

Research report

Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats

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Abstract

In vivo microdialysis was used to monitor extracellular concentrations of dopamine (DA), and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the nucleus accumbens and dorsal striatum of sexually active female rats during tests of locomotor activity, exposure to a novel chamber, exposure to sex odors, the presentation of a sexually active male rat, and copulation. DA increased slightly but significantly in the nucleus accumbens when a sexually active male was placed behind a wire-mesh screen, and further during copulation. DA also increased significantly in the dorsal striatum during copulation; however, the magnitude of this effect was significantly lower than that observed in the nucleus accumbens. The metabolites DOPAC and HVA generally followed DA with a delay, and increased significantly during copulation in both regions. In contrast, forced locomotion on a rotating drum, exposure to a novel testing chamber, and exposure to sex odors did not increase DA significantly in either region, although forced locomotion increased DOPAC significantly in both regions, and HVA significantly in the nucleus accumbens. The magnitude of DA release in the nucleus accumbens was significantly greater during copulation than running, whereas no significant difference was detected for striatal DA release between these two behavioral conditions. These results indicate that novelty or locomotor activity alone do not account for the increase in DA observed in the nucleus accumbens of female rats during copulation, and suggest that DA transmission in the nucleus accumbens is associated with anticipatory and consummatory aspects of sexual activity, as it is in male rats. In the dorsal striatum, however, DA release during copulation may reflect an increase in locomotor activity associated with active pacing of the male.

Keywords: Dopamine; Sex; Lordosis; Female rat; Estrogen; Progesterone; Microdialysis

1. Introduction

Dopamine (DA) plays an important role in incentive motivation and reward [8,52], and in the control of certain neuroendocrine processes such as pituitary prolactin release [35]. Although the role of DA in appetitive and consummatory aspects of male sexual behavior has been studied extensively using a variety of pharmacological and in vivo neurochemical monitoring techniques [17,44,45,47], very little comparable work has been done in females. This is surprising given the well-known ability of estrogen to stimulate DA release and augment DA release and behavior in response to amphetamine administration [2–6]. Much of what is known about the role of brain DA in female

sexual behavior comes from pharmacological studies, many of which have reported inconsistent results. For example, systemic administration of DA receptor agonists can facilitate or inhibit lordosis, the dorsiflexion of the back characteristic of female sexual receptivity, in ovariectomized (OVX) rats primed with estrogen and progesterone or estrogen alone [18,19,23]. Paradoxically, systemic administration of a range of doses of DA receptor antagonists also facilitates lordosis, although the behavioral signature of the effect is different. Whereas DA agonists produce a small increase in lordosis quotients, but a large increase in proceptive behaviors used to solicit and pace sexual contact, DA antagonists produce a large increase in lordosis quotients but abolish proceptive behaviors [10,18]. These effects have led to the suggestion that brain DA systems facilitate ‘active’ behavioral components of sexual behavior (e.g. proceptivity), but inhibit the ‘passive’ behavioral component of lordosis [11]. Alternatively, the effects of DA receptor antagonists could be viewed as decreasing the ability of the female to disengage from lordosis once it is

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initiated, or to switch between lordosis and proceptive behaviors [43]. Both the inhibitory and facilitatory effects of systemic DA receptor agonists appear to act through D_2 receptors, as relatively selective D_1 agonists and antagonists do not affect lordosis or proceptivity [20,22].

Few studies have examined the central sites of action of DA in the female rat. Infusions of the mixed D_1/D_2 receptor agonist apomorphine or DA to the ventromedial hypothalamus (VMH) or medial preoptic area (mPOA) facilitate lordosis in OVX rats primed with low doses of estrone, whereas infusions of the DA receptor antagonists haloperidol or α -flupenthixol to these regions inhibit lordosis [21]. Infusions to the VMH of the selective D_1 agonist SKF 38393, but not the selective D_2 agonist quinpirole, facilitate lordosis [30], indicating that D_1 receptors in the VMH may be responsible for the facilitation of lordosis produced by DA and apomorphine in this region. Consistent with a facilitatory effect of DA agonists in this region on lordosis, *in vivo* microdialysis has revealed that DA release increases in the VMH of female rats during copulation [50]. In contrast, lesions of the mesolimbic DA pathway with 6-hydroxydopamine (6-OHDA) have been reported to facilitate lordosis in female rats [49], consistent with the idea that mesolimbic DA release has an inhibitory effect on lordosis. However, other studies have found no effect of mesolimbic DA lesions on female sexual behaviors [24], and copulation actually increases DA release in the nucleus accumbens of female Syrian hamsters, who hold their lordosis posture for extended periods of time during copulation [34]. No studies have yet examined the effect of DA receptor agonists or antagonists in other regions of the brain.

