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Dihydrotestosterone-Induced Inhibition of Lordosis in Estrogen-Primed Ovariectomized Rats Following 6-Hydroxydopamine or Electrolytic Septal Lesions

F. S. MENNITI, M. S. ERSKINE, S. A. TOBET AND M. J. BAUM

Department of Nutrition and Food Science
Massachusetts Institute of Technology, Cambridge, MA 02139

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MENNITI, F. S., M. S. ERSKINE, S. A. TOBET AND M. J. BAUM. *Dihydrotestosterone-induced inhibition of lordosis in estrogen-primed ovariectomized rats following 6-hydroxydopamine or electrolytic septal lesions.* PHARMAC. BIOCHEM. BEHAV. **16**(2) 211–216, 1982.—The dose-dependent inhibition of lordosis by 5α-dihydrotestosterone propionate in ovariectomized female rats treated concurrently with estradiol benzoate was attenuated neither by intracranial 6-hydroxydopamine injections which reduced dopamine concentrations by approximately 70% in septum or 75% in both septum and n. accumbens septi nor by electrolytic destruction of the lateral or medial septal nuclei or of both septal nuclei. These results suggest that the inhibitory effect of dihydrotestosterone on estrogen-induced lordosis does not critically depend on the mesolimbic dopaminergic innervation of the forebrain or on the septal nuclei.

Mesolimbic dopamine pathway Septal nuclei Lordosis 6-Hydroxydopamine Electrolytic lesion Estrogen 5α-Dihydrotestosterone

THE chronic administration of 5α-dihydrotestosterone (DHT) inhibits estrogen (E_2)-induced sexual receptivity in the female of a number of mammalian species including the rat [2], mouse [15], hamster [5], and rhesus monkey [25]. Concurrent administration of the androgen receptor blocker, flutamide, prevented this effect of chronic DHT treatment in rats, suggesting that binding to cytoplasmic androgen receptors is a prerequisite for the inhibition of lordosis [7]. However, attempts to identify the neuronal mechanism which underlies this action of DHT on lordosis have proved inconclusive. For example, a recent study from this laboratory failed to demonstrate a role for serotonergic neurons in mediating the effect of DHT [18]. In the present experiments the possibility was explored that either mesolimbic dopamine (DA) neurons which project to the septum or n. accumbens septi, or neurons with perikarya in the septum may mediate the inhibitory effect of DHT on lordosis in the female rat.

The septal nuclei contribute to the regulation of feminine sexual receptivity. Electrical stimulation of the lateral septal nucleus inhibited lordosis in the female hamster [28]. In the rat, electrolytic- [10, 16, 20], aspiration- [13], or kainic acid-induced [10] damage of the septum facilitated lordotic responsiveness. In addition, knife cuts which separated the septum and hypothalamus also facilitated the display of lordosis [26,27]. Autoradiographic studies have demonstrated ^{3}H-DHT binding sites in the lateral septal nuclei as well as in the n. accumbens septi [23]. In another study conducted in this laboratory unilateral implantation of crystalline DHT propionate (DHTP) into the lateral septal n., but not into the preoptic area, ventromedial hypothalamus or caudate-putamen, caused partial inhibition of E_2-induced lordosis in ovariectomized female rats (Tobet and Baum, in preparation). These findings raised the possibility that the inhibitory effect of DHT on lordosis is partially mediated by a septal action of the steroid. Previous work has shown that systemic administration of DHT increases the concentration of DA and DA metabolites in septum and n. accumbens septi, but not in the caudate-putamen, suggesting that DHT selectively facilitates DA synaptic activity in terminal regions of mesolimbic DA neurons [1]. Pharmacological studies have shown that manipulations which increase DA synaptic activity, such as the administration of apomorphine [6] or L-dopa [19], inhibit lordosis, whereas manipulations which decrease DA synaptic activity, such as intraventricular administration of 6-hydroxydopamine (6-OHDA) [3] or systemic administration of DA receptor blockers or synthesis inhibitors [8,9] facilitate the behavior. Thus, it seemed

possible that one way in which DHT inhibits lordosis is by facilitating DA synaptic activity in the septum or n. accumbens septi. To test this hypothesis DA nerve terminals in these brain regions were selectively destroyed by intracranial injection of 6-OHDA in an effort to prevent DHT-induced inhibition of lordosis. After this manipulation failed to attenuate the inhibitory effect of DHT on lordosis, a second study was conducted to see whether electrolytic destruction of different portions of the septum could influence lordotic responsiveness to DHT.

