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Muscimol Facilitates Sexual Receptivity in Hamsters When Infused Into the Ventral Tegmentum

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FRYE, C. A. AND J. F. DEBOLD. *Muscimol facilitates sexual receptivity in hamsters when infused into the ventral tegmentum.* PHARMACOL BIOCHEM BEHAV 42(4) 879–887, 1992.—Progestogenic stimulation of both the ventral medial nucleus of the hypothalamus (VMH) and the ventral tegmental area (VTA) within the midbrain is critical for normal receptivity in female hamsters. However, few estrogen-induced progestin receptors have been found in the midbrain. In addition, recent evidence suggests that progestin's action in the VTA is mediated nongenomically at the membrane. The present experiment investigated the possible role of $GABA_A$ receptors in mediating the effects of progesterone in this brain region. Ovariectomized female hamsters were bilaterally implanted with chronic cannulae aimed toward the ventral mesencephalon. Five days after surgery, animals were injected with 10 μg estradiol benzoate SC. Forty hours later, the same animals were injected with either 25 or 100 μg progesterone and at hour 43.5, 50 ng muscimol was infused in 0.5 μl. Control animals received 0.5 μl vehicle, sterile saline, or no infusion. At hour 44, animals were tested for sexual receptivity by placing them in an observation arena with a sexually experienced male for 10 min, during which lordosis duration was recorded. The following week, the same regimen was given with the alternate dose of progesterone. Histology revealed that only those animals that were infused with muscimol into the VTA had total lordosis durations that were significantly longer than the controls. Implants that missed the ventral tegmental area were much less effective. These results indicate that GABA might play a facilitatory role in enhancing the efficacy of threshold doses of progesterone. Whether this interaction is due to a direct effect of progestins on the $GABA_A$ receptor complex awaits further study.

Hamster Sexual behavior Progesterone GABA Lordosis VTA

ESTROGEN and progesterone normally control the onset of sexual receptivity in female rodents (40). There is considerable evidence that estrogen and progesterone control sexual behavior by acting on specific brain regions. For estrogen, the evidence is very strong that its effects on sexual behavior are primarily due to its actions on the ventral medial hypothalamus (VMH). Direct application of estradiol to the VMH is sufficient to prime female rats (44) and hamsters (6,49) for sexual receptivity. The VMH also appears to be an essential site for progesterone's actions in facilitating receptivity in rats (8,45) and hamsters (5,12,39,48). Converging evidence also indicates that in hamsters progestogenic stimulation to a second site, the ventral tegmental area (VTA) in the ventral midbrain, is critical for normal sexual receptivity (5,12,39) and may also play a role in rats (37,43). It is only when progesterone is applied simultaneously to both the VMH and the VTA that the majority of hamsters are receptive (12,39). Furthermore, permanent or temporary lesions to either the VMH or VTA significantly impair sexual receptivity (11,16,22,26,38).

Interestingly, although these data indicate that progestogenic stimulation to the VTA is integral for normal sexual receptivity, few estrogen-induced progestin receptors have been seen in the midbrain of hamsters (33), rats (23), or guinea pigs (3). On the contrary, data suggest that progestins do not have their actions via intracellular estrogen-induced progestin receptors within the hamster midbrain. First, in hamsters estrogen is not essential within the midbrain for responsiveness to progesterone (6,47). Second, progesterone conjugated to bovine serum albumin (BSA), which poorly penetrates membranes (19,20), facilitates lordosis in estrogen-primed hamsters if it is implanted directly in the VTA concurrent with progesterone application to the VMH (12). Finally, changes in midbrain neuronal excitability are seen very rapidly in response to lordosis-relevant stimuli (17) and the timing and quality of the neuronal excitability are not different when progesterone conjugated to Horseradish peroxidase is applied to the membrane (41). Taken together, these data indicate that progesterone is likely exerting effects via a nongenomic mechanism of action in the hamster midbrain.

A possible nongenomic site for progestin's action is the

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neuronal membrane. The $GABA_A$ receptor complex is located on the membrane and it is of interest as a possible mechanism of progestin actions because of recent biochemical evidence. This evidence includes that GABA receptors are known to exist in virtually all parts of the brain including the ventral midbrain (51), progestins acutely interact with the $GABA_A$ complex on the cell membrane to inhibit TBPS binding (24,50), progestins potentiate GABA effects on chloride uptake (18), and progestins enhance flunitrazepam binding (24).

To date, no one has examined the effects of central administration of GABAergic drugs on their ability to promote sexual receptivity in female hamsters. Because this represents a potential locus for a nongenomic mechanism of progestin's actions in the hamster midbrain, it is of interest whether muscimol, a $GABA_A$ agonist, will potentiate low-dose progesterone-induced receptivity if infused into this CNS site.

