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Noradrenergic Innervation to the VMN or MPN Is Not Necessary for Lordosis

B. L. DAVIS,* J. MANZANARES, K. J. LOOKINGLAND, K. E. MOORE AND L. G. CLEMENS*[1]

*Neuroscience Program, *Department of Zoology and Department of Pharmacology/Toxicology*
Michigan State University, East Lansing, MI 48824

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DAVIS, B. L., J. MANZANARES, K. J. LOOKINGLAND, K. E. MOORE AND L. G. CLEMENS. *Noradrenergic innervation to the VMN or MPN is not necessary for lordosis.* PHARMACOL BIOCHEM BEHAV **39**(3) 737–742, 1991.—The purpose of the present study was to determine the importance of noradrenergic neurons terminating in the ventromedial nucleus (VMN) and medial preoptic nucleus (MPN) of the hypothalamus for lordosis behavior in ovariectomized, estrogen/progesterone-treated female rats. Seven days following bilateral injections of the noradrenergic neurotoxin 5-amino-2,4-dihydroxy-α-methylphenylethylamine (5-ADMP) into the ventral noradrenergic bundle (VNAB), norepinephrine (NE) concentrations (ng/mg protein) were reduced to 30–35% of control in the VMN and MPN. 5-ADMP-induced lesions of the VNAB also reduced lordosis quotients in these animals, and this effect was reversed by intracerebral ventricular administration of the α_1-adrenergic receptor agonist phenylephrine. These results indicate that neurotoxin-induced disruption of noradrenergic neurons in the VNAB is associated with a deficit in sexual receptivity in female rats. To determine if the reduction in sexual receptivity following 5-ADMP-induced lesions of the VNAB resulted from loss of noradrenergic neuronal projections specifically to the VMN or MPN, lordosis quotients were determined in ovariectomized, estrogen/progesterone-treated rats in which noradrenergic terminals in these hypothalamic nuclei were selectively lesioned. Injection of 5-ADMP directly into either the VMN or MPN reduced NE concentrations to 17% of control in these hypothalamic nuclei, but failed to alter lordosis. Furthermore, injection of phenylephrine into either the VMN or MPN of VNAB-lesioned rats failed to reinstate lordosis to the levels comparable to sham-lesioned controls. Taken together, these results indicate that noradrenergic neurons terminating in either the VMN or MPN are not essential for gonadal steroid induction of sexual receptivity in ovariectomized female rats.

Norepinephrine Lordosis Sex behavior Ventromedial nucleus Medial preoptic nucleus 5-ADMP
Phenylephrine Estrogen/progesterone Female rats

ESTROGEN and progesterone are required for full expression of sexually receptive behaviors in female rats (37). It has been suggested that these hormones exert facilitatory effects on female sexual receptivity by an action mediated by neurons in the ventromedial nucleus (VMN) and medial preoptic nucleus (MPN) of the hypothalamus [for review, see (24,31)], but the identity of the neurotransmitters mediating these effects remains controversial. Several lines of evidence suggest that hypothalamic noradrenergic neurons mediate the stimulatory effects of gonadal steroids on sexual receptivity in female rats: 1) microinjection of norepinephrine (NE) or adrenergic receptor agonists directly into the VMN (10,11) or MPN (11) induced lordosis in ovariectomized, estrogen-treated female rats; 2) neurotoxin-induced lesions of hypothalamic noradrenergic neurons impaired lordosis in ovariectomized, estrogen/progesterone-treated female rats (12); and 3) NE release in the VMN is elevated in ovariectomized, estrogen/progesterone-treated rats displaying high levels of lordosis behavior (36).

Noradrenergic innervation of the hypothalamus originates from perikara located in subcoeruleus nuclei of the pons medulla [i.e., A_1, A_2, A_5, A_7; (4,17)]. Axons of these neurons ascend to the diencephalon via the ventral noradrenergic bundle (VNAB) and terminate in virtually all regions of the hypothalamus including the VMN and MPN (13, 25, 26). Electrolytically and neurotoxin-induced lesions of the VNAB deplete NE concentration in the hypothalamus and disrupt lordosis in ovariectomized estrogen/progesterone-treated female rats (12), but it is not known if loss of NE in the VMN or MPN following these lesions is responsible for the reduction in lordosis.