METHOD

Animals

One-hundred twenty-two female Long-Evans rats (Charles River Breeding Laboratories, Wilmington, MA) were housed in a temperature controlled room in hanging wire cages with Charles River rat chow (Country Foods, Syracuse, NY) and water supplied ad lib. Lighting in the colony room was on from 0:00 to 12:00 hr. Animals weighed approximately 250 g at the start of experimentation. Ovariectomy was performed under light ether anesthesia via bilateral flank incisions. Stereotaxic surgery was performed under acepromazine (2 mg/animal; Ayerst Laboratories, New York, NY) and ketaset (40 mg/kg; Bristol Laboratories, Syracuse, NY) anesthesia utilizing a Kopf stereotaxic instrument.

The stimulus rats used to test females' sexual receptivity were proven copulators of the Long-Evans strain.

Behavioral Testing

Tests of feminine sexual behavior were carried out several hours after daily hormone administration between 15:00 and 18:00 hr in a room illuminated dimly with a 100 Watt yellow bulb. Testing arenas were 10 gal glass aquaria (30×26×50 cm) containing wood chips. Tests began when the female was placed into a test cage with a single stimulus male and continued until 15 mounts (with pelvic thrusting) had occurred. The intensity of each lordotic response by the female to each mount was rated using the scale of Hardy and DeBold [11]: 0=no concave curvature of the back, 1=slight arching of the back, 2=moderate arching of the back along with head elevation, 3=profound arching of the back together with marked head elevation. A mean lordosis rating was computed for each animal from the 15 scores from each test.

Procedure

Experiment 1. The procedure described below was conducted in two replications; data were combined unless otherwise noted. One to two weeks after ovariectomy, three groups of female rats received intracranial injections of 6-OHDA or vehicle only into the septum or the n. accumbens septi. Four and one hr prior to 6-OHDA injection animals were pretreated with desmethylimipramine (25 mg/kg; USV Chemicals, Tuckahoe, NY; IP in saline) to minimize damage to noradrenergic neurons [22]. 6-OHDA (Sigma, St. Louis, MO) was dissolved in ice cold 0.9% saline containing 0.1% ascorbic acid and was injected bilaterally with a stereotaxically guided 10 μl syringe fitted with a 30 g cannula. Eleven animals received injections of 8 μg 6-OHDA in 2 μl into the n. accumbens septi (+3.4 AP, ±1.7 L, −7.2 DA [21]); 26 animals received injections of 4 μl into the septum (+2.4 AP, ±0.5L, −4.5 DV) and 17 animals received 2 or 1 μl vehicle injections into the n. accumbens septi or septum, respectively. The injection rate was 0.5 μl/min.

Approximately two weeks after stereotaxic surgery, animals began to receive daily SC injection of 17β-estradiol benzoate (EB) (1 μg/100 g in 0.1 ml sesame oil) and were tested for sexual receptivity every 2–4 days, for a total of 4 or 5 tests. The mean lordosis ratings for each animal on the final two tests were averaged and served as a baseline of behavioral responsiveness. One day following the last of these tests animals began to receive daily SC injections of EB (1 μg/100 g) combined with 5α-dihydrotestosterone propionate (DHTP) in doses of first 40 μg/100 g and then 80 μg/100 g (EB+DHTP40, EB+DHTP80). All rats were tested for sexual receptivity on the eight day of each treatment. In replication no. 2 animals were tested following an additional eight daily SC injections of EB in combination with 160 μg DHTP/100 g and again on the following day 3 hr after the administration of α-methyl-p-tyrosine, 100 mg/kg (αMT; Sigma; injected IP in saline). The tyrosine hydroxylase inhibitor, αMT, was given to reduce the synthesis of DA in those septal DA terminals which survived the earlier intracerebral injection of 6-OHDA. In this was it was possible to assess the behavioral effects of DHTP in rats in which the activity of septal DA synapses was maximally suppressed.

