

Sexual Behavior Increases Dopamine Transmission in the Nucleus Accumbens and Striatum of Male Rats: Comparison With Novelty and Locomotion

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Extracellular concentrations of dopamine (DA) and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were examined concurrently, using *in vivo* microdialysis, in the nucleus accumbens and dorsal striatum of sexually active male rats during tests of locomotor activity, exposure to a novel chamber, exposure to sex odors, the presentation of a sexually receptive female, and copulation. DA increased significantly in the nucleus accumbens when the males were presented with a sexually receptive female behind a screen and increased further during copulation. Although DA also increased significantly in the dorsal striatum during copulation, the magnitude of the effect was significantly lower than that observed in the nucleus accumbens. In contrast, forced locomotion on a rotating drum, exposure to a novel chamber, and exposure to sex odors did not increase DA significantly in either region, although both DOPAC and HVA increased significantly in both regions during the locomotion test. These results indicate that novelty or locomotor activity alone cannot account for the increased extracellular DA concentrations observed in the nucleus accumbens of male rats during the presentation of a sexually receptive female behind a screen, nor can they account for the increased DA concentrations observed in both the nucleus accumbens and dorsal striatum of male rats during copulation. The preferential increase in DA transmission in the nucleus accumbens, compared with that in the striatum, suggests that anticipatory and consummatory aspects of sexual activity may belong to a class of naturally occurring events with reward values that are mediated by DA release in the nucleus accumbens.

Much of the evidence linking central dopamine (DA) systems to the control of mammalian sexual behavior comes from pharmacological analyses in rats. Systemic administration of DA receptor agonists stimulates anticipatory and

consummatory aspects of sexual behavior in male rats, whereas DA receptor antagonists disrupt or abolish these aspects of male sexual activity (Everitt, 1990; Pfaus & Phillips, 1991). Central infusions of apomorphine into the medial preoptic area (MPOA) facilitate ejaculation in sexually active males (Hull et al., 1986), whereas infusions of *d*-amphetamine into the nucleus accumbens reduce mount and intromission latencies (Everitt, Cador, & Robbins, 1989). Conversely, infusions of haloperidol into the nucleus accumbens reduce anticipatory sexual behavior without affecting the initiation of copulation, whereas infusions of haloperidol into the MPOA reduce anticipatory sexual behavior, increase the mount and intromission latencies, and decrease the number of ejaculations (Pfaus & Phillips, 1991). Similarly, infusions of the mixed D1–D2 antagonist *cis*-flupenthixol into the MPOA decrease the proportion of male rats that initiate copulation and decrease the number of ejaculations in males that copulate (Pehek et al., 1988). Infusions of haloperidol into the striatum do not appear

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to affect measures of anticipatory or consummatory sexual behavior in male rats (Pfaus & Phillips, 1991).

Several recent studies have used *in vivo* techniques, such as voltammetry and microdialysis, to examine DA release in selected terminal regions during sexual activity in male rats. Using differential pulse voltammetry, Mas, Gonzalez-Mora, Louilot, Sole, and Guadalupe (1990) found a significant increase in DA and dihydroxyphenylacetic acid (DOPAC) concentrations in the nucleus accumbens of sexually active male rats during copulation. Peak heights for DA and DOPAC were assessed at 5-min intervals. During active copulation, the DA signals increased to 160% of baseline, whereas the DOPAC signals increased to 140% of baseline. The increase in DA, but not DOPAC, was maintained for at least 60 min after the sexually receptive female was removed from the testing chamber. The magnitude of the DA signals was significantly greater during sexual activity than during control conditions in which either a sexually nonreceptive female or other male was placed into the chamber with the males.

Using microdialysis, Pleim, Matochik, Barfield, and Auerbach (1990) also found a significant increase in concentrations of DA and DOPAC in the nucleus accumbens during copulation. Microdialysis was performed using an on-line system that monitored DA, DOPAC, and 5-hydroxyindolacetic acid (5-HIAA) at 30-min intervals using high-pressure liquid chromatography coupled with electrochemical detection (HPLC-ED). The males were given unrestricted access to a sexually receptive female for 90 min, and extracellular DA rose progressively to an average of 158% of baseline values during the second 30-min period of active copulation. Although DOPAC and 5-HIAA increased comparably during copulation, they lagged behind the rise in DA by 30 and 60 min, respectively.

We have also compared concentrations of DA, DOPAC, and the secondary DA metabolite homovanillic acid (HVA) in the nucleus accumbens and striatum of sexually active male rats during anticipatory and consummatory phases of sexual behavior using an on-line microdialysis system that assessed DA and its metabolites at 10-min intervals with HPLC-ED (Pfaus, Damsma, et al., 1990). DA concentrations increased significantly in the nucleus accumbens to an average of 131% when the males were placed in a novel mating chamber that contained odors of previous copulations and further, to an average of 140%, when a sexually receptive female was introduced behind a screen that partitioned the chamber. Subsequently, during a 30-min test of copulation, DA increased significantly to a maximum of 195% of baseline. Similar to the effect reported by Mas et al. (1990), DA remained elevated significantly above baseline during the 80-min period after the removal of the female from the chamber. In contrast, striatal DA concentrations increased progressively during the different phases of the test. However, these increases reached statistical significance only during copulation (to a maximum of 140% of baseline) and returned to baseline levels during the 80 min after copulation. DOPAC and HVA concentrations increased in both brain regions during the test, although the patterns were less marked and delayed 10 and 20 min, respectively, in relation to the increases in DA. These results indicated that DA transmission in the nucleus accumbens increases during the anticipatory phase of

sexual behavior and increases in both the nucleus accumbens and striatum during the consummatory phase of copulation.

