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The Effects of 6-OHDA-Induced Dopamine Depletions in the Ventral or Dorsal Striatum on Maternal and Sexual Behavior in the Female Rat

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HANSEN, S., C. HARTHON, E. WALLIN, L. LÖFBERG AND K. SVENSSON. *The effects of 6-OHDA-induced dopamine depletions in the ventral or dorsal striatum on maternal and sexual behavior in the female rat.* PHARMACOL BIOCHEM BEHAV **39**(1) 71–77, 1991.—The effects of dopamine-depleting 6-OHDA infusions in the ventral or dorsal striatum on maternal and sexual behaviors were examined in female rats. Like sham-operated controls, lactating rats receiving 6-OHDA in the ventral striatum built good nests, nursed the infants and showed maternal aggression toward strange intruders. By contrast, the lesioned females performed poorly in tests for pup retrieval, as reflected in greatly protracted retrieval latencies. There was no effect of ventral striatal DA depletions on proceptive and receptive elements of female sexual behavior, which was studied after lactation following ovariectomy and exogenous administration of ovarian hormones, but these animals did show an attenuated hyperactivity response to a low dose of amphetamine. Females with dopamine lesions in the dorsal striatum did not differ from controls with respect to maternal and sexual behavior, but they did show an enhanced hyperactivity response to amphetamine treatment.

Dopamine 6-OHDA Mesolimbic dopamine system Nigrostriatal dopamine system Maternal behavior Sexual behavior Amphetamine Hyperactivity Pup retrieval Nucleus accumbens

THERE is growing evidence suggesting that the brain dopamine (DA) system modulates the responsiveness of female rats to social incentive cues from infants or adult males, and thereby participates in the control of maternal and sexual behaviors. For example, lactating rats treated with DA receptor antagonists show disturbances in pup-caring activities (14, 15, 45), and similarly neuroleptic-treated or 6-OHDA-lesioned estrous females typically fail to show sexual appetitive responses (i.e., hopping, darting, ear-wiggling) towards males (4, 8, 17). These social disabilities probably reflect a more global impairment in the behavioral responsiveness to motivationally significant stimuli in general (1, 2, 6, 10, 33, 36, 37, 47).

The disruptive effect of neuroleptic treatment on maternal behavior may partly be due to the drug's action on the mesolimbic DA system, which originates mainly in the A10 DA cell group of the ventral tegmental area (26,46). Thus previous studies have shown that nonspecific lesions in DA-rich brain areas severely impair maternal responsiveness (13, 30, 31, 40). Moreover, we recently found that mother rats with ventral tegmental 6-OHDA lesions showed a deficit in pup retrieval (15), where the mother carries stray offspring back to the nest (18,35), whereas other maternal responses, such as nursing, nest building and maternal aggression, remained unimpaired by the lesion (15). As expected on the basis of previous studies on the mesolimbic DA system (5, 11, 22, 34), our 6-OHDA females also failed to show a hyperactivity response following an injection of amphetamine. Sexual behavior, by contrast, was not altered by the ventral tegmental 6-OHDA lesions: in particular, there was no neuroleptic-like decrease in proceptivé hopping, darting and ear-wiggling responses (15).

The A10 DA cell bodies preferentially innervate the nucleus accumbens, olfactory tubercle and ventromedial caudate, which collectively form the ventral striatum (16, 26, 46). This means that the pup retrieval deficit seen in females with ventral tegmental area lesions might be attributable to degeneration of DA terminals in the ventral striatum. The present experiment was designed to test this hypothesis, by examining the consequences on maternal behavior of DA-depleting ventral striatal 6-OHDA infusions; sexual behavior and amphetamine hyperactivity were also studied in these animals. For comparative purposes, we also investigated the effect on these parameters of 6-OHDA infused into the dorsal striatum (caudate-putamen),

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which receives its DA input mainly from the substantia nigra (26,46).