The purpose of the present study was to examine the effects of neurotoxin-induced lesions of noradrenergic neurons terminating in the VMN or MPN on lordosis in ovariectomized, estrogen/progesterone-treated female rats. The results reveal that neurotoxin-induced depletion of NE in either the VMN or MPN is not accompanied by a loss of lordosis, indicating that noradrenergic neurons terminating in these hypothalamic nuclei are not essential for the induction of sexual receptivity in ovariectomized female rats by gonadal steroids.

METHOD

Animals

Female Sherman rats weighing 200–250 g were obtained from Camm Research Co. (Wayne, NJ), maintained in a tem-

[1]Requests for reprints should be addressed to Lynwood G. Clemens, 110 Biological Research Center, Department of Zoology, Michigan State University, East Lansing, MI 48824.

perature (21 ± 1°C)- and light (lights on between 2100 and 1100 h)-controlled environment, and provided food (Wayne Lablox) and tap water ad lib. All rats were bilaterally ovariectomized under pentobarbital anesthesia (30 mg/kg; IP) and, one week later, treated with estradiol benzoate and progesterone (see below) and pretested for sexual receptivity (lordosis; see below). Only female rats attaining a lordosis quotient of 70 or greater in the behavioral pretest were used in the present studies.

Drugs

Estradiol benzoate (Sigma Chemical Co., St. Louis, MO) and progesterone (Sigma) were dissolved in sesame oil. Fluoxetine hydrochloride (Eli Lilly and Co., Indianapolis, IN) was dissolved in 0.9% saline. 5-Amino-2,4,dihydroxy-α-methylphenylethylamine dihydrobromide (5-ADMP; synthesized by Dr. John R. Palmer of The Upjohn Co., Kalamazoo, MI) was dissolved in 0.3% saline containing 0.1% ascorbic acid. Phenylephrine hydrochloride (Sigma) was dissolved in artificial CSF. Drugs were administered as indicated in the legends of the table and appropriate figures; doses of fluoxetine, 5-ADMP and phenylephrine were calculated as free base.

Neurochemical Lesions of the Ventral Noradrenergic Bundle

Rats were anesthetized with Equithesin (3 ml/kg; IP) and positioned in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the incisor bar set 3 mm below the horizontal plane. The needle of a 5-μl Hamilton syringe was inserted into the VNAB at coordinates A 0.0 mm, L ±1.3 mm, V −6.8 mm from dura (15), and bilateral injections of either 5-ADMP (8 μg/side) or its vehicle (0.3% saline containing 0.1% ascorbic acid; 0.3 μl/side) were made over a 1-minute period. The needle remained in the brain for an additional 10 minutes after injection to reduce the reflux of the neurotoxin back up the needle track. One hour prior to administration of 5-ADMP, rats were injected with fluoxetine (10 mg/kg; SC) to prevent uptake of neurotoxin into 5-hydroxytryptaminergic neurons. Rats were allowed to recover for 7 days following surgery before behavioral testing was performed.

Neurochemical Lesions of Hypothalamic Nuclei

Rats were anesthetized with Equithesin (3 ml/kg; IP) and positioned in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the incisor bar set 2.4 mm below the horizontal plane (15). For the VMN, the needle of a 5-μl Hamilton syringe was inserted at coordinates A 4.4 mm, L ±0.7 mm, V −8.8 mm from dura (15), and bilateral injections of either 5-ADMP (2 μg/side) or its vehicle (0.3% saline containing 0.1% ascorbic acid; 0.3 μl/side) were made over a 1-minute period. For the MPN, the needle of a 5-μl Hamilton syringe was inserted at coordinates A 6.8 mm, L ±0.7 mm, V −7.7 mm from dura (15), and two bilateral injections of either 5-ADMP (2 μg/site/side) or its vehicle (0.3% saline containing 0.1% ascorbic acid; 0.3 μl/site/side) were made over a 2-minute period by injecting for the first minute at the most ventral position (7.7 mm below dura) and then raising the needle to inject more dorsally (7.0 mm below dura) for the final minute. The needle remained in the brain for an additional 10 minutes after the final injection to reduce the reflux of the neurotoxin back up the needle track. One hour prior to injection of 5-ADMP, rats were injected with fluoxetine (10 mg/kg; SC) to prevent uptake of neurotoxin into 5-hydroxytryptaminergic neurons. Rats were allowed to recover for 7 days following surgery before behavioral testing was performed.