None of these studies ruled out the possibility that increases in motor output accounted for the increases in DA transmission observed during copulation. With regard to our previous study (Pfaus, Damsma, et al., 1990), no control was included that distinguished novelty from the odors of previous copulations. Therefore, the present study was undertaken to examine the effects of locomotion, exposure to a novel chamber, exposure to sex odors, and sexual activity on DA transmission in the nucleus accumbens and striatum of sexually active male rats.

Method

Subjects and Behavioral Training

Six female and 6 male Long-Evans rats (Charles River Canada, St. Constant, Quebec, Canada) were housed 6 to a cage under a reversed 12:12-hr light-dark cycle (lights off at 11:00 a.m.) at 21 °C. Food and water were continuously available. The females were bilaterally ovariectomized under sodium pentobarbital anesthesia (50 mg/kg) at least 3 months before testing. Sexual receptivity was induced in each female by subcutaneous injections of estradiol benzoate (10 µg), 48 hr before each test, and progesterone (500 µg), 4 hr before each test.

The males were given at least 10 trials of sexual behavior at 4-day intervals before the experiment. Each trial lasted 20 min and was conducted in the bilevel chambers described by Pfaus, Mendelson, and Phillips (1990). By the end of the training phase, the 6 males used in this study exhibited consistent parameters of sexual activity, including intromission within 20 s of the presentation of the female, ejaculation within 10 min of the first intromission, and the reinitiation of copulation within 10 min of the first ejaculation.

One day before each experimental test, the rats were habituated to a 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 rat 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 1st minute to 6 m/min. This rotation speed was maintained for an additional 19 min. All rats ran at this speed without obvious signs of stress or fatigue.

Surgery and Microdialysis Probes

Experimental rats were anesthetized with sodium pentobarbital (50 mg/kg ip) and implanted stereotaxically with two microdialysis probes that were aimed at the nucleus accumbens and striatum. The dorsal skull surface was exposed, and holes were drilled for the probes and the three anchoring screws. Vertically oriented probes were then lowered into 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, Pellegrino, & Cushman, 1979) and the left 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 & Watson, 1982). The probes were secured with dental acrylic to the anchoring screws, and the skin was sutured. After surgery, all rats were housed individually in transparent Plexiglas cages (25 × 35 × 35 cm) with food and water freely available.

The microdialysis probe that was used in this study was a variant of the concentric probe designs reported previously (Johnson & Justice, 1983; Robinson & Whishaw, 1988). The probe incorporated a length of hollow acrylonitrile-sodium methallyl sulfonate fiber (Filtral 12 AN69 HF, Hospal) with an inside diameter of 220 μm , an outside diameter of 310 μm , and an expansion factor of an additional 10% when wet. Construction of the probe (Figure 1) began with the preparation of a main shaft of a 23-gauge stainless steel cannula, which was 5–6 mm in length, and two stainless steel 22-gauge cannulas, each approximately 8 mm in length with a bevel at one end, that housed and protected fused silica capillary inlet and outlet tubing that had an inside diameter of 75 μm and an outside diameter of 150 μm (Polymicro Technologies, Phoenix, AZ). The hollow fiber dialysis tube was inserted 1–2 mm into the lumen of the 23-gauge shaft, secured with epoxy resin, and trimmed to a length appropriate for the targeted region (8.5 mm for accumbens and 7 mm for striatum). One of the lengths of fused silica capillary tubing extended throughout the length of the probe and terminated approximately 0.3 mm from an epoxy plug that sealed the tip of the hollow fiber. The opposite end of this silica threaded from the top of the 23-gauge main shaft through the beveled tip of the 22-gauge cannula, which was bent at an angle of approximately 60°, and terminated at the end of this cannula within a matrix of sealing epoxy. This seal ensured the exclusive passage of perfusion solution directly into the lumen of the silica and through it to the ventral tip of the sealed hollow fiber. A shorter length of silica received the dialysate from the lumen of the 23-gauge shaft immediately above the upper end of the hollow fiber and routed it out through the second length of 22-gauge housing cannula. This silica was sealed to the inner surface of the beveled tip of housing cannula before its insertion into the main shaft with epoxy resin to preclude flow of dialysate into the lumen of the outer cannula. Finally, the assembled probe was sealed

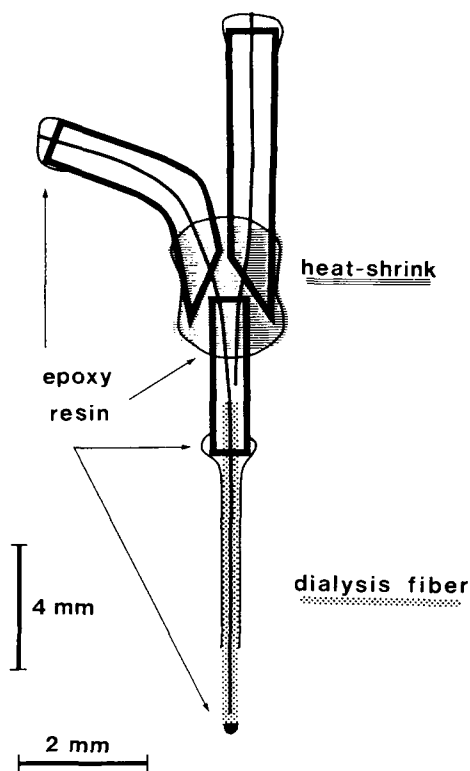


Figure 1. The vertical microdialysis probe.

with epoxy at the junction of the three stainless steel cannulas, and this joint was further secured with an outer casing of heat-shrink tubing. The desired length of exposed dialysis fiber was achieved by coating the remainder of membrane with epoxy.