METHOD

Subjects

Animals were sexually inexperienced, adult, female golden hamsters (*Mesocricetus auratus*, LVG: Lak outbred strain), obtained from Charles River Breeding Laboratories (Wilmington, MA). Hamsters were singly housed in 26 × 20 × 15 cm polycarbonate cages with sawdust bedding in a temperature (72 ± 2°F)- and humidity (30–40%)-controlled room. The light cycle was reversed (14 L : 10 D), with lights on at 2100 h. Rodent chow and water were freely available in animals' cages.

Procedure

Surgical procedures were conducted with subjects anesthetized with sodium pentobarbital (75 mg/kg, IP). Steroids were dissolved in sesame oil and administered in a volume of 0.05 cc.

Female hamsters were ovariectomized at 55 days of age, 1 week after arrival in the laboratory. Prior to stereotaxic surgery, all animals were evaluated with a brief neurological evaluation based upon the methods of Marshall and Teitlebaum (27). This procedure assessed orientation to a tactile flank stimulus, righting response, response to hindlimb extension, and the subject's ability to climb on a vertically oriented cage top. One week later, female hamsters were stereotactically implanted with a pair of cannulae, aimed bilaterally just above the VTA (coordinates from bregma: AP = −2.8, ML = ±0.3, DV = −7.8) within the ventral mesencephalon. The coordinates for these cannulae were based upon a stereotaxic atlas of the hamster forebrain (25) and upon experiments showing the most effective sites for facilitating (5,12,39) and inhibiting (16,22,38) progestin-facilitated lordosis in hamsters. The cannula assembly consisted of a pair of 23-ga thin-walled stainless steel guide tubes with 30-ga removable inserts. The cannulae were attached to the skull with dental cement and a stainless steel screw. The guide tubes were implanted such that their tips were 4 mm dorsal to the targeted site to minimize damage to the site. The day after surgery, 30-ga stylets were placed in the guide cannulae so that their tips extended to just above the intended site. The inserts were removed and cleaned daily in ethanol in an attempt to prevent occlusion of the guide tubes.

One week after stereotaxic surgery, females were injected SC with 10 μg estradiol benzoate (EB) at hour 0. At hour 40, animals were injected with 25 or 100 μg progesterone. At hour 43.5, each animal had 50 ng muscimol, dissolved in 0.5 μl phosphate-buffered saline, infused into each available cannula with a Hamilton microsyringe attached by intramedic tubing to a 30-ga insert. Muscimol or vehicle was infused at a rate of 0.1 μl/10 s while animals were under minimal hand-held restraint. Just after infusion, animals were retested for neurological deficits. Animals that had not gained weight since the original surgery or whose postoperative neurological evaluation differed from their baseline evaluation were excluded from the study (n = 4 of 252). After infusion and neurological evaluation, animals were observed for sexual receptivity at hour 44 by an observer blind to the experimental treatments. This observation was conducted after placing the experimental female into a 25 × 50 × 39 cm glass arena with a sexually experienced, gonadally intact male. During the 10-min observation, the onset and offset of lordosis were recorded with an event recorder. From these records, the total time spent in lordosis (TLD), mean lordosis duration (MLD), latency to first lordosis, and frequency of lordosis were derived. The following week, animals received similar testing except the alternate dose of progesterone was given. Whether the animal initially received 25 or 100 μg progesterone was randomly decided and counterbalanced.

Following the second week's testing, animals were killed with an overdose of sodium pentobarbital and perfused intracardially with 0.9% saline followed by 10% formalin. The frozen fixed brains were sliced in 40-μm coronal sections, stained with cresyl violet, and then examined under low-power light microscopy to identify infusion locations. Based upon the histology and infusion records, all animals were assigned to either unilateral or bilateral infusion groups for analysis. Those animals that had one cannula occluded received unilateral infusions of muscimol or vehicle to one of nine sites: either the VTA, interpeduncular nucleus (IPN), the pontine nuclei (PN), substantia nigra (SN), red nucleus (RN), central grey (CG), central tegmentum (CTG), mammillary peduncles (MP), or medial lemniscus (ML). Those animals receiving bilateral infusions had muscimol infused into the VTA bilaterally, the RN bilaterally, or the CG bilaterally. In a few animals, the muscimol infusions were not bilaterally symmetric; some had one site in the VTA concurrent with contralateral IPN, CG, or SN infusions. There were also some animals with infusions into the ML concurrent with a contralateral SN infusion or with muscimol infused asymmetrically to the CG and RN. Multiple analyses of variance (ANOVAs) with repeated measures (SAS Institute, Cary, NC) was used to determine if behavioral measures varied as a function of what was infused intracranially (vehicle vs. muscimol), site of muscimol administration, and level (25 or 100 μg) of hormone treatment. The general linear model ANOVA was followed by Newman-Keuls tests for differences among the means of various groups.