We have used *in vivo* microdialysis previously to monitor extracellular concentrations of DA and its acid metabolites DOPAC and HVA in the nucleus accumbens and dorsal striatum during appetite and consummatory phases of sexual behavior in sexually experienced [12,45] and naive [51] male rats. Although correlative in nature, these studies have shown that DA release increases slightly but significantly in the nucleus accumbens during the presentation of a sexually receptive female behind a wire-mesh screen, and dramatically during copulation. In contrast, placement of the incentive female behind the screen did not increase DA transmission significantly in the dorsal striatum. Although DA transmission in the striatum increased significantly during copulation, the magnitude of this effect was significantly less than that observed in the nucleus accumbens. These effects were not secondary to increases in locomotion or exposure to a novel testing chamber, as these stimuli did not increase DA transmission significantly in either the nucleus accumbens or striatum [12].

The present study examined the effects of locomotion, exposure to a novel testing chamber, exposure to incentive sex odors, exposure to an incentive male, and copulatory activity on DA transmission in the nucleus accumbens and

dorsal striatum of sexually active female rats. These behavioral treatments were identical to those used in our previous study with sexually experienced males [12].

2. Materials and methods

2.1. Animals

Female and male Long-Evans rats were obtained from Charles River Canada Ltd., St. Constant, Qué. They were separated by sex and the males were housed in groups of 2 or 3 in wire-mesh cages in a colony room that was maintained on a 12:12 h light–dark cycle (lights off at 08.00 h) at approximately 21°C. The females were housed singly in plastic cages in a different colony room maintained on a 12:12 h light–dark cycle (lights on at 08.00 h). Food and water were always available in the animals' home cages.

The females were bilaterally ovariectomized via lumbar incisions under sodium pentobarbital anesthesia (Somnotol, 40 mg/kg, *i.p.*) 2 months before microdialysis probes were inserted. Following ovariectomy, the females were given at least 10 preliminary tests of sexual behavior with sexually active males in bilevel chambers to assure a stable baseline of proceptive behaviors, solicitation, pacing, and lordosis [46]. These tests were conducted at 4-day intervals to approximate the normal estrus cycle of the females. Sexual receptivity was induced in each female by subcutaneous injections of estradiol benzoate (10 μ g) and progesterone (500 μ g) 48 and 4 h before each preliminary test, respectively.

2.2. Surgery and microdialysis probes

Females were anesthetized with sodium pentobarbital (50 mg/kg, *i.p.*) and implanted stereotaxically with two microdialysis probes aimed at the nucleus accumbens and striatum, as reported previously [12,45]. The probes used in these experiments were identical to those described extensively in one of our previous studies with males [12]. The portions of active membrane to be located in the nucleus accumbens and striatum were 2.2 mm and 4.2 mm, respectively. The dorsal skull surface was exposed and holes were drilled for the probes and three anchoring screws. Vertically oriented probes were then lowered to an appropriate depth for the right nucleus accumbens (coordinates of the probe tip in relation to bregma were AP = +4.0 mm, ML = +1.5 mm, and DV = –8.2 mm, according to the atlas of Pellegrino et al. [38]) and left dorsal striatum (coordinates of the probe tip in relation to bregma were AP = +1.2 mm, ML = –2.7 mm, and DV = –7.0 mm, according to the atlas of Paxinos and Watson [37]). The probes were secured with dental acrylic to the anchoring screws, and the skin was closed. After surgery, the rats were housed individually in transparent Plexiglas cages

(25 × 35 × 35 cm) containing 3 cm of organic cellulose animal bedding. Food and water were freely available.

2.3. Microdialysis and biochemical analysis

On-line microdialysis was performed as described previously [12,45,51]. Effluent samples were collected over 10 min sampling periods from the microdialysis probe by perfusing it with a Ringer's solution (147 mM NaCl, 3 mM KCl, 1.3 mM CaCl₂, 1 mM MgCl₂, and 1 mM NaPO₄, pH 7.3) at a flow rate of 5 μl/min through the two lengths of polyethylene tubing (PE-10) connected to the inlet and outlet cannulae. The inlet and outlet tubing were connected to a perfusion pump (Harvard) and to the collection loop of an electrically driven injection valve (No. E10W, Valco) respectively. Each length of PE-10 tubing was measured to contain 50 μl.