The exposed lengths of dialysis surface area were 4.2 mm for striatal probes and 2.2 mm for accumbens probes; each had an error margin of 0.2 mm. The recovery of DA, DOPAC, HVA, and 5-HIAA was measured *in vitro* (Ungerstedt, 1984). For this purpose, a probe was placed in a beaker that contained DA and the acid metabolites (1 μM) that were dissolved in perfusion solution at 37 °C. The probe was then perfused at the standard rate of 5 $\mu\text{l}/\text{min}$, as in the subsequent *in vivo* experiments. Recovery was calculated as the ratio between the concentration of recovered substance in the dialysate compared with the beaker concentration and is expressed as a percentage. Recoveries obtained *in vitro* in this manner for striatal probes ($n = 4$) were 13.1 + 0.8 (DA), 9.1 + 0.6 (DOPAC), 9.7 + 1.3 (HVA), and 9.8 + 1.2 (5-HIAA); for nucleus accumbens probes, recoveries were 6.8 + 0.3 (DA), 4.8 + 0.4 (DOPAC), 4.7 + 0.4 (HVA), and 4.7 + 0.4 (5-HIAA).

Microdialysis and Biochemical Analysis

On-line microdialysis was performed by connecting the dialysis probe directly to the analytical equipment (Damsma, Boisvert, Mudrick, Wenkstern, & Fibiger, 1990). The inlet and outlet cannulas were joined by two lengths of polyethylene tubing (PE-10, inside diameter of 0.28 mm) to the perfusion pump (Harvard) and to the collection loop of the electrically actuated injection valve (No. E10W, Valco). Each length of PE-10 tubing was measured to contain 50 μl (approximately 80 cm). The load and inject modes (9.8 min and 12 s, respectively) were controlled in sequence by a digital valve sequence programmer (Valco) that repeated these modes automatically every 10 min. Probes were perfused with a solution that contained NaCl (147 mM), KCl (3.0 mM), CaCl_2 (1.3 mM), MgCl_2 (1.0 mM), and NaPO_4 (1.5 mM and pH 7.3). The concentration of these ions in the perfusion solution was chosen to approximate their concentration in the interstitial fluid of the brain.

Concentrations of DA, DOPAC, and HVA were quantified by HPLC-ED as described previously (Damsma et al., 1990). The mobile phase (consisting of 33 mM sodium acetate trihydrate adjusted to pH 4.1 with glacial acetic acid, 0.01 mM EDTA, 0.4–0.5 mM octanesulfonic acid sodium salt [Sigma], and 100 ml methanol per liter) was delivered by an HPLC pump (BioRad No. 1350) at a rate of 1.5–1.8 ml/min. A pulse dampener (SSI) and a precolumn (50 \times 3 mm Nucleosil 5 C 18) were placed between the pump and injector. Constituents in the samples were separated by reverse-phase liquid chromatography (150 \times 4.8 mm Nucleosil 5 C 18).

Electrochemical detection of the effluent from the accumbens probe was carried out on a BAS amperometric detector Model LC4B that contained a glassy carbon working electrode set to 700 mV against the Ag-AgCl reference electrode. Striatal samples were delivered by a second Valco injector to a comparable 150 \times 4.8 mm Nucleosil column from which they passed through a Model 5011 High Sensitivity analytical cell (ESA) that contained a coulometric and amperometric electrode in series. Signals from the analytical cell were controlled and monitored by the dual detectors of a Model 5100A Coulochem Detector (ESA) set to oxidizing and reducing potentials of 400 mV and -200 mV, respectively. Each detection system registered chromatograms on its own dual-pen chart recorder (Kipp & Zonen Model BD 41), with pens set individually to an appropriate range to accommodate differences between the substances measured in each sample. Concentrations of DA, DOPAC, and HVA were quantified by comparing peak heights in the dialysate samples with the peak heights of known amounts in standard solutions. The detection limit of the assay was 5 fmol/injection for DA and DOPAC and 20 fmol/injection for HVA.

Experimental Procedure

Experimental tests of locomotor activity, novelty, and sexual behavior were conducted 2 days (44–52 hr) after surgery during the middle of the rats' dark cycle in a lighted testing room. While in their home cages, the rats were connected to the microdialysis equipment and effluent samples were monitored at 10-min intervals until a stable output of DA in the dialysate had been obtained in four consecutive samples. Rats were then tested in sequence for locomotion, novelty, and sexual behavior.

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 were also conducted in sequence and began at least 60 min after the locomotion test. The rats were 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 (Pfaus, Damsma, et al., 1990). 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 partner was placed behind the screen; and (e) the screen was removed to allow sexual interaction. On completion of the sexual behavior test, the rats were transferred 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 were recorded during each 10-min period until the screen was removed. During sexual interaction, the number of mounts, intromissions, ejaculations, and their latencies were recorded. The chambers were cleaned thoroughly after each test with soap and alcohol, and the soiled bedding was replaced with fresh bedding. After each experiment, the males were decapitated under sodium pentobarbital anesthesia (120 mg/kg ip), and their brains were sliced on a cryostat (50 μm), stained (Nissl), and examined microscopically for probe placement (Figure 2).