After behavioral tests were completed the concentrations of DA in septum, n. accumbens septi, and rostral caudate-putamen were measured in each animal utilizing high pressure liquid chromatography with electrochemical detection as described in detail previously [17]. DA concentrations in each brain region are expressed as μg DA/g tissue wet wt. (replication no. 1) or ng DA/mg protein (replication no. 2). Protein determinations were conducted using the method of Lowry *et al.* [14]. Behavioral data from 22 animals were omitted from analyses either because no reduction in DA concentrations, relative to controls, was found or because the animals had died during the experiment.

Experiment 2. One to two weeks after ovariectomy, groups of female rats received bilateral electrolytic lesions of the lateral septal n. (dorsal group), the lateral septum including its most rostral aspect (rostro-dorsal group), the medial septal n. (ventral group) or both the lateral and medial septal nuclei (complete group) or sham lesions (sham group). The electrode was an epoxylite-insulated stainless steel insect pin (size 00) with an uninsulated tip. Lesions were made by passing a 2 mA anodal current through the stereotaxically-positioned electrode to a rectal cathode. The paramenters of electrode tip placement and dimensions and current duration are given for each group in Table 1.

Beginning approximately four weeks after stereotaxic surgery, all animals received 12 daily SC injections of 1 μg EB/100 g and were tested for sexual receptivity on days 3, 6, 9, and 12 of treatment. On day 13, animals were tested again 4–6 hr after an SC injection of 500 μg progesterone (P1; in 0.1 ml sesame oil). On the day following this test animals began to receive 1 μg EB/100 g in combination with 40 μg and then 80 μg DHTP/100 g and were tested on the eighth day of each treatment. On the day following this last test, animals were tested a final time 4–6 hr after 500 μg progesterone (P2).

After behavioral tests were completed animals were anesthetized with an overdose of sodium pentobarbital and perfused intracardially with 0.9% saline followed by 10% Formalin in 0.9% saline (formal-saline). Brains were removed and stored in formal-saline containig 30% sucrose until 40 μm thick coronal serial sections were cut on a minotome

TABLE 1

PARAMETERS USED IN MAKING DIFFERENT SEPTAL LESIONS IN EXPERIMENT 2

Group Name	Stereotaxic Coordinates (mm)* A–P	M–L	D–V	Electrode Tip Dimensions Length (mm)	Shape	Current Duration in seconds
Dorsal Lesion	+1.4	±0.75	−4.0	0.5	pointed	20
Dorsal-Rostral Lesion	+2.4	±0.5	−4.5	0.5	pointed	20
Ventral Lesion	+1.8	±0.7	−5.5	0.5	squared	20
Complete Lesion	+1.8	±0.7	−5.0	1.0	pointed	40
Sham	†			†		0

*With reference to Bregma (Pellegrino *et al.* [21]). A–P, anterior-posterior; M–L, medial-lateral; D–V, dorsal-ventral.

†Sham group includes coordinates and tip dimensions from each lesioned group.

(Damon-IEC). Sections throughout the extent of each lesion were stained with thionin and examined using a projection microscope. Behavioral data from 24 animals in which electrolytic lesions were not bilateral and/or were not similar to those of others in that lesion group or who died during experimentation were excluded from further analyses.

RESULTS

Experiment 1

The injection of 6-OHDA into the septum or into the n. accumbens septi significantly reduced DA concentrations by approximately 70% in septum and by approximately 75% in both septum and n. accumbens septi, respectively, compared with DA concentrations in the vehicle-injected control group (Table 2). In neither group were DA concentrations in the rostral caudate-putamen significantly affected.

Destruction of DA nerve terminals in the septal region alone or in the septum and n. accumbens septi did not attenuate the ability of DHTP to inhibit EB-induced lordosis (Fig. 1). A two-way analysis of variance for repeated measures, comparing the mean lordosis ratings for each group after EB and EB+DHTP 40 and 80 treatments, showed a significant effect of hormone treatment, $F(2,58)=24.14$, $p \leq 0.001$ but no effect of group, $F(2,29)=1.7$ and no group × hormone interaction, $F(4,58)=0.484$). Administration of either dosage of DHTP concurrently with EB decreased the mean lordosis ratings to an equivalent degree in each group (Tukey test, EB vs EB+DHTP40, EB vs EB+DHTP80 collapsed across groups, $p \leq 0.05$). Although the 80 μg DHTP/100 g dosage tended to produce a greater decrement in this measure than did 40 μg DHTP/100 g, this trend failed to reach statistical significance. However, in a separate analysis of the subgroups of the septal 6-OHDA-injected and vehicle-injected animals of replication no. 2, the 160 μg DHTP/100 g dosage did produce a significant decrement in mean lordosis ratings when compared to the level of this behavior at 40 μg DHTP/100 g (collapsed across groups, $p \leq 0.05$). In addition, the administration of αMT produced a slight, though non-significant, increment in mean lordosis ratings in both groups when compared to the previous EB+DHTP160 test scores. A Dunnett's test showed that there was no significant difference in lordosis ratings between the 6-OHDA-n. accumbens septi and the vehicle-injected groups during the initial tests when only EB was given.

