more direct measures of the number and affinity of striatal DA receptors in both sexes. Moreover, female rats were more sensitive than males to the inhibiting effects of haloperidol, the DA receptor blocker, on activity, which might imply sex differences in postsynaptic mechanisms, although sex differences in haloperidol metabolism may be important as well (see [16,25]).

At present several possible explanations for the sex difference in stereotyped behavior elicited by amphetamine merit further examination. The role of gonadal hormones also remains to be determined.

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