Concentrations of DA, DOPAC, and HVA were measured by HPLC-ED as described previously [12,45,51]. The mobile phase (consisting of 33 mM sodium acetate trihydrate adjusted to pH 4.0 with glacial acetic acid, 0.01 mM EDTA, 0.4–0.5 mM octanesulfonic acid sodium salt, and 120 ml methanol per litre) was delivered by an HPLC pump (BioRad No. 1350) at a rate of 1.5–1.8 ml/min. A pulse dampener (SSI) was placed between the pump and injector. Constituents in the samples were separated by reverse-phase liquid chromatography (150 × 4.6 mm Nucleosil 5 C19, Chromopack). Electrochemical detection of the effluent was carried out on either a BAS amperometric detector (model LC4B) containing a glassy carbon working electrode set to +700 mV against the Ag/AgCl reference electrode, or on an ESA Coulochem Model 5100A dual detector in combination with a model 5011 flow-through analytical cell, with the oxidizing portion of the cell set to +400 mV and the reduction set to –350 mV against the reference. Chromatograms were registered on a dual-pen chart recorder (Kipp & Zonen Model BD41), with pen sensitivity set individually to accommodate concentration differences between substances measured in each sample. DA, DOPAC, and HVA were quantified from each sample by comparing peak heights in the dialysate with peak heights of known amounts in a standard solution. The detection limit of the assay was 5 fmol/injection for DA and DOPAC, and 20 fmol/injection for HVA.

2.4. Experimental procedure

Experimental tests of locomotor activity, novelty, and sexual behavior were conducted 2 days (44–52 h) after implantation of microdialysis probes. All females were injected with estradiol benzoate and progesterone 48 and 4 h, respectively, before these tests. One day before the experimental tests, each female was acclimated to the forced-locomotion apparatus. This apparatus consisted of a rotating wheel (23 cm wide × 19 cm in diameter) that was elevated 1 m from the floor by wooden slats attached to

each side of the wheel axle, which was driven by a variable speed motor. The surface of the wheel was covered tightly with foam rubber, which yielded a total circumference of 60 cm. Each female was placed on the wheel for 20 min in a stationary position, after which the wheel began turning. The rotation speed increased progressively during the first min to 6 m/min. This rotation speed was maintained for an additional 19 min. All females ran at this speed without obvious signs of stress or fatigue.

On the morning of the experimental tests, each female was connected to the microdialysis equipment while in the home cage and effluent samples were monitored at 10-min intervals until a relatively stable output of DA in the dialysate was obtained in four consecutive samples (i.e. less than 10% variation between consecutive samples) [12,45,51]. Each female was then tested in sequence for locomotion, novelty, and sexual behavior, as we had done in our previous experiment with males [12]. All tests were carried out between 11.00 and 18.00 h.

For the locomotion test, rats were transferred from their home cages to the wheel for a 20-min adaptation period, which was followed by a 20-min test of locomotion (run at 6 m/min, as in the training phase). After the locomotion test, rats were returned to their home cages. Tests of novelty and sexual behavior began at least 60 min after the locomotion test. The rats were again transferred from their home cages to a novel transparent Plexiglas testing chamber (35 × 35 × 40 cm), which contained a vertical wire-mesh screen (16 × 16 cm) that divided the chamber into two equal compartments [12,45,47]. The floor of the chamber was made of wire-mesh that sat 4 cm above fresh Sanicel bedding in a removable pan. The test of novelty and sexual behavior consisted of five consecutive 20-min periods initiated by the following events. (a) The rat was transferred from the home cage to one side of the novel test chamber; (b) bedding was replaced with fresh bedding; (c) bedding was replaced with soiled bedding obtained from the bilevel chambers after training sessions for sexual behavior; (d) a sexually active male was placed behind the screen; and (e) the screen was removed to allow sexual interaction. After the 20-min test of sexual behavior the females were transferred back to their home cages, and three additional dialysis samples were collected. To obtain an index of general activity, the total number of nose pokes through the vertical wire-mesh screen was recorded during each 10-min period until the screen was removed. During sexual interaction, lordosis quotients, lordosis reflex magnitudes, proceptivity counts/mount, and rejection responses/mount were recorded for each female. The total number of mounts, intromissions, and ejaculations each female received by the male was recorded to provide an index of the total amount of sexual stimulation. The testing chambers were cleaned thoroughly after each test with soap and alcohol, and the soiled bedding was replaced with fresh bedding. After each experiment, the females were decapitated under sodium pentobarbital anesthesia (120

mg/kg, i.p.), and their brains were sliced on a cryostat (50 μ m), stained (Nissl), and examined microscopically for probe placement.

Simultaneous sampling of nucleus accumbens and striatum in the same animal was obtained in 5 of the female rats. Data from an additional 6 females, 3 with patent dialysis probes in the nucleus accumbens and 3 with patent probes in the striatum, were also included despite postsur-

gical blockage of the opposite dialysis probe. The inclusion of unpaired data provided a final $n = 8$ females.