Lateral Ventricular Cannulation

Animals receiving intracerebroventricular (ICV) injections of phenylephrine or its vehicle were implanted with a stainless steel guide cannula into a lateral cerebral ventricle 7 days prior to the experiment. Rats were anesthetized with Equithesin (3 ml/kg; IP) and positioned in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the incisor bar set 2.4 mm below the horizontal plane (15). A 23-gauge stainless steel guide cannula was implanted such that the tip was 1.4 mm lateral to bregma and 3.2 mm below dura, and anchored to the skull with stainless steel screws and dental cement. On the day of the experiment, phenylephrine or its artificial CSF vehicle were injected in a volume of 5 μl with a 10-μl Hamilton microsyringe connected to a 30-gauge stainless steel injector which protruded 1 mm beyond the tip of the cannula guide and into the lateral ventricle.

Intracerebral Injections into Hypothalamic Nuclei

Animals receiving intracerebral (IC) injections of phenylephrine or its vehicle into the VMN or MPN were implanted with stainless steel guide cannula 7 days prior to the experiment. Rats were anesthetized with Equithesin (3 ml/kg; IP) and positioned in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the incisor bar set 2.4 mm below the horizontal plane (15). For the VMN, bilateral 23-gauge stainless steel cannulae were implanted ±0.7 mm from midline, 2.6 mm posterior to bregma and 8.8 mm below dura. For the MPN, bilateral 23-gauge stainless steel cannulae were implanted ±0.7 mm from midline, 2.4 mm posterior to bregma and 7.4 mm below dura. Phenylephrine (1 μg/side) or its artificial CSF vehicle (0.3 μl/side) were injected bilaterally into the VMN or MPN with a 10-μl Hamilton microsyringe connected to a 30-gauge stainless steel injector 30 minutes prior to behavioral testing.

Behavioral Testing

All females were injected with estradiol benzoate (0.5 μg/0.1 ml/rat; IM) 72, 48, and 24 hours before behavioral testing, and with progesterone (500 μg/0.1 ml/rat; IM) 5 hours before behavioral testing. In all studies, female rats were tested for sexual receptivity by placing them with a sexually experienced male rat which had been adapted to the testing arena (45 × 50 × 58-cm Plexiglas cage). Lordosis behavior was measured as a lordosis quotient (LQ), which is defined as the frequency of lordosis postures to ten mounts divided by ten and multiplied by 100 (LQ = number of lordosis responses/10 × 100). A mount was counted when the male palpated the female's flank with his forepaws and exhibited pelvic thrusting. Each test session was limited to 10 mounts.

Tissue Dissection and Neurochemical Analyses

Within one hour following behavioral testing, animals were decapitated, and brains were removed from the skull and frozen on aluminum foil placed directly over dry ice. Frontal brain sections (600 μm) beginning approximately at 9220 μm (15) were prepared in a cryostat (−9°C), and the VMN and MPN were dissected from these sections according to a modification (18) of the method of Palkovits (27). Tissue samples were placed in 60 μl of 0.1 M phosphate-citrate buffer (pH 2.5) containing 15%

TABLE 1

EFFECT OF BILATERAL INJECTIONS OF 5-ADMP INTO THE VENTRAL NORADRENERGIC BUNDLE (VNAB) ON AMINE CONCENTRATIONS IN THE VENTROMEDIAL NUCLEUS (VMN) AND MEDIAL PREOPTIC NUCLEUS (MPN) OF OVARIECTOMIZED, ESTROGEN/PROGESTERONE-TREATED FEMALE RATS

		Amine Concentration (ng/mg Protein)		
		NE	DA	5HT
VMN	Vehicle	14.5 ± 1.1*	1.2 ± 0.1	6.1 ± 0.3
	5-ADMP†	5.1 ± 0.7‡	1.1 ± 0.1	6.4 ± 0.4
MPN	Vehicle	24.3 ± 1.5	6.7 ± 2.7	10.4 ± 0.5
	5-ADMP	7.2 ± 0.7‡	5.5 ± 2.2	10.3 ± 0.5

*Values represent the means ± 1 S.E.M. of 9–11 determinations.

†Rats were injected with 5-ADMP or its vehicle into the VNAB and killed by decapitation 7 days later.

‡Values for 5-ADMP-treated rats that are significantly different from vehicle-treated controls ($p<0.05$).

methanol and stored at −20°C until assayed.

On the day of the assay, tissue samples were thawed, sonicated for 3 s (Sonicator Cell Disruptor, Heat Systems-Ultrasonic, Plainview, NY), and centrifuged for 30 s in a Beckman 152 Microfuge. NE, dopamine (DA) and 5-hydroxytryptamine (5HT) concentrations in supernatants were measured by high-performance liquid chromatography with electrochemical detection as described previously (3). Tissue pellets were dissolved in 1.0 N NaOH and assayed for protein (19).