Data Analysis

The amount of the recovered substance in each microdialysis sample was recorded as femtomoles per minute. For normalization of the variation in absolute concentrations between 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

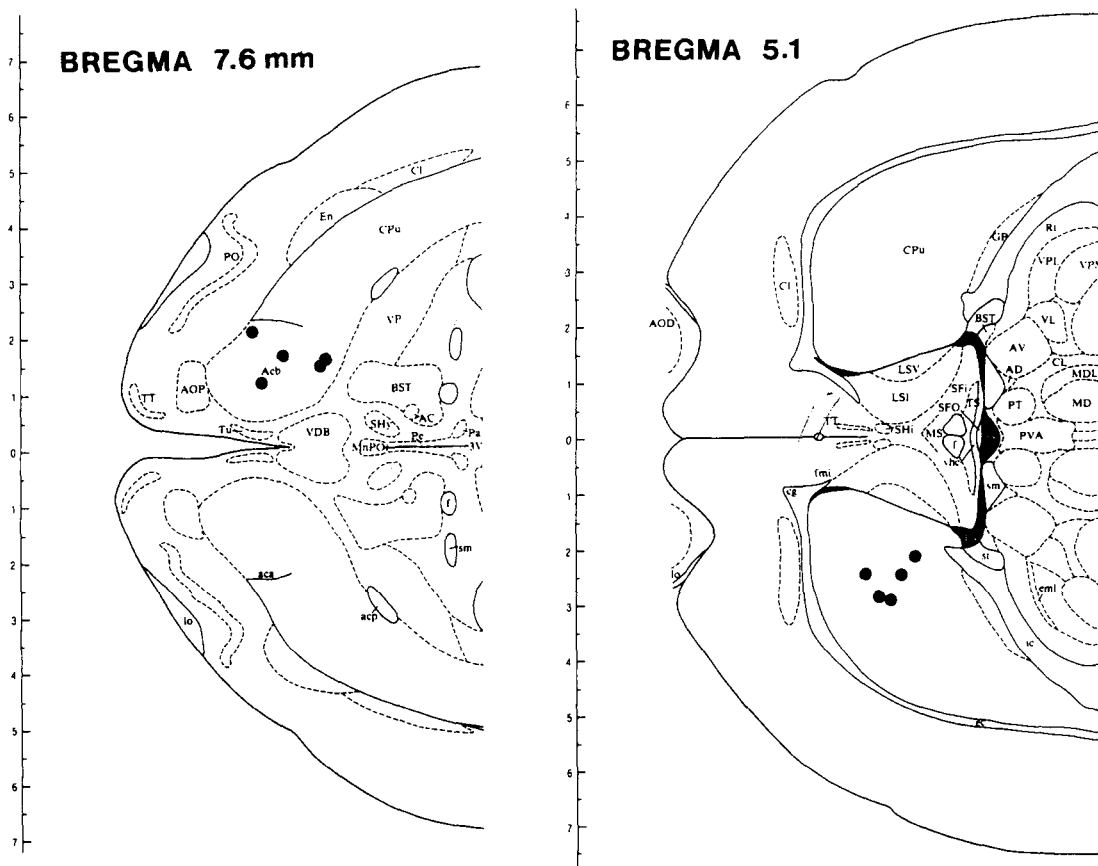


Figure 2. Probe placements in the nucleus accumbens (left panel) and striatum (right panel). (Adapted from *The Rat Brain in Stereotaxic Coordinates* (Plates 56 and 61) by G. Paxinos and C. Watson, 1982, San Diego, CA: Academic Press; copyright 1982 by Academic Press; adapted by permission.)

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 during 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 partner behind the screen, and the 2 samples during copulation). A mixed-design ANOVA compared DA levels in the nucleus accumbens and striatum during baseline, locomotion, novelty, and copulation. This analysis tested whether locomotion or novelty alone could account for the increases in DA transmission during copulation. Finally, a within-subjects ANOVA for repeated measures was conducted on the number of nose pokes displayed by males in the sex 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 (Overall & Rhoades, 1987). The adjusted Bonferroni alphas were $p < .01$ for locomotor activity, $p < .005$ for novelty–sexual behavior, and $p < .007$ 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, $p < .05$.

Results

Simultaneous sampling of nucleus accumbens and striatum was performed in 6 experimental rats. Dialysates collected from the nucleus accumbens of 1 rat, and from the striatum of another rat, had to be discarded because of inaccurate probe placement or chromatography. For statistical purposes, the remaining data of these 2 rats were paired into one complete set, which left a total statistical subject population of 5 rats.

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. Locomotion on the wheel was not accompanied by obvious signs of stress or fatigue.

When the rats were transferred to the novel sex chamber, they did not display the active exploration that was observed in our previous study (Pfaus, Damsma, et al., 1990). However, all rats displayed a small amount of nose pokes through the wire-mesh screen during the first 10-min sample in the chamber (Figures 3 and 4). The rats remained relatively inactive until the soiled bedding was placed under the wire-mesh floor. Active sniffing, rearing, locomotion, and nose poking through the grid floor, and to a lesser extent through the vertical screen, were observed. When the receptive female was placed behind the 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 with the female behind the screen (Figures 3 and 4). However, the number of nose pokes declined during the second 10 min with the female behind the screen. The ANOVA detected a significant overall effect on nose pokes, $F(7, 28) = 16.89$, $p < .00001$. Post hoc comparisons of the individual time points revealed that the number of nose pokes during the first 10 min with the female behind the screen was significantly higher than the number observed during the other time points. However, the number of nose pokes during the first 10 min in the novel chamber and during the second 10 min

with the female behind the screen were also significantly higher than those observed during the remaining time points. Immediately after the screen was removed, the rats engaged in copulatory activity (Table 1). After they returned to their home cages, the males displayed little activity, except bouts of grooming during the first 10-min period.

