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8-OH-DPAT in the Midbrain Central Gray Inhibits Lordosis Behavior

LYNDA UPHOUSE,[1] MARJAY CALDAROLA-PASTUSZKA AND MICHAEL DROGE

Department of Biology, Texas Woman's University, Denton, TX 76204

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UPHOUSE, L., M. CALDAROLA-PASTUSZKA AND M. DROGE. *8-OH-DPAT in the midbrain central gray inhibits lordosis behavior.* PHARMACOL BIOCHEM BEHAV **43**(3) 833–838, 1992.—Sexually receptive female rats were infused intracranially with 500–2,000 ng 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) into the midbrain central gray (MCG), in the vicinity of the dorsal raphe nucleus (DRN), or directly into the DRN. When cannulae were located within the DRN, there was little evidence of change in lordosis behavior but a decrease in locomotor activity was commonly observed. In contrast, when cannulae were located anterior, ventromedial, or lateral to the DRN inhibition of lordosis behavior was rapid and robust. Both the lordosis-to-mount ratio (L/M) and the quality of the lordosis reflex were reduced following the infusion. The MCG receives lordosis-facilitating input from the ventromedial nucleus of the hypothalamus and from ascending sensory pathways and contributes information to descending motor systems involved in the lordosis response. Thus, the MCG is a critical link in the completion of the estrogen-dependent lordosis reflex. The present results suggest that 5-hydroxytryptamine$_{1A}$ receptors in the MCG prevent the completion of this reflex.

Proestrous female rats Ventromedial hypothalamus Lordosis Serotonin
Ventrolateral midbrain central gray

RECENT evidence suggests that serotonin (5-HT) neurons within the CNS can either facilitate or inhibit female rodent sexual behavior depending upon which 5-HT receptors are preferentially activated. In estrogen–progesterone-primed, ovariectomized females, drugs that act as 5-HT$_{1A}$ agonists or 5-HT$_2$ antagonists decrease lordosis behavior (1,13,14,25). We have confirmed the inhibitory effect of 5-HT$_{1A}$ agonists in intact, regularly cycling proestrous rats and have shown that 5-HT$_{1A}$ receptors within the ventromedial nucleus of the hypothalamus (VMN) can mediate this inhibition (21). It is possible, however, that sites in addition to the VMN are involved in the inhibition of lordosis behavior after systemic treatment with 5-HT$_{1A}$ agonists.

Of particular interest is the potential role of somatodendritic 5-HT$_{1A}$ autoreceptors in modulating female sexual behavior. Lakoski (11) suggested that 5-HT$_{1A}$ receptors in the dorsal raphe nucleus (DRN) are reduced by estradiol and recent work in our laboratory suggests that these receptors are modulated during the estrous cycle (22). An increase in 5-HT release in reproductively relevant terminal fields is thought to reduce female sexual behavior (15). Thus, it is unlikely that activation of somatodendritic autoreceptors [which should decrease 5-HT release from terminal fields (5, 20)] would reduce lordosis behavior. However, systemic doses of the 5-HT$_{1A}$ agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), which are effective in reducing lordosis behavior, are relatively low (21) and within the range of doses suggested to preferentially activate DRN autoreceptors (4,24). Therefore, in the following study the effect of 8-OH-DPAT infusions into the DRN was examined. Furthermore, the effect of infusions of 8-OH-DPAT into portions of the midbrain central gray (MCG) adjacent to the DRN was also examined.

METHOD

Materials

8-OH-DPAT HBr was purchased from Research Biochemicals, Inc. (Natick, MA). Cranioplastic and intracranial cannulae were purchased from Plastic Products, Inc. (Roanoke, VA) and dental acrylic was purchased from Reliance Dental Mfg. Co. (Worth, IL). All other supplies came from Fisher Scientific (Houston, TX).

Animals and Housing Conditions

Adult, female rats (CDF-344) were bred in our laboratory from stock obtained from Charles River Laboratories (Kingston, NY) or purchased as adults from Sasco Laboratories (Omaha, NE). Colony-bred rats were weaned into polycarbonate shoebox cages at 25–30 days of age and were housed three or four per cage with like-sex littermates. Purchased rats were housed three per cage upon arrival and were implanted with guide cannulae 1–2 weeks later. The colony room was maintained at 72°F and 55% relative humidity on a 12 L : 12

[1] To whom requests for reprints should be addressed.