2.5. Data analysis

The amount of the recovered substance in each microdialysis sample was recorded as fmol/min. For normalization of the variation in absolute concentrations between

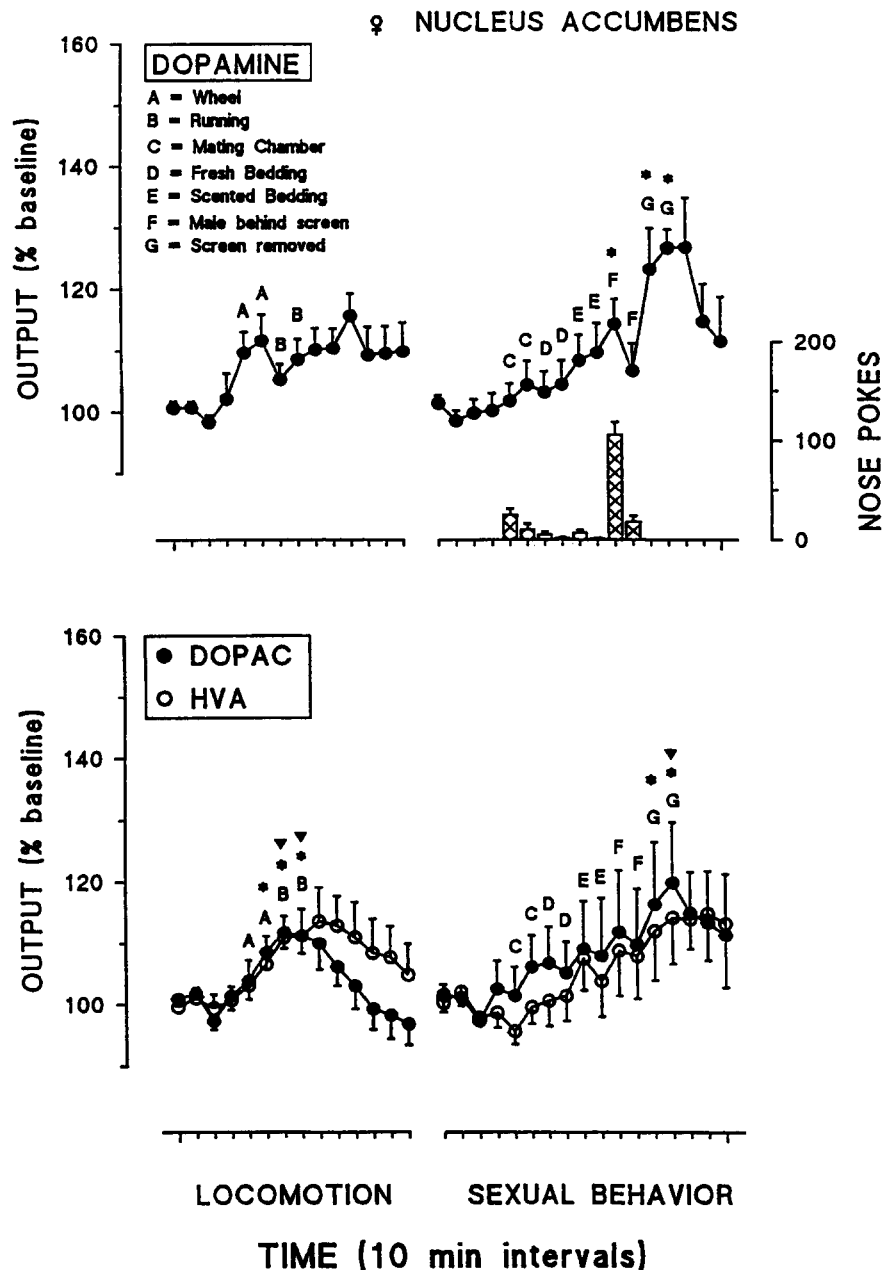


Fig. 1. Temporal changes in dialysate concentrations of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the nucleus accumbens of female rats during the locomotion phase (left side) and the novelty-sexual behavior phase (right side) of the experiment. (Basal concentrations (mean \pm S.E.M.) for DA, DOPAC, and HVA, respectively, were 3.3 ± 0.6 , 1015.0 ± 149.7 , and 528.8 ± 68.2 fmol/min (values not corrected for individual probe recovery). * $P < 0.05$ from the last baseline sample for DA and DOPAC; ▼ $P < 0.05$ from the last baseline sample for HVA.