Concentrations of DA, DOPAC, and HVA During the Locomotion Test

A stable baseline (i.e., less than 10% variation between consecutive samples of the substances measured in the dialysate) was obtained for all rats within 1 hr of the onset of perfusion.

During the locomotion test, DA concentrations in the nucleus accumbens increased to a maximum of nearly 110% during the first 10-min sample on the wheel (Figure 3) but did not increase further during the 20-min period of active locomotion. The ANOVA did not detect a significant overall effect of the locomotion test on DA concentrations, $F(4, 16) = 2.09$, $p > .05$. Similarly, although DA concentrations in the striatum rose to a maximum of 113% during the test (Figure 4), this increase did not reach statistical significance, $F(4, 16) = 2.75$, $p > .05$.

Concentrations of DOPAC increased to a maximum of nearly 119% in the nucleus accumbens and 115% in the dorsal striatum during active locomotion. The ANOVA detected a significant overall effect of the locomotion test on DOPAC levels in the nucleus accumbens, $F(4, 16) = 15.79$, $p < .00001$, and striatum, $F(4, 16) = 6.20$, $p < .004$. Post hoc comparisons of each time point revealed that DOPAC in the nucleus accumbens was elevated significantly from baseline by the second sample on the wheel. Although there was a further increase of DOPAC during active locomotion, subsequent samples did not differ significantly from the second sample on the wheel. Post hoc comparisons of striatal DOPAC concentrations revealed that the two samples taken during active locomotion were significantly higher than the other samples but did not differ from one another.

Concentrations of HVA increased to a maximum of 119% in the nucleus accumbens and 113% in the dorsal striatum during active locomotion. The ANOVA detected a significant overall effect of the locomotion test on HVA levels in the nucleus accumbens, $F(4, 16) = 15.40$, $p < .00001$. Post hoc comparisons of HVA concentrations in the nucleus accumbens revealed that both samples taken during active locomotion were elevated significantly from the other samples. Although the ANOVA detected an overall effect of the locomotion test on striatal HVA concentrations, $F(4, 16) = 3.96$, $p < .03$, the magnitude of this effect did not reach the level of significance required by the Bonferroni correction.

Concentrations of DA, DOPAC, and HVA During Tests of Novelty and Sexual Behavior

Concentrations of DA remained elevated slightly from the original baseline in the nucleus accumbens (average = 112%) and striatum (average = 111%) after the locomotion test (Figures 3 and 4). Once these values reached the criterion of stability (described earlier), four additional samples were taken as a new baseline set at 100%.

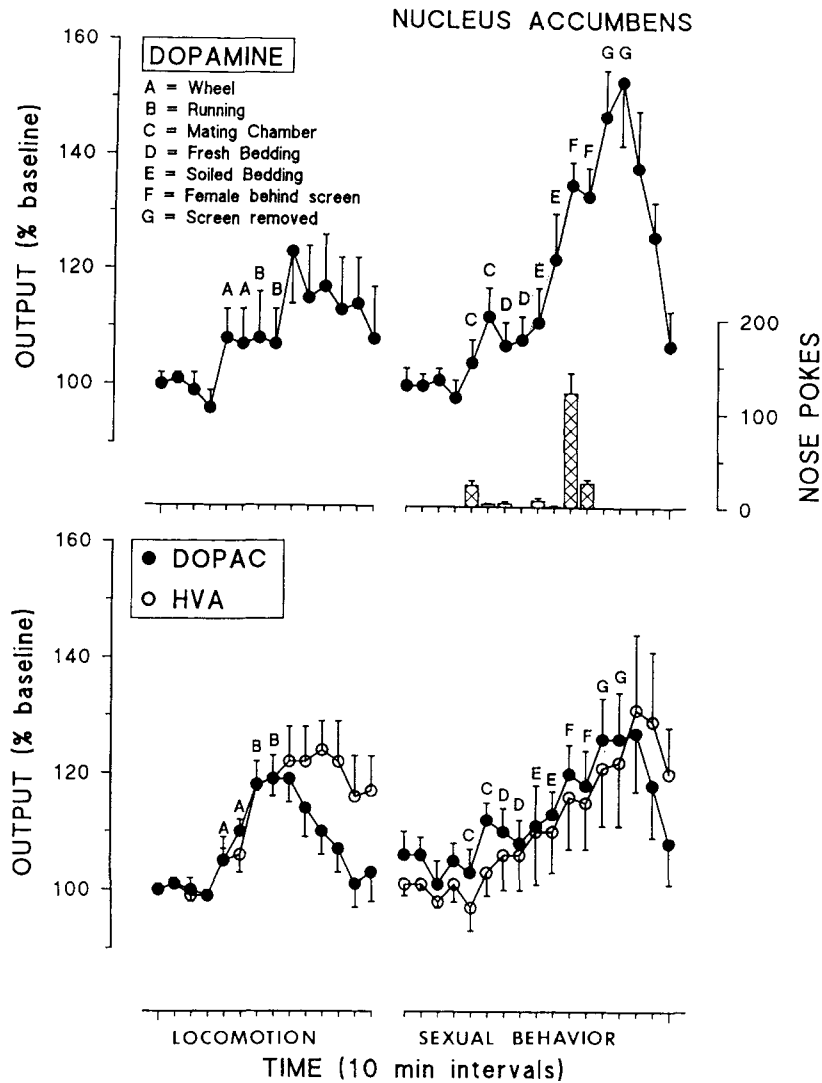


Figure 3. Temporal changes in dialysate concentrations of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the nucleus accumbens of male rats during the locomotion phase (left side) and the novelty-sexual behavior phase (right side) of the experiment. (Basal concentrations [$M + SE$] for DA, DOPAC, and HVA, respectively, were $3.4 + 0.6$, $727.8 + 77.4$, and $436.4 + 56.5$ fmol/min [values not corrected for individual probe recovery]. $p < .05$ from the last baseline sample.)