Experiment 2

Schematic representations of typical electrolytic lesions in each group are presented in Fig. 2. The complete septal lesion (Fig. 2a) destroyed nearly all the medial (MS) and lateral septal (LS) nuclei. This lesion extended from the rostral tip of the septum to the hippocampal commissure; in two cases the hippocampal commissure was also damaged. In seven of nine cases this lesion included damage to the corpus callosum and, in one case, to the anterior commissure. The dorsal septal lesion (Fig. 2b) typically destroyed the large caudal portion of the LS beginning rostrally at approximately A.P. plane +2.2 [21] and extended caudally to the hippocampal commissure. The corpus callosum was damaged in all cases whereas the MS and rostral LS were spared. The rostral-dorsal septal lesion (Fig. 2c) typically damaged the LS from the rostral tip (A.P. plane +3.3) to the caudal border at the hippocampal commissure. Damage to the corpus callosum was observed in four of seven cases whereas no damage was observed in the MS. Finally, the ventral septal lesion (Fig. 2d) destroyed a large portion of the MS and the ventral aspect of the LS, with damage extending from the posterior border of the medial paraolfactory area to the hippocampal commissure. In some cases the rostral-dorsal thalamic nuclei were also damaged. In five of six cases the anterior commissure was also destroyed.

None of the electrolytic septal lesions reliably affected the ability of DHTP to inhibit EB-induced lordosis (Fig. 3). A two-way analysis of variance for repeated measures, comparing mean lordosis ratings for groups at each hormone treatment, showed a significant effect of hormone treatment,

TABLE 2

EFFECT OF BILATERAL INJECTION OF 6-HYDROXYDOPAMINE (6-OHDA) INTO SEPTUM OR N. ACCUMBENS SPETI ON DA CONCENTRATIONS IN SEPTUM, N. ACCUMBENS SEPTI AND ROSTRAL CAUDATE-PUTAMEN

Intracerebral Treatment	N	Brain Region: septum	n.accumbens septi	caudate-putamen
		μg DA/g tissue wet wt.		
Vehicle	5	2.21 ± 0.39	7.45 ± 0.68	6.45 ± 1.03
6-OHDA/ Septum	6	0.72 ± 0.20*	7.45 ± 1.02	4.85 ± 0.66
6-OHDA/ n. accumbens septi	8	0.49 ± 0.15*	2.03 ± 0.41*	4.73 ± 0.84
		ng DA/mg protein		
Vehicle	8	28.03 ± 5.29	89.76 ± 11.32	78.47 ± 5.49
6-OHDA/ Septum	5	7.60 ± 1.62†	87.35 ± 16.51	73.69 ± 6.60

*Significantly different from vehicle-injected group, one-way analysis of variance followed by Tukey test, $p<0.05$.

†Significantly different from vehicle-injected group, t-test, $p<0.05$.