subjects, the changes over time were expressed in relation to each animal's baseline value, defined as the average of the four samples obtained before the locomotor or novelty-sexual behavior phases of the experiment. Mean percentages of baseline were thus calculated for each 10-min sample. Three within-subjects analyses of variance (ANOVAs) with repeated measures were conducted separately on levels of DA, DOPAC, and HVA derived from

either the nucleus accumbens or striatum during the two phases of the experiment. The locomotor phase comprised 5 repeated samples (the last baseline sample, the 2 samples on the wheel, and the 2 samples of active locomotion). The novelty-sexual behavior phase comprised 11 repeated samples (the last baseline sample, the 2 samples in the novel testing chamber, the 2 samples with fresh bedding, the 2 samples with soiled bedding, the 2 samples with the male

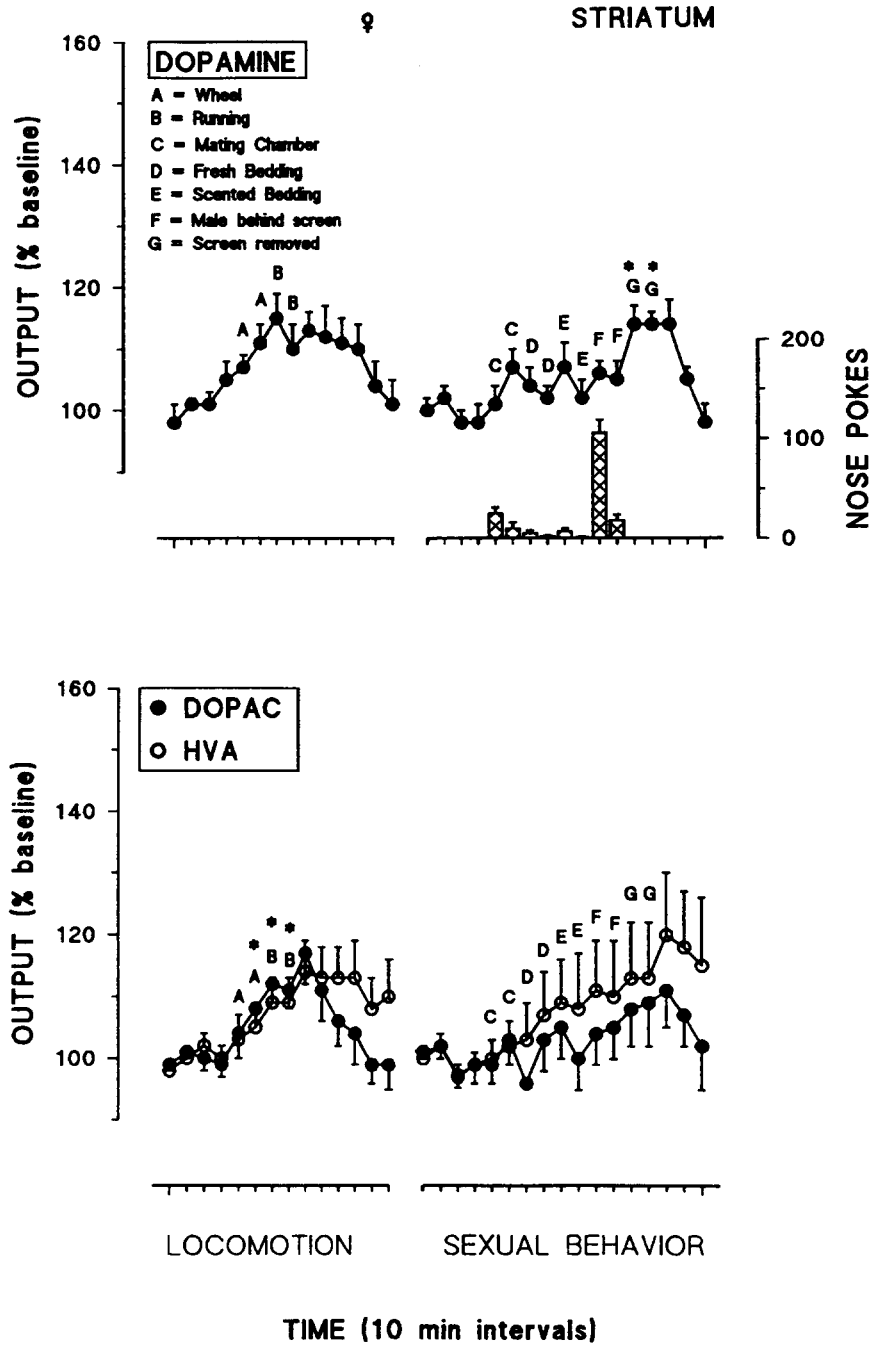


Fig. 2. Temporal changes in dialysate concentrations of dopamine (DA), dihydroxyphenylacetic acid, (DOPAC), and homovanillic acid (HVA) in the dorsal striatum of female rats during the locomotion phase (left side) and the novelty-sexual behavior phase (right side) of the experiment. (Basal concentrations (mean \pm S.E.M.) for DA, DOPAC, and HVA, respectively, were 14.0 ± 3.0 , 1260.0 ± 74.2 , and 957.3 ± 110.1 fmol/min (values not corrected for individual probe recovery). * $P < 0.05$ from the last baseline sample for DA and DOPAC.