RESULTS

The overall statistical analyses revealed that there was a significant effect of the experimental treatment on TLD, $F(3, 301) = 5.24$, $p < 0.001$, MLD, $F(3, 301) = 3.24$, $p < 0.05$, and frequency of lordosis, $F(3, 301) = 5.96$, $p < 0.001$. Similarly, latency to first lordosis was significantly decreased, $F(3, 301) = 7.42$, $p < 0.001$, by the experimental condition. Post-hoc comparisons indicated that muscimol infusions significantly enhanced receptivity. As the purpose of this study was to assess whether muscimol might enhance progesterone facilitated receptivity when infused specifically within the VTA, histology and infusion records were also considered. Animals were subcategorized based upon the location of infusion and whether they received unilateral or bilateral muscimol.

The effects of unilateral muscimol on TLD, $F(17, 107) = 3.07, p < 0.001$, MLD, $F(17, 107) = 1.74, p < 0.05$, latency to first lordosis, $F(17, 107) = 2.85, p < 0.001$, and frequency of lordosis, $F(17, 107) = 2.91, p < 0.001$, all varied as a function of site of infusion and progesterone dose. Only those hamsters receiving unilateral muscimol into the VTA had enhanced receptivity, having significantly greater TLDs than animals with muscimol infused into any other site (Newman-Keuls, $p < 0.01$). Animals with the higher (100 μg) dose of progesterone also had significantly longer total lordosis durations than animals receiving the lower dose (Newman-Keuls, $p < 0.001$). A similar pattern of results across sites was seen when MLD, lordosis latency, and frequency were used as the dependent measures.

Behavioral results from animals with unilateral infusion to the MP, PN, IPN, ML, and RN were not significantly different (see Table 1). These groups were combined for further analysis because of the small number of animals in each group and the lack of effectiveness of muscimol infused into any of these sites. These animals were designated the "other midbrain" group. In addition, behavioral results from animals with muscimol infused into the CTG were combined with animals that had muscimol infused into the CG because infusions in both of these nearby sites were ineffective (see Table 1). These animals were designated the "central midbrain" group. Thus, animals with unilateral infusions were classified as having muscimol infused into either the VTA, SN, central midbrain, or other midbrain. At the higher (100 μg) progesterone dose, TLD, $F(3, 53) = 12.63, p < 0.001$, MLD, $F(3, 53) = 4.89, p < 0.01$, latency to first lordosis, $F(3, 53) = 6.71, p < 0.001$, and frequency of lordosis, $F(3, 53) = 5.40, p < 0.001$, all varied as a function of site of administration of muscimol. At the lower (25 μg) progesterone dose, TLD, $F(3, 53) = 4.18, p < 0.01$, MLD, $F(3, 53) = 4.77, p < 0.005$, latency, $F(3, 53) = 5.86, p < 0.001$, but not frequency, $F(3, 53) = 1.89$, ns, also varied with the site of administration of muscimol. Even with this broader classification schema, only those animals with muscimol infused into the VTA again showed a significant facilitation of sexual receptivity (see Fig. 1).

The effect of bilateral muscimol on total lordosis duration, $F(17, 193) = 3.07, p < 0.0001$, latency, $F(17, 193) = 4.84, p < 0.001$, frequency, $F(17, 193) = 5.08, p < 0.0001$, but not mean lordosis duration, $F(17, 193) = 0.67$, ns, varied as a function of site of administration and dose of progesterone. Only those animals with muscimol infused bilaterally into the VTA were significantly more receptive than those in any other group (Newman-Keuls, $p < 0.001$). Since bilateral infusions with one cannula in the VTA and one in a nearby site appeared somewhat effective at facilitating lordosis, although not significantly so, these groups were not combined (see Fig. 2). Animals given the higher (100 μg) progesterone dose were more receptive than animals given the 25-μg progesterone dose (Newman-Keuls, $p < 0.001$). The site specificity of the VTA