D cycle with lights off at 12:00 p.m. (CST). Food and water were available ad lib. After surgery, vaginal smears of rats were monitored daily until the occurrence of a proestrous smear and the presence of sexual receptivity. Vaginal smears with nucleated cells, or primarily nucleated with a few cornified cells but an absence of leukocytes, were judged as proestrous smears. A sexually receptive state was confirmed by brief mating tests prior to initiation of the experiment.

Experimental Procedures

Females were anesthetized with the inhalant methoxyflurane (Metofane) and implanted bilaterally with 22-ga stainless steel guide cannulae advanced stereotaxically into the DRN or MCG, adjacent to the DRN. Atlas coordinates (AP 1.6, ML 0.0, DV −4.8) were derived from Konig and Klippel (9) and were modified for the stereotaxic apparatus as necessary (AP 1.0, ML 2.8, DV −5.8 implanted from a 23° angle) for the Fischer inbred rat. In 6 rats, a single cannula was implanted unilaterally; in 16 rats, implants were bilateral. Guide cannulae were secured with cranioplastic or dental acrylic and were anchored to the skull with three stainless steel screws. Stainless steel dummy cannulae (28 ga) were placed in the guide cannulae at the time of surgery to prevent clogging.

Dummy cannulae were gently turned at the time of vaginal smearing to facilitate their ease of removal at the time of infusion and adapt the females to the type of handling and manipulation that occurred on the day of testing. On the day that females showed a proestrous smear, they were briefly pretested for sexual receptivity with a sexually experienced male. Receptive females had their dummy cannulae replaced with 28-ga stainless steel internal cannulae (terminating 0.5