METHOD

Subjects

The animals were albino Wistar rats obtained from Möllegaard Inc. (Denmark) that were 3–5 months old. They were maintained in a colony room in which the lights were off between 10:00 a.m. and 10:00 p.m. Food (Ewos 34 pellets) and tap water were always available. The cage bedding material consisted of Finn-Tapvei aspen chips. When in behavioral estrus, as determined by manual stimulation, females were housed overnight with a sexually active male, and they were housed individually in a transparent cage (45 × 28 × 26 cm) a few days before delivery and thereafter. Litter size was adjusted to 10 pups on day 1 postpartum.

Surgery

The bilateral striatal 6-OHDA infusions were made 2–3 days postpartum, while the rats were anesthetized with Brietal (sodium methohexithal, Lilly; 10–15 mg/rat) and fixed in a Kopf stereotaxic instrument. 6-OHDA hydrochloride (Sigma) was infused through a stainless steel cannula (outer diameter 0.25 mm) using a CMA100 microinjection pump (Carnegie Medicin AB, Stockholm). Two microliters of 6-OHDA (4 μg/μl of the base) was given over 4 min and the cannula was left in situ for an additional 3 min before being retracted from the brain. Thirty minutes before the infusion each rat received IP injections of the noradrenergic uptake blocker, desipramine (25 mg/kg) and the MAO inhibitor, pargyline (50 mg/kg). These compounds minimize destruction of noradrenaline neurons and potentiate the neurotoxic action of 6-OHDA, respectively (50). The following coordinates were employed (32): ventral striatum: 1.6 mm anterior to bregma, 1.5 mm lateral to midline, 8.3 mm below the skull (n = 9); dorsal striatum: level to bregma, 3.0 mm lateral to midline, 5.0 mm below the skull (n = 9). Four rats received vehicle (0.01% ascorbic acid in saline) in the ventral striatum and 5 females received vehicle infusions in the dorsal striatum. Since the behaviors of these vehicle rats were similar, the data from these rats were pooled to form a single control group (n = 9). The mothers remained separated from their litters for 3–4 hours after the operation.

Behavioral Tests

The observations for maternal behaviors began 2 days after surgery and continued daily for 6 days. *Nursing behavior* was examined 3 times per day (morning, noon, afternoon) by determining whether or not the mother was crouching over the pups in the nest. To assess *nest building*, each rat was provided with 10 g of shredded newspaper strips on the day of giving birth. Nest building was assessed each morning, according to the following rating scale: 0: no nest, paper remains scattered over the floor of the cage; 1: poor nest, not all the paper is used, and the nest consists of a flat pad of paper strips; 2: good nest with walls, all paper is used. At the end of each pup retrieval test (see below), the existing nests were destroyed. Tests for *pup retrieving* were initiated by removing the pups from the home cage. After 2–3 min, three pups were placed in the corner opposite to the nest site. The time taken for the mother to retrieve the pups into the nest was measured, the tests being terminated after the retrieval of the third pup or after 10 min. After completion of this task, the entire litter was replaced into the nest. Five days after surgery the mothers' *aggressiveness* toward female intruder rats was determined in 5-min tests. The observations were carried out in the colony room under dim white light, and the number of attacks (mother lunges toward intruder), bites, lateral threats (mother approaches intruder sideways), intruder submissions (sitting on haunches with forepaws raised off the ground, or lying on the back) were recorded. Each intruder was used once.

Upon completion of the observations for maternal behavior, the pups were discarded and the females were ovariectomized under Brietal anesthesia. Two weeks later, the animals were assessed for *sexual behavior*. The rats received two SC injections of β-estradiol benzoate (10 μg dissolved in peanut oil) 48 and 24 h before testing, and were given one injection of 500 μg progesterone 6 h before testing. The female was placed in a cage together with a male, whereupon the female was continuously stimulated for 30 s on the back and flanks by the experimenter. This manual stimulation technique reliably elicits proceptive behaviors, such as hopping, darting and ear-wiggling, in the estrous rat. The quality of the proceptive responses were assessed by 2 independent observers, blind to the experimental treatments of the subjects, according to the following rating scale: 0: no proceptive behaviors, 1: few proceptive episodes of weak intensity, 2: vigourous proceptive behaviors shown almost continuously. The latency to show the first definite hop-dart episode following the onset of stimulation was also recorded. After completion of this test, the occurrence of lordosis behavior (a measure of sexual receptivity) was observed by combining flank stimulation with perineal stimulation.