Statistics

Statistical analyses of monoamine concentrations were performed using Student's *t*-test to compare differences between two groups, and one-way analysis of variance followed by the least significant difference test for the comparison of multiple groups (34). Lordosis quotients were analyzed with Kruskal-Wallis one-way analysis of variance by ranks followed by the Mann-Whitney U-test for comparisons between two groups (33). Differences were considered significant if the probability of error was less than 5%.

RESULTS

As shown in Table 1, NE concentrations were significantly reduced to 35% of control in the VMN and to 30% of control in the MPN 7 days following bilateral injections of 5-ADMP into the VNAB. In contrast, 5-ADMP had no effect on the concentrations of DA or 5HT in these brain regions. 5-ADMP injections into the VNAB significantly reduced lordosis quotients in ovariectomized, estrogen/progesterone-treated female rats (Fig. 1), and this effect was reversed by ICV administration of the α_1-adrenergic receptor agonist phenylephrine (Fig. 2). Taken together, these results suggest that neurotoxin-induced disruption of noradrenergic neurons is associated with a deficit in sexual receptivity in female rats.

To determine if the reduction in sexual receptivity following 5-ADMP-induced lesions of the VNAB resulted from loss of noradrenergic neuronal projections to the VMN or MPN, lordosis quotients were determined in ovariectomized, estrogen/progesterone-treated rats in which noradrenergic terminals in these hypothalamic nuclei were selectively lesioned. As shown in Fig. 3, injection of 5-ADMP directly into the VMN reduced NE concentrations in the VMN to 17% of control, but failed to alter lordosis quotients as compared with vehicle-treated controls. Similarly, direct injection of 5-ADMP into the MPN reduced NE concentrations in the MPN to 17% of control, but failed to alter lordosis quotients as compared with vehicle-treated controls (Fig. 4). In addition, injection of phenylephrine into either the VMN or MPN of VNAB-lesioned rats failed to reinstate lordosis quotients to the levels determined in the sham-lesioned controls (Fig. 5). Taken together, these results indicate that noradrenergic neurons terminating in either the VMN or MPN are not necessary for sexual receptivity in ovariectomized, estrogen/progesterone-treated female rats.

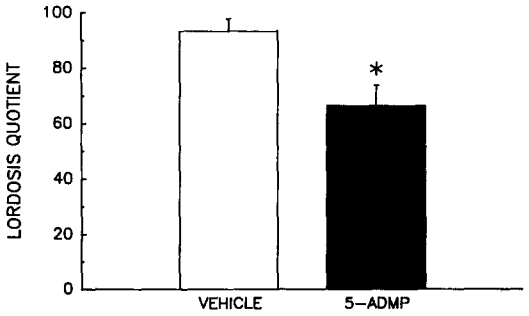

FIG. 1. Effects of bilateral injections of 5-ADMP into the ventral noradrenergic bundle (VNAB) on lordosis in ovariectomized, estrogen/progesterone-treated female rats. Rats were injected with either 5-ADMP (8 μg/side; IC) or its vehicle (0.3% saline containing 0.1% ascorbic acid; 0.3 μl/side) into the VNAB 7 days prior to behavioral testing. Columns represent the means and vertical lines 1 S.E.M. of 9–11 determinations of sexual receptivity (lordosis quotient) in vehicle (open column)- or 5-ADMP-treated (solid column) rats. *Values for 5-ADMP-treated rats that are significantly different from vehicle-treated controls ($p<0.05$).

DISCUSSION

Sexually receptive behaviors in female rats require estrogen and progesterone for their full expression (37). Although multi-

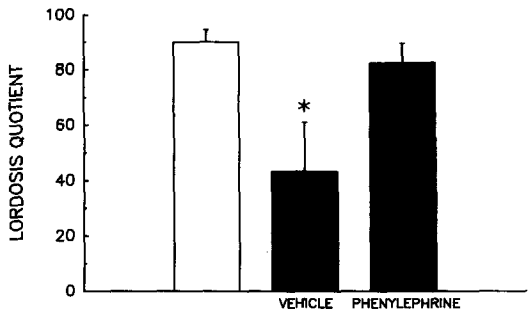

FIG. 2. Effect of phenylephrine on lordosis in VNAB-lesioned ovariectomized, estrogen/progesterone-treated female rats. VNAB-lesioned rats were injected with either phenylephrine (1 μg/rat; ICV) or its vehicle (artificial CSF; 5 μl/rat; ICV) thirty minutes before behavioral testing. Columns represent the means and vertical lines 1 S.E.M. of 6–8 determinations of sexual receptivity (lordosis quotient) in sham (open column)- or VNAB-lesioned (solid columns) rats. *Values for VNAB-lesioned rats that are significantly different from sham-lesioned controls ($p<0.05$).