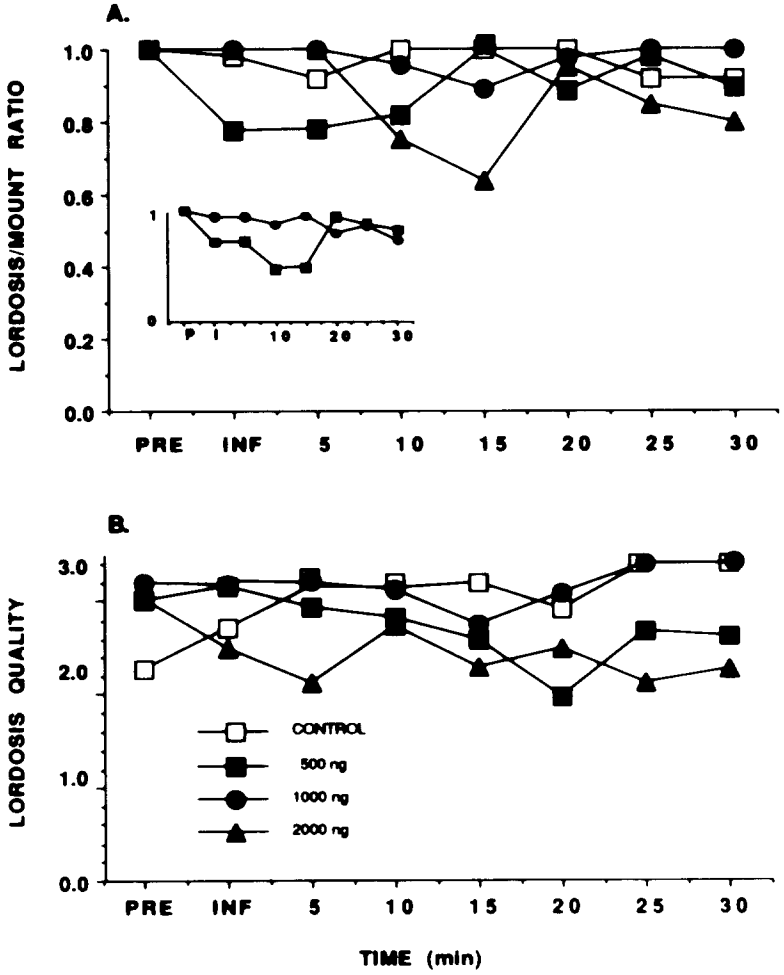

FIG. 1. Failure of DRN infusions of 8-OH-DPAT to suppress female lordosis behavior. Data are lordosis/mount ratios (A) and lordosis quality scores (B) for eight rats infused bilaterally with 8-OH-DPAT and three rats infused with saline (CONTROL) into the DRN. The data are the means for three, two, and three rats infused, respectively, with 500, 1,000, or 2,000 ng 8-OH-DPAT. For ANOVA, the data were collapsed across dose of 8-OH-DPAT; the overall error variance for the L/M ratio was 0.029. The inset shows the average L/M ratio for two rats where slight inhibition occurred late in the testing session and for two rats in which an initial inhibition was followed by relatively rapid recovery. Error variance following ANOVA, collapsed across dose of 8-OH-DPAT, for lordosdis quality was 0.12.

mm below the guide cannulae) attached by tubing (I.D. = 0.58 mm; O.D. = 0.96 mm) to a BAS (Lafayette, IN) (CMA/100) microinjector.

Female sexual behavior was tested within a CMA/120 containment system (BAS). This system consists of a clear circular chamber for behavioral observations. The system is equipped with an overhanging "arm" and liquid swivel for attachment to the infusion pump. The system is especially designed for studies with unanesthetized animals. The female was allowed to adjust to the chamber for 5–10 min. The male (previously adapted to the containment system and the infusion apparatus) was then placed with the female. The female's behavior was recorded for 5–10 mounts prior to infusion. Infusion was then initiated and behavior was recorded for an additional 30 min. The infusion solution consisted of either 8-OH-DPAT (500, 1,000, or 2,000 ng/cannula site) or saline. Infusions were administered at 0.24–0.26 μl/min to a final infusion volume per site of 0.5 μl. Postinfusion data were divided into 5-min intervals.

Sexual Behavior

All testing was performed during the dark portion of the light–dark cycle and was initiated within the first 1–3 h after lights off. For each mount by the male, the presence or absence of a lordosis reflex by the female was recorded. Sexual receptivity was monitored as previously described (21) and was quantified as the lordosis-to-mount (L/M) ratio (i.e., number of lordosis responses by the female divided by the number of mounts by the male). The quality of each lordosis response was scored as described by Hardy and DeBold (6). The occurrence of hopping and darting responses, characterized as proceptive behaviors by Beach (3), was also recorded. Resistive behavior was recorded whenever the female showed kicking, boxing, rolling over, or running away from the male.

Histological Procedures

Females were anesthetized with Metofane and perfused intracardially with 0.9% saline followed by 10% buffered formalin. The brain was excised and placed in 10% buffered formalin for a minimum of 24 h before sectioning (100 μm) with a Lancer (St. Louis, MO) vibratome. Tissue sections were stained with cresyl violet and cannulae locations were verified according to Konig and Klippel (9).

Statistical Methods

Within experimental conditions, L/M data were organized into pretest period, infusion period, and consecutive 5-min intervals postinfusion. Over the dose range examined, a dose-response effect of 8-OH-DPAT was not apparent. Therefore, the data were collapsed across dose and analyzed by repeated-measures analysis of variance (ANOVA) with time as the repeated factor. If a single 5-min interval occurred in which no successful mounts had taken place, the mean for that animal of the data preceding and following that cell was inserted for data analysis. If data were missing for two consecutive 5-min intervals, the data for that animal were excluded from the ANOVA. When significant overall effects were obtained, the mean L/M ratios (within a treatment and time interval) were compared to control values by Dunnett's *t*-test. When only two time points were compared, data were evaluated by *t*-test for matched pairs. In all cases, the statistical reference was Zar (26).

RESULTS

Figure 1 shows that neither the L/M ratio nor the lordosis quality score was significantly suppressed following infusions of 8-OH-DPAT into the DRN (ANOVA for the repeated-measures factor of time, $p > 0.05$). Cannulae sites are indicated in Fig. 2. Two rats did show a transient decline in lordosis behavior near the end of the testing session and two showed a robust suppression within 10 min of the infusion but recovered rapidly to normal lordosis behavior. The average L/M ratios for these two rats are indicated in the inset to Fig. 1.