One month after surgery, *locomotor activity* was measured in a bank of four photocell boxes (70 × 70 cm; walls 35 cm high; Kungsbacka Mät-och Reglerteknik AB, Sweden), placed into separate sound-attenuated boxes. Spontaneous horizontal activity was recorded during 1 h. The rats were then injected SC with 1 mg/kg D-amphetamine sulfate (Sigma) and returned to the photocell boxes for one additional hour.

Neurochemical Determinations

The rats were decapitated and the brains were put on an ice-chilled petri dish. The ventral (containing the nucleus accumbens and olfactory tubercle) and dorsal (caudate-putamen) parts of the striatum were dissected out, and the tissue samples were stored at −70°C until analyzed for DA and noradrenaline by means of high performance liquid chromatography with electrochemical detection (9).

Statistics

The data on maternal and sexual behaviors are represented as medians ± semi-interquartile ranges, and were analyzed by non-parametric statistical tests (38). Locomotor activity data and monoamine concentrations are represented as means ± standard errors, and were analyzed by analysis of variance (24). All p values are two-tailed.

RESULTS

Maternal Behavior

Two rats in the ventral striatum 6-OHDA group and 1 sham-operated rat cannibalized their litters 1, 3 and 1 days after the operation, respectively. This reduced group size to 7 in the ventral striatum group and to 8 in the sham-operated group.

There were no differences between the groups with respect to the body weight change during the test period. The weight

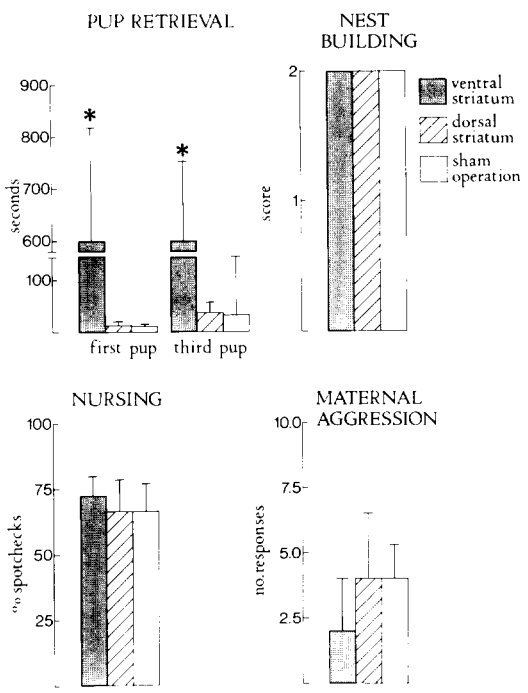

FIG. 1. Maternal behavior of female rats receiving 6-OHDA in the ventral or dorsal striatum, or vehicle infusions. The results are represented as medians ± semi-interquartile ranges. *$p<0.05$ in comparison to sham-operated controls (Mann-Whitney U-test).

difference between the last day of observation and the day of surgery was -4.0 ± 13.5 g in the ventral striatum group, -2.0 ± 12.3 g in the dorsal striatum group, and $+10.0 \pm 9.5$ g in the control group ($H = 2.6$, NS, Kruskal-Wallis one-way analysis of variance).