DA concentrations increased to a maximum of 153% in the nucleus accumbens and 130% in the striatum during copulation (Figures 3 and 4). The ANOVA detected a significant overall effect of the novelty and sexual behavior test on DA levels in the nucleus accumbens, $F(10, 40) = 12.13$, $p < .00001$, and striatum, $F(10, 40) = 4.52$, $p < .0005$. Post hoc comparisons of each time point revealed that DA in the nucleus accumbens was elevated significantly from baseline by the first sample with the female behind the screen and remained so during both samples of copulation. Striatal DA was elevated significantly from baseline only during the first sample of copulation.

DOPAC concentrations increased to a maximum of 126% in the nucleus accumbens and 113% in the dorsal striatum during

copulation. The ANOVA detected a significant overall effect of the novelty-sexual behavior test on DOPAC levels in the nucleus accumbens, $F(10, 40) = 8.11$, $p < .0001$, and striatum, $F(10, 40) = 3.73$, $p < .002$. Post hoc comparisons of each time point revealed that DOPAC in both the nucleus accumbens and striatum was elevated significantly from baseline by the first sample with the female behind the screen and remained so during copulation.

Concentrations of HVA increased to a maximum of 116% in the nucleus accumbens and 121% in the dorsal striatum. The ANOVA detected a significant overall effect of the novelty-sexual behavior test on HVA levels in the nucleus accumbens, $F(10, 40) = 5.83$, $p < .0001$, and striatum, $F(10, 40) = 6.95$, $p < .0001$. Post hoc comparisons of each time point revealed

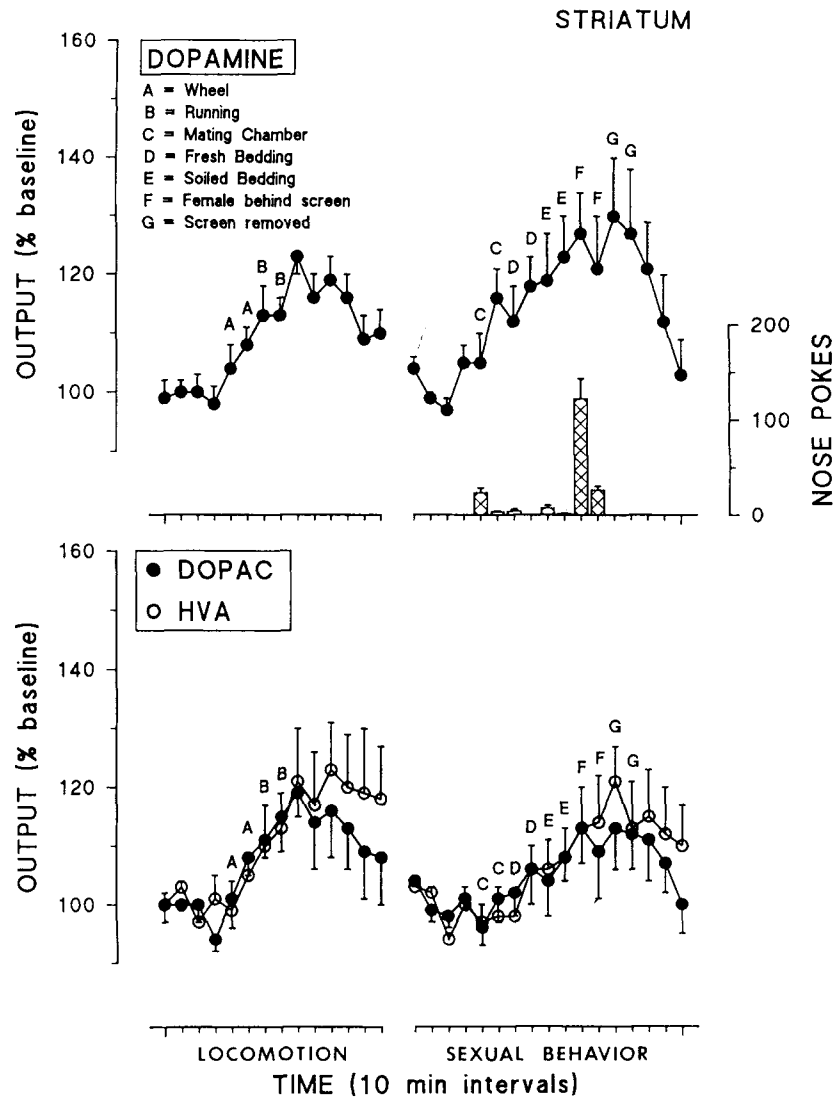


Figure 4. Temporal changes in dialysate concentrations of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the striatum of male rats during the locomotion phase (left side) and the novelty-sexual behavior phase (right side) of the experiment. (Basal concentrations $[M + SE]$ for DA, DOPAC, and HVA, respectively, were $6.9 + 0.9$, $1,161.1 + 105.3$, and $824.8 + 65.0$ fmol/min [values not corrected for individual probe recoveries]. $p < .05$ from the last baseline sample.)

that HVA was elevated significantly in the nucleus accumbens during both samples of copulation, whereas striatal HVA was elevated significantly only during the first sample of copulation.