Only one female infused with 8-OH-DPAT into the DRN showed any active resistance to the male. In contrast, females were characteristically passive, with five of eight rats showing a decline in locomotor activity following the infusion. Nevertheless, four of eight females continued to show periodic hopping and darting behavior during the 30-min test session.

Because the decision to terminate the experiment after 30 min was an arbitrary one, based upon findings in the VMN

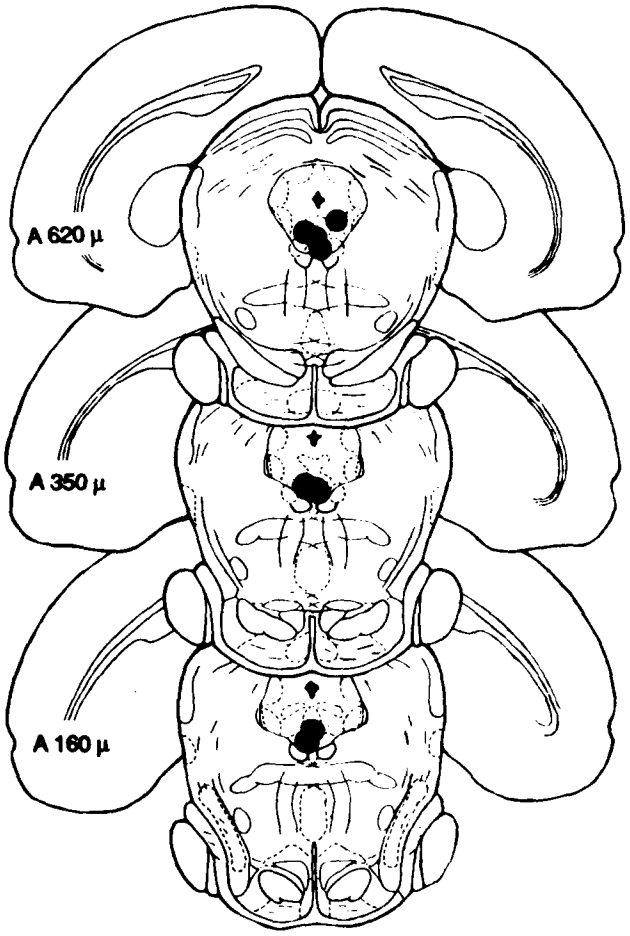

FIG. 2. Cannulae locations for eight rats with DRN infusions. The drawings are of coronal sections through the midbrain showing sites where bilateral cannulae sites were located within the dorsal raphe. Each circle indicates the location of cannulae determined histologically in rats after testing for sexual receptivity. In none of the rats did the infusion lead to a rapid and long-lasting inhibition of lordosis behavior. Inhibition was defined as at least two consecutive 5-min testing intervals in which the L/M ratio was no higher than 0.75.

(21), two rats were retested 90 and 120 min after DRN infusion. Neither rat showed suppression of lordosis behavior.

A robust suppression of lordosis behavior occurred after infusion of 8-OH-DPAT into MCG sites rostral, lateral, or ventromedial to the DRN (Figs. 3 and 4). Across all doses, there was a significant effect of time after infusion, $F(7, 70) = 10.52$, $p \leq 0.0001$, with little difference among the three doses of 8-OH-DPAT. Eleven of 11 rats with cannulae located in the MCG sites indicated in Fig. 4 showed reduced L/M ratios by 5–10 min after infusion with 8-OH-DPAT (Dunnett's t-test, $p \leq 0.05$). Nine of these 11 rats also showed a reduced lordosis quality score following infusion and, over all rats, quality was significantly decreased, $F(7, 56) = 4.106$, $p \leq 0.001$. Lordosis quality was significantly different from pretest levels at every 5-min interval after infusion except at the 10-min interval (Dunnett, $p < 0.05$).