behind the screen, and the 2 samples of copulation). A mixed-design ANOVA compared DA levels in the nucleus accumbens and striatum during locomotion and copulation to assess differences between the two regions during these active behaviors, and to determine whether locomotion alone could account for increases in DA transmission observed during copulation. Finally, a within-subjects ANOVA for repeated measures was conducted on the number of nose pokes displayed by females in the testing chambers before the removal of the wire-mesh screen. For each ANOVA, the Bonferroni method was used to correct for the elevated experimentwise error that occurs with a large number of repeated samples [36]. The adjusted Bonferroni alphas were $P < 0.01$ for locomotor activity, $P < 0.005$ for novelty-sexual behavior, and $P < 0.007$ for nose pokes. For each significant ANOVA, post-hoc comparisons were made among the samples from the nucleus accumbens or striatum using the Tukey method, $P < 0.05$.

3. Results

3.1. Behavioral observations

All rats displayed bouts of sniffing and rearing during the first 10-min adaptation period on the running wheel, but were considerably less active during the second 10-min adaptation period, as has been observed previously in males [12]. Locomotion on the wheel was not accompanied by obvious signs of stress or fatigue.

When the females were transferred to the novel testing chamber they displayed a small number of nose pokes through the wire-mesh screen during the first 10-min sample in the chamber (Figs. 1 and 2). Like males, the females remained relatively inactive until the soiled bedding was placed under the wire-mesh floor, when they began to actively sniff at the bedding. When the male was placed behind the wire mesh screen, both animals displayed active locomotion and most attempted to climb the screen. A pronounced increase in the number of nose pokes occurred during the first 10-min sample with the male behind the screen (Figs. 1 and 2). However, this effect declined during the second 10-min sample. The ANOVA detected a significant overall effect on nose

pokes ($F_{7,42} = 41.97$, $P < 0.0001$). Post-hoc comparisons of the individual time points revealed that the number of nose pokes during the first 10-min with the male behind the screen was significantly higher than the numbers observed during the other time points. Immediately after the screen was removed, the rats engaged in copulatory activity (Table 1). After they returned to their home cages, the females displayed little activity except for occasional bouts of rearing, sniffing, and grooming.

3.2. Concentrations of DA, DOPAC, and HVA during the locomotion test

A stable baseline was obtained for all females within 1 h of the onset of perfusion. During the locomotion test, DA concentrations in the nucleus accumbens increased to a maximum of 116% during the second 10-min sample on the wheel, but declined during the periods of active locomotion (Fig. 1). The ANOVA did not detect a significant overall effect of the locomotion test on DA concentrations ($F_{4,28} = 1.91$, $P > 0.05$). Similarly, although DA concentrations in the striatum rose to a maximum of 118% during the first 10-min sample of active locomotion (Fig. 2), this effect did not reach statistical significance ($F_{4,28} = 2.78$, $P < 0.05$).

Concentrations of DOPAC increased to a maximum of 115% in the nucleus accumbens and 117% in the striatum during active locomotion. The ANOVA detected a significant overall effect of the locomotion test on DOPAC levels in the nucleus accumbens ($F_{4,28} = 8.61$, $P < 0.0003$) and striatum ($F_{4,28} = 7.97$, $P < 0.0004$). Post-hoc comparisons of each time point revealed that DOPAC in the nucleus accumbens was elevated significantly from baseline during the second 10-min sample on the wheel and during the two 10-min samples of active locomotion. Post-hoc comparisons of striatal DOPAC revealed an identical pattern.

Concentrations of HVA increased to a maximum of 115% in the nucleus accumbens and 109% in the striatum during active locomotion. The ANOVA detected a significant overall effect of the locomotion test on HVA levels in the nucleus accumbens ($F_{4,28} = 7.65$, $P < 0.0005$). Post-hoc comparisons of HVA concentrations in the nucleus accumbens revealed that both samples taken during active locomotion were elevated significantly from baseline. Al-

Table 1
Sexual behaviors displayed and stimulation received by female rats during dialysis testing

Parameter of sexual behavior						
LQ	LM	PS	RS	NM	NI	NE
96.88 ± 2.84	2.77 ± 0.15	1.44 ± 0.18	0	10.20 ± 1.4	23.43 ± 0.98	2.21 ± 0.10