Comparison of DA Concentrations During Locomotion, Novelty, and Sexual Behavior

Finally, DA concentrations in the nucleus accumbens and striatum were compared during the last two baseline samples before each phase of the experiment, during the two samples of active locomotion, during the two samples of novelty, and during the two samples of copulation. The ANOVA did not detect a significant overall effect between the two brain regions, $F(1, 8) = 0.16$, $p > .05$, but did detect a significant

overall within-subjects effect for event, $F(7, 56) = 18.52$, $p < .00001$, and a significant interaction of brain region and event, $F(7, 56) = 2.85$, $p < .02$. Post hoc comparisons of the interaction means revealed that DA concentrations in both brain areas were elevated significantly from the baselines during copulation; however, the increase in the nucleus accumbens was significantly greater than the increase in the striatum. Although the novelty-sexual behavior baseline was higher than the locomotion baseline, the two did not differ significantly.

Discussion

These results replicate and extend those of our previous study (Pfaus, Damsma, et al., 1990). Copulation, but not

Table 1
Measures of Sexual Behavior (M ± SE) Displayed by Male Rats During Dialysis Testing

Measure	M	SE
Mount latency	5.20	0.99
Intromission latency	8.20	2.08
Ejaculation latency	173.00	46.30
Postejaculatory interval	322.20	29.45
Number of mounts	3.80	0.90
Number of intromissions	10.20	1.08
Intromission ratio	0.73	0.05
Interintromission interval	21.84	2.24
Total number of ejaculations	2.00	0.30

Note. All latencies and intervals were recorded during the first ejaculatory series and are expressed in seconds. The postejaculatory interval was calculated as the time from ejaculation to the next intromission. The intromission ratio was calculated as the number of intromissions/number of mounts + number of intromissions. The interintromission interval was calculated as the ejaculation latency/number of intromissions. The total number of ejaculations was calculated for the entire 20-min test period ($n = 6$).

novelty or locomotion, increased DA concentrations significantly in the nucleus accumbens and striatum of sexually active male rats. Moreover, in the nucleus accumbens, but not in the striatum, DA concentrations were significantly higher than baseline during the presentation of the female behind the screen. Thus, neither novelty nor locomotor activity can account for the increased DA in the nucleus accumbens during the presentation of a sexually receptive female behind a screen, nor can these variables account for the increased DA in both the nucleus accumbens and dorsal striatum during copulation.

Despite these consistent findings, the relative increases in extracellular DA in both brain regions during copulation were somewhat lower than those observed in our previous study (Pfaus, Damsma, et al., 1990). Striatal DA reached a maximum average value of nearly 140% during copulation in the previous study, whereas those values were approximately 10% lower in the present study. However, the baseline taken before the novelty and sexual behavior phase of the present experiment was an average of 11% higher than the baseline taken before the locomotion test. Had the locomotion baseline been used as a general baseline for all subsequent analyses, the magnitude of the increase in striatal DA levels during copulation would have been nearly identical to that observed in the previous study. It is more difficult to apply this explanation to the smaller DA increase observed in the nucleus accumbens during copulation. Even if the average 12% increase in the novelty-sexual behavior baseline was added to the DA measured in the nucleus accumbens during copulation, the maximum average value would still be 30% lower than the maximum average observed in the previous study. An intriguing possibility is that the different maximum values resulted from the placement of probes into different subregions of the nucleus accumbens (see Heimer, Zahm, Churchill, Kalivas, & Wohltmann, 1991). Indeed, a reexamination of probe placements in our previous study revealed that most were implanted in the shell of the accumbens, whereas by chance the probes were located largely in the core in the present study. Although

it is tempting to suggest that the relatively lower maximum increases might have been derived from DA release in the core, it must be noted that the present study used a more complex behavioral paradigm. Further work is required to examine whether DA transmission is regulated differentially in the shell and core of the nucleus accumbens during sexual activity.

In the Pfaus, Damsma, et al. (1990) study, male rats were transferred from their home cages to a novel chamber that contained the odors of previous copulations, and DA transmission increased significantly in both the nucleus accumbens and striatum during the first 10-min period in this chamber. However, in the present study, placing the males into a novel chamber that had been cleaned between tests did not elevate DA transmission significantly in either region. This suggests that the presence of sex odors in the chamber may have been responsible for the significant increase in DA transmission in the earlier study; however, the introduction of sex odors on bedding produced a small but nonsignificant increase in DA transmission in the nucleus accumbens and striatum, even though the males responded to their introduction with intense bouts of sniffing directed at the bedding. Because it is likely that the rats had become habituated to the chambers by the time the sex odors were presented, the combination of novelty and sex odors in the previous study, rather than either one alone, may have led to the significant increases in DA transmission.