The effect of 6-OHDA microinfusions in the dorsal or ventral divisions of the striatum on maternal behavior is shown in Fig. 1. Kruskal-Wallis one-way analyses of variance revealed that the two 6-OHDA groups did not differ significantly from controls with respect to nest score [$H(2) = 0$], incidence of nursing ($H = 1.0$) or maternal aggression ($H = 2.3$). However, there was a significant overall effect with respect to pup retrieving latency (first pup: $H = 12.4$, $p<0.002$; third pup: $H = 10.9$, $p<0.004$). Subsequent pairwise comparisons revealed that mothers with ventral striatal 6-OHDA lesions were considerably slower than sham-operated controls to retrieve either the first or third pup (p's<0.05, Mann-Whitney U-test). By contrast, the pup retrieval performance of females with dorsal striatal 6-OHDA lesions was comparable to that of controls (Fig. 1).

Table 1 shows further details of the pup retrieval deficit in females with ventral striatal 6-OHDA lesions. It is seen that over half of these females (4/7) retrieved at least one pup on at least one test. However, retrieval occurred on only about one-third of observations and only rarely did ventral striatal 6-OHDA mothers deposit all of the 3 test pups in the nest (Table 1).

Informal observations of the ventral striatal 6-OHDA females during the retrieval tests showed that they invariably sniffed and investigated the displaced pups at the beginning of the test. Instead of carrying the offspring back into the nesting area, however, they would typically indulge in some other activity, such as feeding, preening or nest repairing, for the remainder of the test. If retrieval of a single pup did occur, it was not uncommon to see a female start nursing it, and thereby neglect the infants remaining outside the nest. Occasionally, nonretrieving females with ventral striatal 6-OHDA lesions were observed to carry nest material to the site where the displaced test pups were located, instead of transporting the pups to the nest as is usual in normal animals. We also observed lesioned females to crouch over and nurse the test pups while lying outside the nest.

Sexual Behavior

Following ovariectomy and treatment with estradiol benzoate and progesterone, the females (including those cannibalizing the young) were tested for sexual behavior. All rats showed proceptive (hopping, darting, ear-wiggling) and receptive (lordosis) behavior in response to manual stimulation. Figure 2 shows that

TABLE 1

MATERNAL BEHAVIOR OF FEMALE RATS RECEIVING 6-OHDA IN THE VENTRAL STRIATUM, DORSAL STRIATUM, OR VEHICLE INFUSIONS

	% Females Retrieving ≥1 Pup on ≥1 Test	% Females Retrieving 3 Pups on ≥1 Test	% Tests on Which Retrieval of 1 Pup Occurred	% Tests on Which Retrieval of 3 Pups Occurred	% Females Showing Nursing Behavior	% Females Showing Maternal Aggression
6-OHDA ventral striatum	57.1*	28.6†	33.3 ± 25.0‡	0.0 ± 16.7‡	100	71.4
6-OHDA dorsal striatum	100	100	100.0 ± 8.4	100 ± 8.4	100	100
vehicle	100	100	83.3 ± 12.5	66.6 ± 8.3	100	100

Note. The values in the two middle columns are medians ± semi-interquartile ranges.

*$p = 0.06$, †$p = 0.005$ vs. vehicle group (Fisher exact probability test; a Chi-square test using all groups was not applicable here because of too low expected values).

‡$p<0.002$ vs. vehicle group (Mann-Whitney U-test). Kruskal-Wallis ANOVAs were significant both with respect to the first ($H = 14.0$, $p<0.001$) and third pup ($H = 16.9$, $p<0.001$) criterion.

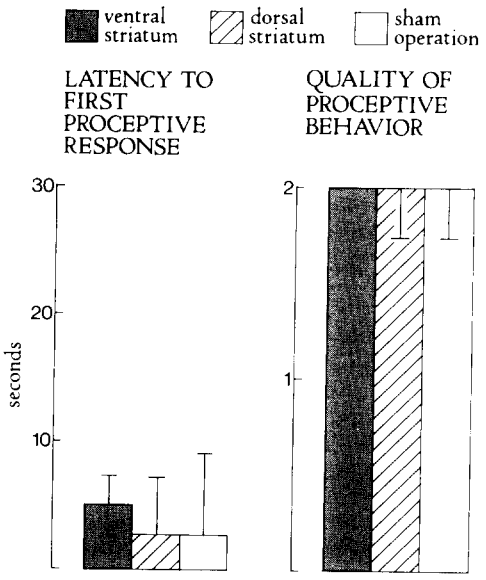

FIG. 2. Sexual proceptivity of female rats receiving 6-OHDA in the ventral or dorsal striatum, or vehicle infusions. The results are represented as medians ± semi-interquartile ranges. The groups are not significantly different.