Values are means ± S.E.M. LQ = lordosis quotient, calculated separately for each female as the percentage of mounts by the male that result in a lordosis; LM = lordosis reflex magnitude (1 = weak dorsiflexion, 2 = moderate dorsiflexion, 3 = full dorsiflexion, as described previously [25]); PS = proceptivity score, calculated as the incidents of proceptive behaviors, e.g. hopping, darting, solicitations, prior to each mount; RS = rejection score, calculated as incidents of rejection behaviors, e.g. escape runs, kicks, boxings, prior to each mount; NM = number of mounts without intromission received by females during the 20-min test; NI = number of intromissions received by females during the 20-min test; NE = number of ejaculations received by females during the 20-min test; $n = 8$ females.

though the ANOVA detected an overall effect of the locomotion test on striatal HVA concentrations ($F_{4,28} = 3.87$, $P < 0.02$), this effect did not reach the level of significance required by the Bonferroni correction.

3.3. Concentrations of DA, DOPAC, and HVA during tests of novelty and sexual behavior

As observed previously in males [12], concentrations of DA remained elevated slightly from the original baseline in the nucleus accumbens and striatum after the locomotion test (Figs. 1 and 2). Once these values reached the criterion of stability (described earlier), four additional samples were taken as a new baseline set at 100%.

DA concentrations increased to a maximum 128% in the nucleus accumbens and 117% in the striatum during copulation (Figs. 1 and 2). The ANOVA detected a significant overall effect of the novelty-sexual behavior test on DA levels in the nucleus accumbens ($F_{10,70} = 8.74$, $P < 0.0001$) and striatum ($F_{10,70} = 5.07$, $P < 0.0001$). Post-hoc comparisons of each time point revealed that DA in the nucleus accumbens was elevated significantly from baseline during the first sample with the male behind the screen, and increased further during both samples of copulation. Striatal DA was elevated significantly from baseline only during copulation.

DOPAC concentrations increased to a maximum of 120% in the nucleus accumbens and 112% in the striatum during copulation. The ANOVA detected a significant overall effect of the novelty-sexual behavior test on DOPAC levels in the nucleus accumbens ($F_{10,70} = 3.29$, $P < 0.002$). Post-hoc comparisons of each time point revealed that DOPAC was elevated significantly from baseline during both samples of copulation. Although the ANOVA detected an overall effect of the novelty-sexual behavior test on striatal DOPAC concentrations ($F_{10,50} = 2.16$, $P < 0.04$), this effect did not reach the level of significance required by the Bonferroni correction.

Concentrations of HVA increased to a maximum of 116% in the nucleus accumbens and 114% in the striatum during copulation. The ANOVA detected a significant overall effect of the novelty-sexual behavior test on HVA levels in the nucleus accumbens ($F_{10,70} = 3.60$, $P < 0.001$). Post-hoc comparisons of each time point revealed that HVA was elevated significantly from baseline during the second 10-min sample of copulation. Although the ANOVA detected an overall effect of the novelty-sexual behavior test on striatal HVA concentrations ($F_{10,50} = 2.27$, $P < 0.02$), this effect did not reach the level of significance required by the Bonferroni correction.

3.4. Comparison of DA concentrations during locomotion and sexual behavior

DA concentrations in the nucleus accumbens and striatum were compared during the two samples of active

locomotion and copulation. The ANOVA did not detect a significant overall effect between the two brain regions ($F_{1,13} = 0.62$, $P > 0.05$), but did detect a significant overall within-subjects effect for event ($F_{3,39} = 4.60$, $P < 0.008$) and a significant interaction of brain region and event ($F_{3,39} = 3.91$, $P < 0.02$). Post-hoc comparisons of the interaction means revealed that DA concentrations in the nucleus accumbens, but not striatum, differed significantly between locomotion and copulation.

4. Discussion

This study demonstrates significant increases in DA transmission in the nucleus accumbens, and to a lesser extent in the striatum, of female rats during copulation. Smaller but significant increases were also observed in the nucleus accumbens, but not striatum, during the presentation of a male behind the screen. Neither of these effects in the nucleus accumbens appeared to be secondary to novelty or active locomotion. However, in the striatum the magnitude of increase in DA transmission during copulation was nearly identical to that observed during active locomotion, suggesting that locomotion during copulation (i.e. proceptive behaviors or attempts to pace the male), could have accounted for the increase in this region. Consistent with this interpretation, a recent report by Mermelstein and Becker [32] demonstrated that paced copulation (occurring in a chamber bisected by a barrier through which the female could control her access to the male) produced a larger increase in DA transmission in the striatum compared to non-paced copulation (occurring in the same chamber without the barrier).