Whether females had cannulae placements directly within the DRN or outside the DRN, they appeared to remain attractive to males during the testing period. There were no differences in the number of mounts received by rats infused with saline or with 8-OH-DPAT and animals with DRN locations did not differ from those with cannulae outside the DRN (all $p > 0.05$). Most females also received an ejaculation during the 30-min testing period. The exception was those females with cannulae placements outside the DRN; ejaculation occurred in only 3 of the 11 females. Because females with cannulae outside the DRN were relatively passive and failed to show high-quality lordosis behavior, the relative absence of

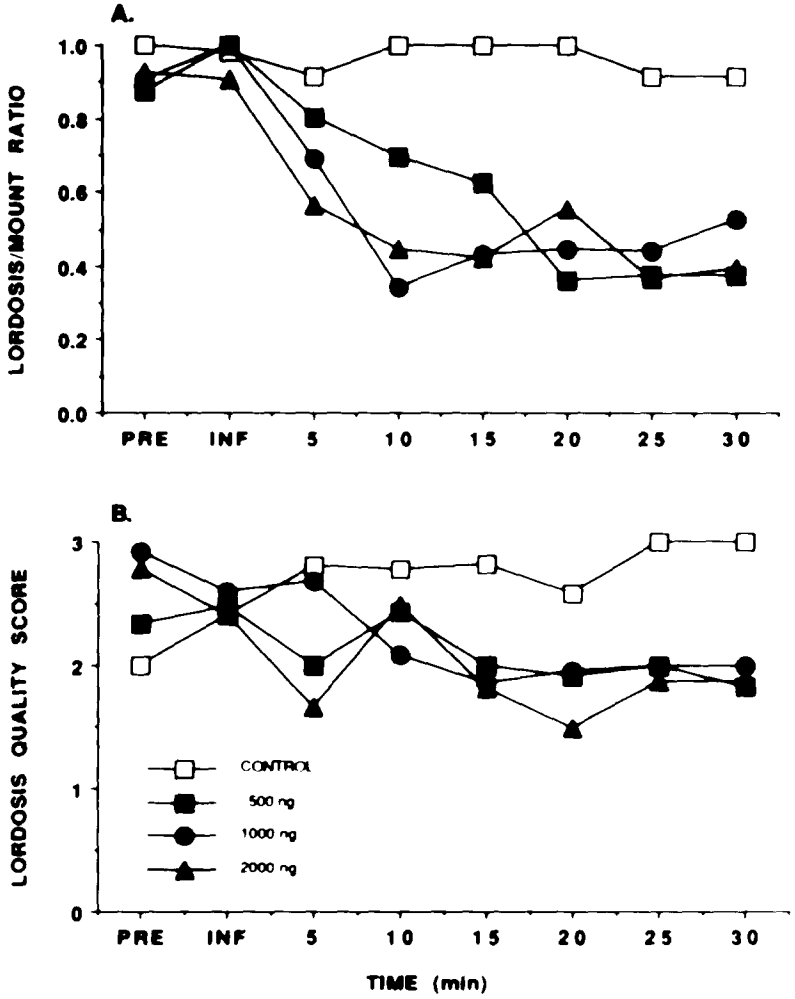

FIG. 3. Effect of MCG infusions of 8-OH-DPAT on female lordosis behavior. Data are lordosis/mount ratios (A) and lordosis quality scores (B) of 11 rats infused with 8-OH-DPAT and 3 rats infused with saline into the MCG. Six rats received unilateral infusions of 8-OH-DPAT and five received bilateral infusions with 8-OH-DPAT. Because there was no difference in the unilateral vs. the bilateral conditions, the data have been combined for presentation. The figure indicates the mean L/M for two, four, and five rats infused, respectively, with 500 (one unilateral; one bilateral), 1,000 (three unilateral; one bilateral), or 2,000 (two unilateral, three bilateral) ng 8-OH-DPAT. For ANOVA, the data were collapsed across dose of 8-OH-DPAT. The overall error variance for the 4-m ratio was 0.053. For lordosis quality, the error variance, collapsed across dose of 8-OH-DPAT, was 0.413.