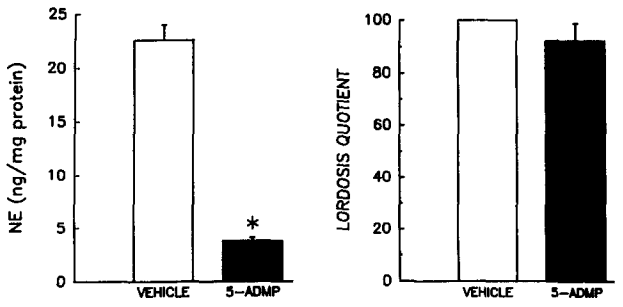

FIG. 3. Effects of bilateral injections of 5-ADMP into the ventromedial nucleus (VMN) on NE concentrations in the VMN and lordosis in ovariectomized, estrogen/progesterone-treated female rats. Rats were injected with either 5-ADMP (2 μg/side; IC) or its vehicle (0.3% saline containing 0.1% ascorbic acid; 0.3 μl/side) into the VMN 7 days prior to behavioral testing. Columns represent the means and vertical lines 1 S.E.M. of 9 determinations of NE concentrations (ng/mg protein) in the VMN (left panel) or sexual receptivity (lordosis quotient; right panel) in vehicle (open column)- or 5-ADMP-treated (solid column) rats. *Values for 5-ADMP-treated rats that are significantly different from vehicle-treated controls ($p<0.05$).

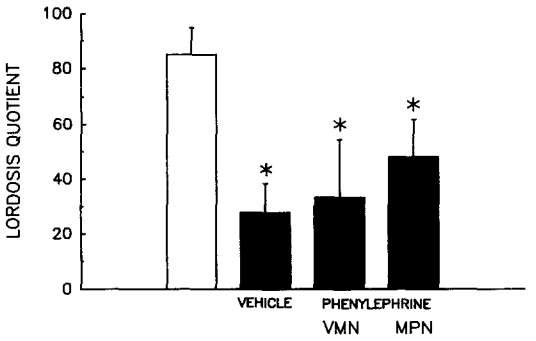

FIG. 5. Effects of administration of phenylephrine into the ventromedial nucleus (VMN) or medial preoptic nucleus (MPN) on lordosis in VNAB-lesioned ovariectomized, estrogen/progesterone-treated female rats. VNAB-lesioned rats were injected with either phenylephrine (1 μg/side) or its vehicle (artificial CSF; 0.3 μl/side) into either the VMN or MPN 30 minutes before behavioral testing. Columns represent the means and vertical lines 1 S.E.M. of 6–14 determinations of sexual receptivity (lordosis quotient) in sham (open column)- or VNAB-lesioned (solid columns) rats. *Values for VNAB-lesioned rats that are significantly different from sham-lesioned controls ($p<0.05$).

ple sites of action probably exist for estrogen and progesterone, evidence suggests that these hormones exert facilitatory effects on female sexual receptivity by an action mediated by neurons located in the VMN and MPN of the hypothalamus. Neurons located in these regions concentrate labeled estrogen (29,35) and progesterone (6, 20, 28), and ovariectomized female rats become receptive when given VMN implants of estrogen and systemic injections of progesterone (32). Conversely, implants of antiestrogens into the VMN block the stimulatory effects of estrogen/progesterone treatment on receptivity in ovariectomized female rats (23), and electrolytic lesions of the VMN abolish lordosis (22,30). Electrolytic lesions of the dorsal region of the MPN reduce lordosis in ovariectomized female rats given systemic injections of estrogen and progesterone (16), and in ovariectomized female rats implanted with estrogen in the VMN and injected systemically with progesterone (1). Thus, while neurons in the VMN and MPN are implicated in mediating gonadal steroid-induced sexually receptive behaviors in female rats, the identity of the neurotransmitters involved in this action are less well defined.