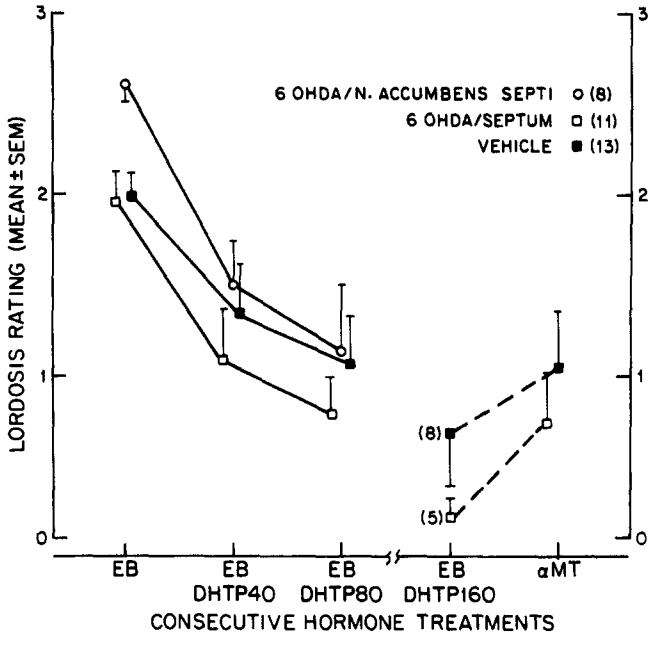

FIG. 1. Effect of intracranial injection of 6-hydroxydopamine (6-OHDA) or vehicle into the n. accumbens septi or septum on mean lordosis ratings of groups of ovariectomized female rats given consecutive hormone treatments and α-methyl-p-tyrosine (αMT). Data in the right-hand panel are from animals of replication no. 2 only (see text). The number of rats in each group is given in parentheses.

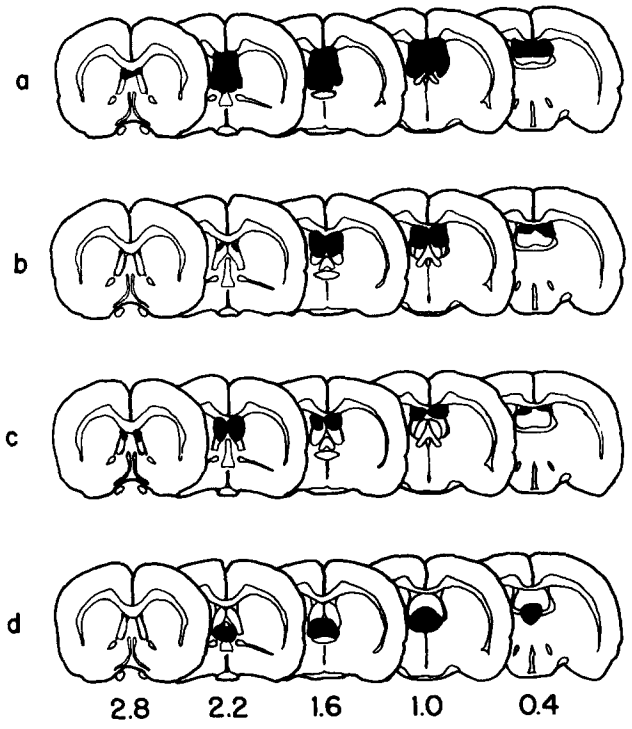

FIG. 2. Schematic representation of the electrolytic lesion (shaded area) in a representative case from each of the 4 lesioned groups of rats in Experiment 2. (a) Complete lesion, (b) Dorsal lesion, (c) Rostro-dorsal lesion, (d) Ventral lesion. Diagrams of coronal sections and A.P. coordinates were adapted from Pellegrino *et al.* [21].

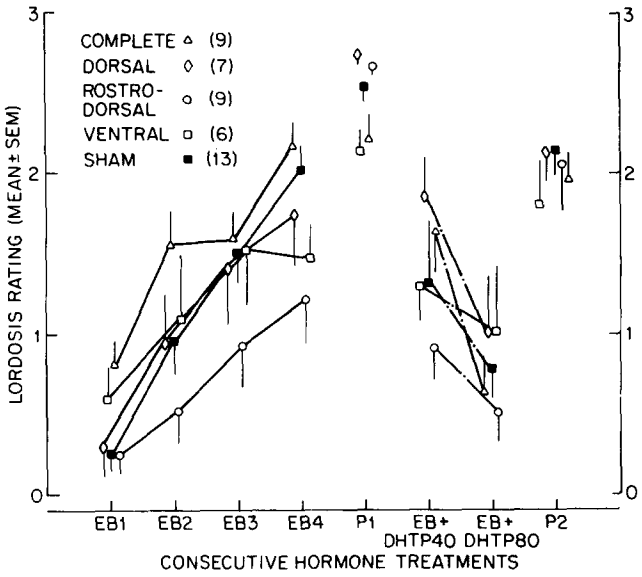

FIG. 3. Effect of electrolytic or sham lesions of different parts of the septum on mean lordosis ratings of groups of ovariectomized female rats given consecutive hormone treatments. See text for explanation of the groups. The number of rats in each group is given in parentheses.