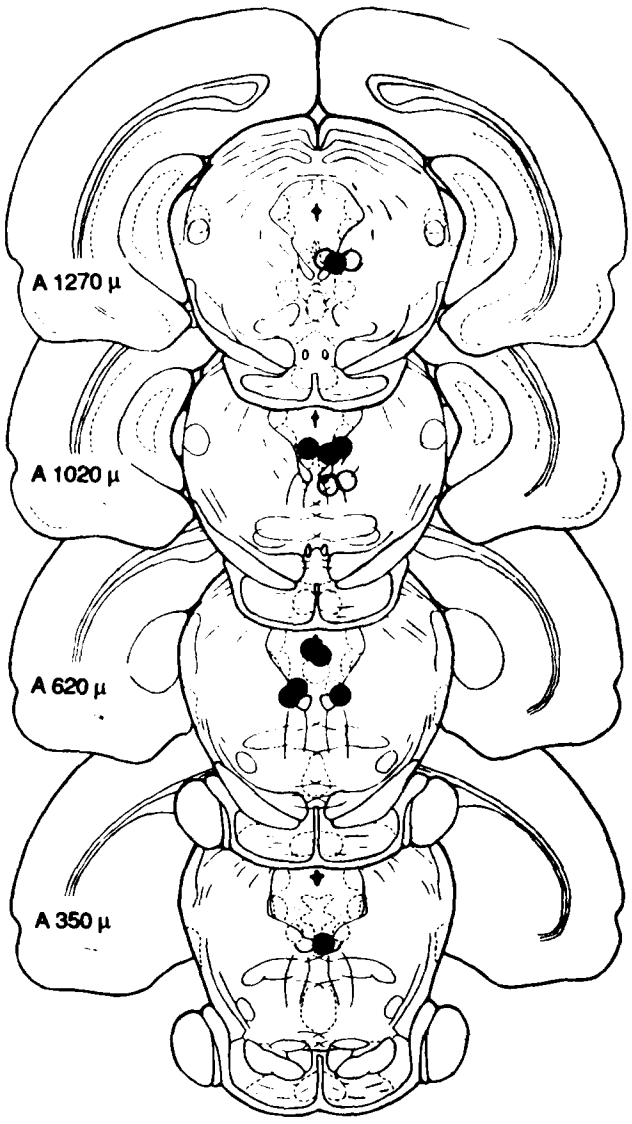

FIG. 4. Cannulae locations for 11 rats with MCG infusions of 8-OH-DPAT. The drawings are of coronal sections through the midbrain showing MCG sites where cannulae were located in proestrous female rats that showed inhibition of lordosis behavior following infusion with 8-OH-DPAT. Each circle indicates the location of cannulae determined histologically in rats after testing for sexual receptivity. (●), cannulae locations in rats that had bilateral implants; (○), cannulae locations in rats that had unilateral implants. Inhibition was defined as at least two consecutive 5-min testing intervals in which the L/M ratio was no higher than 0.75.

ejaculations probably reflects the male's difficulty in achieving intromissions.

Four rats were retested 1½-2 h after completion of infusion. Although there was some recovery during this time period, the L/M ratio had not returned to preinfusion levels (mean ± SE at 30 and 120 min, respectively, = 0.22 ± 0.13 and 0.64 ± 0.13).

In addition to a decrease in lordosis behavior, 7 of 11 rats infused with 8-OH-DPAT into the MCG showed one or more symptoms of the serotonin syndrome. Flattened posture was seen in five rats; forepaw treading was observed in three rats; and hindlimb splaying was evident in one rat. In addition to the serotonin syndrome, excessive digging, excessive grooming, or sedation/immobility was observed respectively in three, two, and three rats. There was no obvious difference in the cannulae locations of rats that did or did not show these behaviors.