TABLE 2

CONCENTRATION (ng/g TISSUE) OF DOPAMINE (DA) AND NORADRENALINE (NA) IN THE STRIATAL COMPLEX OF FEMALE RATS THAT HAD RECEIVED 6-OHDA OR VEHICLE INFUSIONS IN THE VENTRAL OR DORSAL STRIATUM

Dopamine	DA Content (ng/g) in Ventral Striatum	DA Content (ng/g) in Dorsal Striatum
6-OHDA in ventral striatum	1708 ± 624†	5160 ± 884†
6-OHDA in dorsal striatum	5252 ± 242	2943 ± 417†
vehicle	5414 ± 363	9420 ± 354
F-value	22.42	34.29
p	0.0001	0.0001
Noradrenaline	**NA Content (ng/g) in Ventral Striatum**	**NA Content (ng/g) in Dorsal Striatum**
6-OHDA in ventral striatum	999 ± 48*	149 ± 17
6-OHDA in dorsal striatum	1332 ± 103	111 ± 18
vehicle	1422 ± 141	149 ± 15
F-value	4.84	1.70
p	0.018	NS

Note. The values are means ± standard errors.
*$p<0.05$, †$p<0.01$ vs. vehicle group (Dunnett's *t*-test).

the 3 groups did not differ with regard to the latency to show proceptive behavior ($H=0.2$) or in its perceived quality ($H=0.9$).

Spontaneous and Amphetamine-Induced Locomotor Activity

Figure 3 shows spontaneous and amphetamine-induced locomotor activity in the 3 groups. Split-plot analysis of variance revealed a significant Interaction effect, $F(2,24)=5.46$, $p<0.01$. Pairwise comparisons between individual group means by the Tukey HSD test showed that there were no group differences with regard to spontaneous locomotion. When given amphetamine (1 mg/kg), the controls showed increased activity, but this effect was not evident in the ventral striatum group. Thus there was a significant difference in the number of activity-counts between these 2 groups under the amphetamine conditions ($p<0.01$). Animals with dorsal striatal lesions, by contrast, showed an enhanced response to amphetamine relative to controls ($p<0.01$). In summary, then, ventral striatal lesions reduced, and dorsal striatal lesions enhanced, the hyperactivity response to amphetamine.

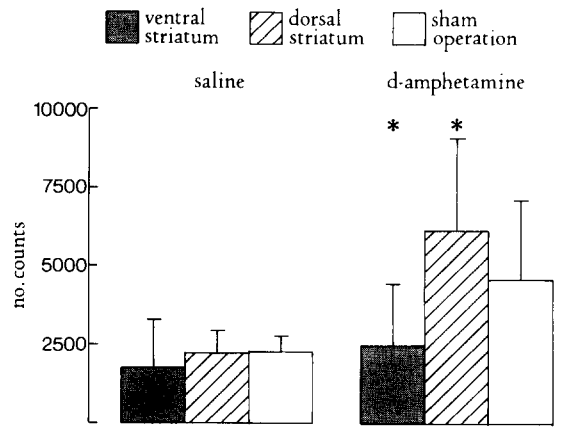

FIG. 3. Spontaneous and amphetamine-induced locomotor activity of female rats receiving 6-OHDA in the ventral or dorsal striatum, or vehicle infusions. The results are represented as means ± standard errors. $p<0.01$ in comparison to sham-operated controls (Tukey's HSD test).