There is a large body of pharmacological evidence indicating that DA in the nucleus accumbens mediates locomotor activity (e.g., Clarke, Jakubovic, & Fibiger, 1988; Kelley & Iversen, 1975; Pijnenburg, Honig, van der Heyden, & van Rossum, 1976), whereas DA in the dorsal striatum or nucleus accumbens mediates certain forms of stereotypy (e.g., Robinson, 1984; Ungerstedt & Arbuthnott, 1970; Yamamoto & Freed, 1982). Ex vivo studies have reported increases in DA transmission and metabolism in these regions after forced treadmill locomotion (Freed & Yamamoto, 1985) or conditioned turning (Szostak, Jakubovic, Phillips, & Fibiger, 1986, 1989). It is of considerable interest, therefore, that the small average increases in extracellular DA in the nucleus accumbens (10%) and dorsal striatum (13%) during continuous locomotion on the rotating wheel failed to reach statistical significance. However, the lack of significant elevation of DA should not be taken as firm evidence that DA transmission in either region was unaffected by locomotion. DOPAC and HVA increased significantly in both regions during locomotion, suggesting that either increased DA release (e.g., Roth, Murrin, & Walters, 1976) or synthesis (Imperato & Di Chiara, 1985) had occurred. It is possible that a relatively small increase in DA release is not sufficient to overcome the highly efficient intrasynaptic DA uptake system and results in a nonsignificant change in extracellular and dialysate DA concentrations. In such a case, changes in metabolites might reflect changes in DA transmission more accurately. A nearly identical pattern of data was reported in a recent microdialysis study by Sabol, Richards, and Freed (1990) in which DOPAC but not DA increased slightly but significantly in the nucleus accumbens and striatum of rats forced to turn in a circular treadmill. Thus, although locomotion alone, as we have tested it, cannot account for the

magnitude of the increases in DA transmission observed in the nucleus accumbens and striatum during copulation, locomotion can increase DA metabolism in both regions. However, this pattern of data is consistent with the interpretation that mesolimbic DA mediates motor responses directed toward primary or secondary incentive stimuli, rather than motor responses per se (e.g., see Salamone, 1991).

DA transmission in the nucleus accumbens plays an important role in the reward properties of many drugs of abuse (e.g., Carboni, Imperato, Perezzi, & Di Chiara, 1989; Carr, Fibiger, & Phillips, 1989; Di Chiara & Imperato, 1988; Hoebel et al., 1983; Wise & Bozarth, 1987), feeding (e.g., Hernandez & Hoebel, 1988; Radhakishun, van Ree, & Westerink, 1988), and electrical stimulation of the hypothalamus or ventral tegmentum (e.g., Fibiger & Phillips, 1987; Hernandez & Hoebel, 1988). Copulatory activity is also recognized as a type of reward. Male rats will work to engage in copulation (Sheffield, Wulff, & Backer, 1955; Whalen, 1961) or for access to a second-order stimulus associated with copulation (Everitt et al., 1989). Like amphetamine, copulation also induces robust place preferences (Everitt, 1990; Mehrara & Baum, 1990; Miller & Baum, 1987). Bilateral infusion of the DA receptor antagonist haloperidol to the nucleus accumbens disrupts anticipatory aspects of sexual behavior in male rats (Pfaus & Phillips, 1991), whereas extensive 6-hydroxydopamine (6-OHDA) lesions of DA terminals in the nucleus accumbens disrupt the initiation of copulation (Brackett, Iuvone, & Edwards, 1986; Everitt, 1990; Robbins, Cador, Taylor, & Everitt, 1989). The results of the present study, along with those of other microdialysis and voltammetric studies (e.g., Mas et al., 1990; Pfaus, Damsma, et al., 1990; Phillips, Pfaus, & Blaha, 1991; Pleim et al., 1990), suggest that anticipatory and consummatory aspects of sexual behavior may belong to a class of naturally occurring events with reward values that are mediated by increased DA release in the nucleus accumbens.

There may be other consequences of increased DA release during copulation. Repeated administration of amphetamine leads to a form of behavioral sensitization that is characterized by an enhancement of certain amphetamine-induced responses (Rebec & Bashore, 1984; Robinson, 1984; Robinson & Becker, 1986). Robinson, Jurson, Bennett, and Bentgen (1988) have also demonstrated that repeated amphetamine administration sensitizes DA release in the nucleus accumbens. In that study, rats were implanted with microdialysis probes that were aimed at the nucleus accumbens after a 6-week period of daily amphetamine or saline administration. Although basal concentrations of DA and behavioral stereotypy were nearly identical in the two groups, the amphetamine-pretreated rats responded to a challenge dose of amphetamine with a significantly greater increase in DA release. These results raise the possibility that the increased DA transmission in the nucleus accumbens during copulation may sensitize certain behavioral patterns in male rats (e.g., anticipatory sexual behaviors or the initiation of copulatory mounts) that are elicited either by the primary sensory cues of a sexually receptive female rat or by second-order stimuli associated with those primary cues.

Increased DA transmission in the dorsal striatum during copulation may also act to control certain motor aspects of copulation. Although bilateral infusions of haloperidol to the

striatum have little effect on copulation (Pfaus & Phillips, 1991), 6-OHDA lesions of this region increase the mount and intromission latencies, reduce the number of intromissions, and reduce the total number of ejaculations (Brackett et al., 1986). However, Robbins et al. (1989) reported that 6-OHDA lesions of the striatum disrupted the initiation of copulation only if the males were paired with females that displayed proceptive behaviors during the test. If those males were paired with females treated with α -flupenthixol (to eliminate proceptive pacing and solicitation), then their mount and intromission latencies did not differ from those of sham-lesioned controls. Thus, striatal DA may contribute to the males' ability to track and act upon a moving target.

Finally, it should be noted that DA transmission in other brain areas may contribute to male sexual behavior. In particular, pharmacological evidence suggests that DA transmission in the MPOA plays an important role in anticipatory and consummatory aspects of male sexual behavior (Bitran, Hull, Holmes, & Lookingland, 1988; Hull et al., 1986; Pehek et al., 1988; Pfaus & Phillips, 1991; Warner et al., 1991). The methods used in the present study should be useful for the study of DA transmission in other brain areas during sexual behavior.

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