$F(7,273)=55.72$, $p\leq0.001$, but no overall effect of group, $F(4,39)=1.35$). The hormone treatment × group interaction just reached statistical significance, $F(28,273)=1.52$, $p=0.05$. To evaluate the interaction, individual lesioned groups were compared to the sham-operated group on different tests using Dunnett's test; however, no lesioned group was found to differ significantly from the sham-operated group on any test. Because of this result, and because there was no overall significant groups effect, mean lordosis ratings were collapsed across groups and the main effect of hormone treatment was evaluated. Successive administration of EB caused a significant, incremental rise in mean lordosis rating on each of the tests prior to which only EB was given (Tukey tests, $p\leq0.05$ in each case), and the administration of P induced a further increment in this measure (EB4 vs P1, $p\leq0.05$). Administration of DHTP caused a significant, dose-dependent decrement in mean lordosis ratings (EB4 vs EB+DHTP40, EB+DHTP40 vs EB+DHTP80, $p\leq0.05$). Finally, the administration of P after combined EB+DHTP treatment increased mean lordosis ratings (EB+DHTP80 vs P2, $p\leq0.05$) but not to as great an extent as after its initial administration (P1 vs P2, $p\leq0.05$).

As mentioned above, large electrolytic or aspiration lesions of the septum were previously found to facilitate the display of lordosis [10, 13, 16, 20]. Typically in those studies, lesioned or sham-lesioned ovariectomized female rats were administered 3 daily injections of 2 μg EB/animal and then were tested for sexual receptivity on the fourth day. In the present experiment the complete septal lesioned group and the sham-operated group received a similar sequence of EB injections prior to the first behavioral test. Since a lesion-induced increase in lordosis was expected, the lordosis ratings of these two groups were compared for the EB-1 test using a 1-tailed t-test based on the within groups error term from the overall ANOVA. The mean lordosis ratings of the complete lesioned group were significantly higher ($p\leq0.05$) than those of the sham-operated group on this first behavioral test.

DISCUSSION

The results in Experiment 1 provide no evidence that DHTP inhibits feminine sexual receptivity by augmenting activity at mesolimbic DA synapses. The destruction of mesolimbic DA terminals should have attenuated the ability of DHT to inhibit lordosis had these neurons contributed to this behavioral effect. It is possible that DA neurons remaining after neurotoxic damage to these mesolimbic pathways were sufficient to mediate the effects of DHTP. Much evidence suggests that the functional level of DA synaptic activity may be maintained following partial lesions of dopaminergic pathways by mechanisms which include increased firing and release of DA by surviving neurons, DA terminal sprouting, and post-synaptic DA receptor supersensitivity [24]. However, the lack of a differential effect of αMT on the behavior of animals which received septal injections of 6-OHDA argues against this possibility. Administration of low doses of αMT to animals with partial lesions of the nigrostriatal [4,29] or mesolimbic (F. S. Menniti, personal observation) DA pathways has been found transiently to mimic the effects of more complete destruction of these pathways on a number of behaviors, including feminine sexual behavior [12]. Thus, even severe inhibition of synaptic activity in DA neurons innervating the septum did not attenuate the dose-dependent inhibitory effect of DHTP on lordosis.

The results of Experiment 2 also provide no evidence that neurons whose perikarya lie in the septum or whose axons pass through the septum contribute to the inhibitory effect of DHTP on lordosis. As noted above, electrolytic lesions of the septum previously have been found to augment lordotic responsiveness to estradiol in the female rat [10, 16, 20]. A similar effect was observed in animals with combined lateral and medial septal nuclei destruction during their first behavioral test, although its magnitude was not as great as that reported by others. Differences in the hormonal regimens used or in testing procedures may account for this discrepancy and for the attenuation of the initial facilitatory effect with repeated testing. The possibility remains that septal lesions which more effectively enhanced estrogen-induced lordosis would also have more effectively attenuated the inhibitory action of DHT on this behavior.

As stated in the Introduction, DHTP implanted directly into the lateral septum caused a modest, though statistically significant decrement in the lordotic responsiveness of ovariectomized, E_2-primed female rats (Tobet and Baum, in preparation). The results of the present study demonstrate that following destruction of septal neurons or their dopaminergic innervation the ability of DHT to inhibit lordosis is not diminished. Thus, while septal neurons may be capable of mediating the effect of DHT on lordosis, they are not obligatory for this behavioral effect.

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