Neurochemical Determinations

Table 2 shows the brain catecholamine concentrations in the 3 groups of animals. The ventral striatal DA concentrations were significantly reduced by about 70% in rats infused with 6-OHDA in the ventral striatum. The DA levels in the dorsal striatum were also lowered by about 45%. An identical pattern was observed with regard to DOPAC levels in this group of animals (data not shown), and there was also a small (30%) but significant depletion of ventral striatal noradrenaline.

In females exposed to dorsal striatal 6-OHDA infusions there was an approximately 70% DA depletion in the dorsal striatum, whereas the levels of DA in the ventral striatum were similar to those of controls. DOPAC concentrations were also reduced in the dorsal but not ventral part of the striatal complex (data not shown). There was no effect of dorsal striatal 6-OHDA on noradrenaline levels in the examined brain regions.

DISCUSSION

The major finding here was that 6-OHDA lesions in the region of the nucleus accumbens interfered with pup retrieval in maternal rats. Thus the mothers with ventral striatal DA depletions either left the pups unattended outside nest, or showed partial retrieving responses (e.g., bringing 1 of the 3 test pups back into the nest). By contrast, there were no apparent effects of the lesions on the other maternal activities studied, such as nursing, nest building or maternal aggression. It is quite possible, however, that more fine-grained behavioral analyses will

reveal subtler alterations in these behaviors. For example, in our brief spotchecks of nursing behavior, we did not distinguish between different nursing postures (43) which might well be differentially affected by ventral striatal 6-OHDA lesions. Also, although data on the quality of the nests were collected, we did not systematically examine nest building activity per se, the particulars of which might well be altered in females with mesolimbic 6-OHDA lesions.

The ventral striatal DA levels were depleted by about 70% in the rats receiving 6-OHDA in the accumbens area. This suggests that DA terminals innervating the ventral striatum play an important role for maternal pup retrieval. However, it should be noted that the present ventral striatal 6-OHDA lesions were not entirely specific: there was a slight (30%) but consistent depletion of noradrenaline in the ventral striatum, and also a 45% reduction of the DA levels in the dorsal striatum, both of which might have contributed to the deficits in pup retrieving. Thus the question of whether the behavioral deficit was due to DA denervation of the ventral striatum alone or to combined ventral-dorsal lesions can only be answered by studies involving more specific DA lesions. On the other hand, it seems quite clear that DA lesions restricted to the dorsal striatum are insufficient to precipitate disturbances in maternal behavior. Thus we showed here that selective DA depletions of the dorsal striatum did not affect pup retrieval. Also, Kirkby (25) showed that large electrolytic lesions in the caudate nucleus were without effect on maternal behavior.

The finding of preserved retrieving following dorsal striatal DA lesions is important also because it shows that the behavioral deficit of ventral striatal 6-OHDA females is not secondary to any nonspecific action of the neurotoxin, and that the site of infusion within the striatal complex is most important for the behavioral outcome. However, the lack of effect of dorsal striatal 6-OHDA should not be taken as evidence that the nigrostriatal DA system plays no role whatsoever in maternal behavior. On the contrary, it seems quite likely that greater DA depletions of the caudate-putamen than those achieved by the present procedure would have resulted in maternal impairments. We have indeed previously observed that maternal behavior of mothers with severe nigrostriatal DA dysfunction is restricted to the quiescent nursing response, while nest building, maternal aggression and pup retrieval are reduced (15). Thus most active maternal behaviors disappear following severe DA depletions in the dorsal striatum. DA lesions in the ventral striatum, by contrast, selectively attenuate the pup retrieval response, with no apparent deficits in other maternal behaviors.