We have previously observed a preferential increase in DA transmission in the nucleus accumbens, compared with that in the striatum, in male rats during appetitive and consummatory phases of sexual behavior [12,45]. Despite comparatively smaller magnitudes in DA release in the nucleus accumbens during these phases of sexual behavior, the pattern observed for the females was very similar to that observed in our previous studies with males. As with the males, this pattern consists of a small increase in DA release during the appetitive phase and a much larger increase during the consummatory phase of active copulation. However, the sexual activity of female rats does not afford a clear distinction between appetitive and consummatory behaviors. Female rats control virtually all aspects of sexual interaction with a male, including the initiation and temporal patterning of copulation [1,29,31,42]. During copulation, this occurs by means of a complex interaction of appetitive behaviors, used to attract and solicit sexual contact, pacing behaviors, used to control the rate of copulatory contact, and defensive behaviors, used either to pace copulatory contact if the female cannot do so otherwise, or to terminate the sexual interaction. These behaviors serve to optimize the rate and strength of sexual

stimulation that the female receives, which in turn affects subsequent behavioral and neuroendocrine functions [15,16]. The complex switching of behaviors during copulation, especially between pacing and lordosis, can be viewed as an example of the mutually-exclusive behavioral patterns described by Konorski [27]. In this regard, it is interesting that systemic administration of DA receptor antagonists inhibits the display of proceptive behaviors but enhances the strength and duration of lordosis. It is possible, therefore, that DA release in the nucleus accumbens facilitates the ability of female rats to display active solicitational or other proceptive behaviors. Interestingly, in the study by Mermelstein and Becker [32], DA transmission increased in the nucleus accumbens during periods in which the females actively approached the male, but decreased during periods in which the number of approaches decreased.

DA release in the nucleus accumbens of female rats can be also viewed as part of a neural substrate for sexual reward. However, unlike male rats, there is little evidence that female rats find copulation rewarding. Although estrogen and progesterone treatment alone facilitate partner preference and instrumental responding for a male [7,13,14,33], the degree of sexual stimulation during copulation correlates negatively with subsequent appetitive or consummatory sexual behavior in the female rat. Studies of instrumental responding have shown that sexually receptive females that receive mounts with intromission are slower to respond subsequently for a male compared with females that receive mounts without intromission [7]. Similarly, sexually receptive females who copulate separately with males that mount with intromission or without intromission (following the application of lidocaine to the penis) show a preference for the males that mount without intromission in a subsequent partner preference test [25]. However, in a similar test, the speed to reach either male was not affected by prior copulatory experience [9]. A small number of mounts with intromission, or manual vaginocervical stimulation, can facilitate the subsequent display of lordosis and pacing behavior [26,48], whereas a large number leads to a faster termination of estrous behavior, especially under conditions where the female can pace the intromissions [16,25]. Thus, it would appear that sexual stimulation, and in particular a large amount of vaginocervical stimulation during copulation, serves to decrease subsequent appetitive and consummatory sexual motivation in females. It would be interesting to examine DA release in female rats during estrous termination, a time when they display active avoidance of the male. If DA release in the nucleus accumbens mediates a preparedness to respond [8], rather than reward per se, then increased DA release would be expected during active appetitive or aversive sexual behaviors.

It would also be important to examine the effects of ovarian hormones, especially estrogen, on DA release in the nucleus accumbens and striatum during different phases

of female sexual behavior. The sensitivity of female rats to indirect DA agonists, such as amphetamine, changes regularly across the estrous cycle, with females being most sensitive during estrus [6]. The ability of estrogen to stimulate DA release directly and to augment DA release and behavior in response to amphetamine is now well-established [2]. Thus it would appear that brain DA systems, and in particular, terminal regions in the striatum, can be primed by estrogens in such a way that basal levels of extracellular DA are increased, and that DA release itself is augmented during periods of stimulation.

Finally, we note that DA transmission in other brain regions may contribute to female sexual behavior and this should be examined in future studies. Mesocorticolimbic DA projections from the ventral tegmentum terminate within regions of the medial prefrontal cortex, olfactory tubercle, lateral septum, dorsal regions of the interstitial nucleus of the stria terminalis, and central nucleus of the amygdala [28]. Many of these terminal regions also contain high densities of estrogen receptor mRNA and protein [39,41]. DA systems in the diencephalon, including the tuberoinfundibular, incerto-hypothalamic, and periventricular, terminate within hypothalamic regions such as the medial preoptic area and ventromedial hypothalamus that contain estrogen receptors and are known to modulate female sexual behaviors and neuroendocrine reflexes associated with pregnancy [40]. Presently, only one study has examined DA and noradrenaline release in the ventromedial hypothalamus of females during sexual behavior [50]. Although the size of many of these terminal regions is small, the microdialysis technique should be useful to determine whether dynamic changes in DA transmission occur within other DA terminal regions during female sexual behavior.

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