DISCUSSION

The original objective of these studies was to evaluate the effect on female sexual behavior of 8-OH-DPAT infusions onto DRN 5-HT_{1A} autoreceptors. Because DRN infusions had minimal effects on lordosis behavior, activation of DRN 5-HT_{1A} receptors (including 5-HT_{1A} autoreceptors) does not appear to reduce female lordosis behavior. However, because only three doses of 8-OH-DPAT were examined we cannot rule out a different effect of 8-OH-DPAT at higher or lower doses of the drug. Such dose-dependent effects of 5-HT have been reported in the male following DRN infusions (7) even though infusions of 8-OH-DPAT into the DRN did not significantly affect male sexual behavior (8). Nevertheless, the failure of 8-OH-DPAT to reduce lordosis behavior at doses consistently leading to inhibition when infused outside the raphe or within other brain areas (21) is consistent with the hypothesis that an increase (and not a decrease) in 5-HT release in terminal fields is inhibitory to female sexual behavior. In fact, stimulation of DRN autoreceptors might be expected to facilitate rather than inhibit lordosis behavior. Unfortunately, any facilitatory effects of 8-OH-DPAT infusions into the DRN would not have been evident in the already highly receptive proestrous rat.

Infusions of 8-OH-DPAT into the MCG ventromedial, ventrolateral, or rostral to the DRN reduced both the L/M ratio and the lordosis quality score. However, in contrast to 8-OH-DPAT's effects in the VMN MCG infusions did not increase the female's resistance to the male. Most females continued to exhibit solicitous actions toward the male even though they responded minimally, if at all, when mounted by a male. The behavior was suggestive of a female that either failed to "process" the stimulus input or was unable to produce the appropriate motor output. Because 3 of 11 females also showed flattened posture, these results suggest that 8-OH-DPAT may have interfered with the completion of the MCG-mediated supraspinal sensorimotor processing necessary for the lordosis reflex.

The MCG, required for the VMN's facilitation of the lordosis reflex, is essential for completion of the sensorimotor loop that leads to the execution of the lordosis reflex (16,17). As reviewed in Pfaff and Modianos (16), lordosis-relevant sensory information travels, relatively dispersed, within the anterolateral column of the spinal cord to terminate widely throughout the brainstem reticular formation (including the nucleus gigantocellularis) and in the mesencephalon (deep tectal layers and lateral MCG), as well as a few projections to more rostral areas. The most likely contributors to the supraspinal motor component of the lordosis reflex are thought to travel to the spinal cord via the reticulospinal and/or vestibulospinal tracts.

It is significant, therefore, that the MCG areas where 8-OH-DPAT reduced lordosis behavior overlap those areas: a) where VMN efferents terminate in the MCG; b) in which MCG lesions abolish VMN facilitation of lordosis behavior; and c) where components of the lordosis reflex can be elicited by electrical stimulation of the MCG (2,10,17-19). Further-

more, the rostral, ventromedial MCG, and supraoculomotor nucleus (wherein our most rostrally placed effective sites reside) sends efferents to the abducens nucleus, lateral and dorsal nucleus paragigantocellularis (PGi), and nucleus ambiguus (23). Ventrolateral MCG areas (those represented by our effective sites ventral and lateral to the DRN) project to the medial PGi, nucleus gigantocellularis, and midline raphe magnus (23). Thus, there appears to be ample opportunity for convergence of those MCG areas in which 8-OH-DPAT reduced lordosis behavior onto regions contributing to vestibulospinal and especially to reticulospinal input to the spinal cord.

However, it should be noted that there also appears to be ample opportunity for the effective MCG regions to influence the autonomic nervous system (ANS) (12,23). With the present data, we cannot determine if the MCG infusions of 8-OH-DPAT reduced sensory input, decreased motor output, or produced ANS changes that interfered with the female's execution of the lordosis reflex. Our subjective impression is that females did not "object" to the male's mounts. Seven of 11 rats produced a slight and transient head or neck movement in response to the male's mounts, but no back reflex was detectable. Consequently, we suspect that 8-OH-DPAT disrupted descending motor information required for the complete lordosis response.

If our speculations are correct, 5-HT neurons are able to modulate the MCG contribution to the lordosis reflex. Because infusions of 8-OH-DPAT directly within the DRN did not decrease the L/M ratio, it is unlikely that the drug acted in the MCG via DRN 5-HT_{1A} autoreceptors. However, we cannot rule out the presence of 5-HT_{1A} autoreceptors on DRN dendrites distant from the cell body and within the regions of effective MCG sites. Nevertheless, the present data are most consistent with the existence of 5-HT_{1A} receptors postsynaptic to 5-HT axons. Whether these axons are derived from the nearby DRN or outside the DRN is currently unknown.

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