Why do mothers with mesolimbic DA lesions fail to pup retrieve? It seems unlikely that the deficit was due to gross motor impairments, because spontaneous locomotor activity was comparable to that of controls in the photocell cages. Moreover, other behaviors requiring sustained motor effort, such as maternal aggression where females attack strange intruders placed in the homecage (12), were not affected by the lesion. Another "motor" hypothesis is that ventral striatal DA depletions specifically disrupt the ability of rats to carry objects in their mouths. This hypothesis is supported by the findings that mesolimbic DA lesions also diminish food hoarding (21), and that the systemic administration of haloperidol to lactating rats also disrupts, in addition to pup retrieving, nest building (14) and pup licking (45). On the other hand, it could also be argued that since the nests built by the present ventral striatal 6-OHDA rats appeared normal, it would seem less likely that the lesion acted specifically to disrupt all oral manipulatory skills.

Other research suggests that the mesolimbic DA system is involved also in motivational processes, in that it mediates the activational or energizing impact of hedonic stimuli by facilitating locomotor excitement as well as more specific appetitive motor sequences (1, 2, 6, 10, 33, 36, 37, 49). Thus mesolimbic DA lesions may impair pup retrieval by making the mother less sensitive to the stimulus of distressed infants in an unsheltered area. Another complementary hypothesis is that the pup retrieval disorder of mothers with mesolimbic DA lesions stems from an inability to suppress competing responses, such as food intake or nest repairing, elicited by other incentives in the homecage. Obviously, much further work is required to characterize the psychological nature of the deficit in maternal behavior induced by ventral striatal 6-OHDA lesions.

Besides its input from mesencephalic DA neurons, the ventral striatum also receives afferents from limbic sources (16, 27, 29) and much current work aims at understanding the way in which limbic and DA mechanisms interact in the ventral striatum to control behavior (3, 6, 7, 29, 33, 47). In view of the prominent input from the hippocampal formation to the ventral striatum (20), it is interesting that mothers with lesions to the fimbria also show aberrant retrieval responses in that they deposit pups at several locations in the observation cage (48). It is likely that this disturbance reflects the impaired ability of hippocampal-lesioned rats to utilize spatial cues to guide its actions (48). However, when the ventral striatal 6-OHDA females of the present study did retrieve, they usually deposited the pup within the nesting area. Desensitization of the snout has also been reported to produce a deficit in retrieval behavior (23, 42, 44) but, unlike females with mesolimbic DA lesions, perioral anesthesia disrupts several other maternal activities, such as nursing and maternal aggression (42,44). Nevertheless, it is interesting in this context to note that recent studies have revealed a close functional link between the vibrissae and the DA system (28,41).

Compared to maternal behavior, female sexual behavior appeared quite resilient to 6-OHDA-induced DA depletion in the ventral or dorsal striatum. Because DA receptor blockade or extensive DA lesions induced by intraventricular 6-OHDA (4, 8, 17) interfere with proceptive behavior in particular (hopping, darting and ear-wiggling), we paid particular attention to possible changes in these behaviors. However, in none of the parameters recorded (proportion of responding subjects, latency to show proceptive behavior, and its perceived intensity) did 6-OHDA females differ from controls, and all subjects showed lordosis behavior. The results obtained in females with ventral striatal 6-OHDA lesions are in line with our previous observation that 6-OHDA infusions in the mesencephalic A10 region leaves female sexual behavior unaffected (15). It may be, then, that very profound DA depletions of the entire striatal complex are needed in order to disrupt the proceptive elements of female sexual behavior in the rat [cf. (4,17)].

It has been repeatedly shown that DA depletion in the ventral striatum attenuates amphetamine-induced hyperactivity (5, 11, 22, 34). Using this behavioral assay of mesolimbic DA dysfunction, we confirmed that our ventral striatal 6-OHDA females indeed showed reduced sensitivity to the activating effects of amphetamine. We also found that females with 6-OHDA lesions in dorsal striatum showed an enhanced locomotor response to amphetamine in comparison to controls. A similar phenomenon of an increased hyperactivity response to amphetamine has been reported by Joyce and Iversen (19) following DA depletion in the posterior head of the caudate nucleus, and by Simon and co-workers (39) following lesions of DA terminals in the amygdala. The latter effect appears to be due to increased DA activity in the nucleus accumbens (39).

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