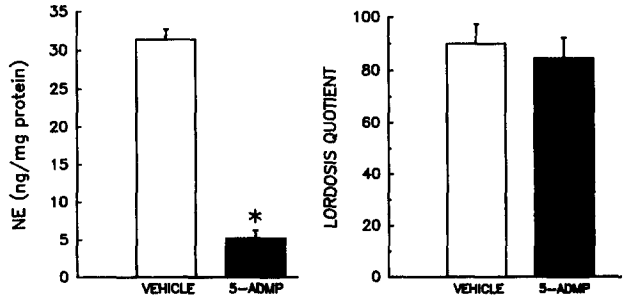

FIG. 4. Effects of bilateral injections of 5-ADMP into the medial preoptic nucleus (MPN) on NE concentrations in the MPN and lordosis in ovariectomized, estrogen/progesterone-treated female rats. Rats were injected with either 5-ADMP (4 μg/side; IC) or its vehicle (0.3% saline containing 0.1% ascorbic acid; 0.6 μl/side) into the MPN 7 days prior to behavioral testing. Columns represent the means and vertical lines 1 S.E.M. of 10–11 determinations of NE concentrations (ng/mg protein) in the MPN (left panel) or sexual receptivity (lordosis quotient; right panel) in vehicle (open column)- or 5-ADMP-treated (solid column) rats. *Values for 5-ADMP-treated rats that are significantly different from vehicle-treated controls ($p<0.05$).

In the present study, disruption of subcoeruleus noradrenergic neurons in the VNAB following IC administration of the selective noradrenergic neurotoxin 5-ADMP (14) resulted in the loss of lordosis behavior in ovariectomized, estrogen/progesterone-treated female rats. These results are consistent with previous reports of an inhibitory effect of electrolytic- and neurotoxin-induced lesion of the VNAB on lordosis behavior (12), and indicate that subcoeruleus noradrenergic neurons are important for the control of sexual receptivity.

The results of the present study indicate that the facilitative effects of NE on female sexual receptivity are mediated by α_1-adrenergic receptors, since ICV injection of the α_1-adrenergic receptor agonist phenylephrine restores lordosis in VNAB-lesioned female rats. These results are consistent with previous reports suggesting a role of adrenergic receptors in the control of lordosis (9,10), but the specific adrenergic receptor subtype mediating this effect is not clear. For example, systemic injections of either α_1- or β-adrenergic receptor antagonists inhibit lordosis in estrogen/progesterone-treated female rats (9), suggesting that both of these adrenergic receptor subtypes are involved in the facilitative action of NE on lordosis. Our results strongly support the hypothesis that α_1-adrenergic receptor stimulation is required for lordosis, although the involvement of β-adrenergic receptors cannot be ruled out by our studies.

A number of reports have implicated either the VMN or MPN as a possible site of action of NE on lordosis in female rats, but the role of noradrenergic neurons in these brain regions remains controversial. For example, on the basis of studies employing direct IC injection of NE, or adrenergic receptor agonists or antagonists directly into the VMN or MPN, NE has been reported to facilitate (7,10), inhibit (2,11) or have no effect (5) on lordosis in ovariectomized, steroid-treated female rats. Further support for a stimulatory role of noradrenergic neurons in the VMN is the observation that NE concentrations in dialysates of the VMN increase in receptive estrogen/progesterone-treated female rats (36). In the present study, however, depletion of NE in either the VMN or MPN did not reduce lordosis in ovariectomized, estrogen/progesterone-treated female rats, and injection

of the α_1-adrenergic receptor agonist phenylephrine into either of these brain regions of VNAB-lesioned females failed to restore lordosis. These results suggest that noradrenergic neurons in the VMN or MPN alone are not necessary for lordosis in ovariectomized, estrogen/progesterone-treated female rats.

Another region of the brain reported to be important for sexual receptivity in female rats is the corticomedial amygdala, and disruption of noradrenergic innervation to this brain region following VNAB lesions could account for the observed loss of lordosis in our studies (8). Indeed, the amygdala contains neurons that concentrate labeled estrogen (29,35), and electrolytic lesions in the anterior portion of the corticomedial amygdala disrupts lordosis, and electrochemical stimulation of this region facilitates lordosis in ovariectomized, steroid-treated female rats (21). Alternatively, NE may play a neuromodulatory role in facilitating lordosis, and noradrenergic innervation to multiple brain nuclei (including the VMN and MPN) may be required for full expression of sexual receptivity in female rats. This is a possibility that cannot be ruled out by our studies.

In conclusion, although previous reports indicate that the VMN and MPN are important hypothalamic regions for the control of lordosis, the results of the present study indicate that noradrenergic neurons terminating in either of these regions are not essential for gonadal steroid induction of sexual receptivity in ovariectomized female rats.

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