TABLE 1

VARIOUS UNILATERAL INFUSION SITES WHERE MUSCIMOL WAS EFFECTIVE AND INEFFECTIVE IN FACILITATING SEXUAL BEHAVIOR

Unilateral Sites	*n*	TLD ± SE (seconds)	MLD ± SE (seconds)	LAT ± SE (seconds)	FREQ ± SE
VTA					
100 μg	17	260 ± 45.4	74 ± 24.0	173 ± 47.5	5 ± 1.0
25 μg	17	137 ± 53.8	35 ± 12.1	299 ± 64.8	2 ± 0.7
SN					
100 μg	7	49 ± 48.0	13 ± 12.1	445 ± 91.8	1 ± 0.4
25 μg	7	3 ± 3.0	3 ± 3.0	497 ± 83.5	1 ± 0.2
MP					
100 μg	2	0	0	600	0
25 μg	2	0	0	600	0
PN					
100 μg	3	106 ± 98.1	8 ± 5.2	239 ± 181.9	5 ± 3.5
25 μg	3	0	0	600	0
IPN					
100 μg	4	75 ± 75.0	8 ± 8.0	453 ± 147.0	2 ± 2.0
25 μg	4	27 ± 25.0	2 ± 1.0	465 ± 125.0	8 ± 4.0
RN					
100 μg	2	0	0	600	0
25 μg	2	0	0	600	0
ML					
100 μg	2	0	0	600	0
25 μg	2	0	0	600	0
CG					
100 μg	5	10 ± 10.3	2 ± 2.1	500 ± 99.7	1 ± 1.0
25 μg	5	17 ± 16.5	8 ± 8.5	549 ± 50.5	1 ± 0.4
CTG					
100 μg	12	15 ± 9.8	11 ± 8.1	461 ± 67.3	1 ± 0.4
25 μg	12	0	0	551 ± 98.5	0

Other midbrain sites include animals with infusions to the MP, PN, IPN, RN, and ML. Central midbrain sites were those animals with infusions to the CG or CTG.

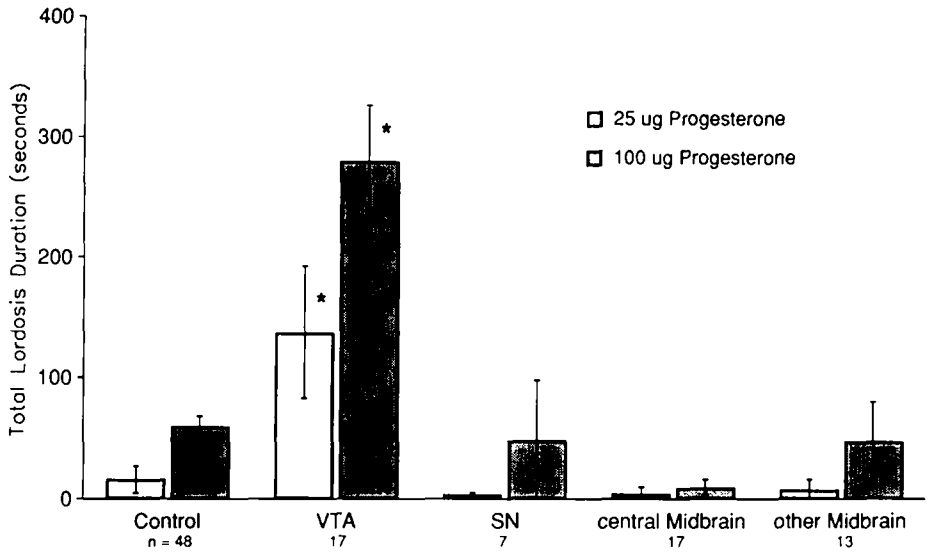

FIG. 1. Total lordosis duration in seconds by estrogen-primed female hamsters treated with either 25 or 100 μg progesterone after unilateral muscimol infusion or vehicle. *significantly greater than all other groups at the same dose of progesterone, $p < 0.01$.

was only seen after 100 μg progesterone with bilateral muscimol administration. A schematic of the location of all unilateral and bilateral infusion sites and the respective total lordosis durations is shown for animals after 25 μg progesterone and muscimol in Fig. 3 and 100 μg progesterone in Fig. 4.

DISCUSSION

Muscimol, when infused unilaterally or bilaterally into the ventral tegmentum, facilitates lordosis in hamsters primed with EB and 100 μg progesterone. At the 25-μg progesterone dose, unilateral infusions of muscimol to the VTA also facilitated sexual receptivity. Muscimol infusions in other nearby midbrain sites did not significantly increase receptivity with either dose of progesterone. This site specificity of muscimol to facilitate sexual receptivity only when infused into the ventral tegmentum is consistent with previous findings from our lab in which progesterone implants are only effective if centered in the VTA and coupled with concurrent implants to the VMH (12,39).

Unlike unilateral infusions into the VTA, bilateral muscimol infusions did not significantly enhance sexual receptivity

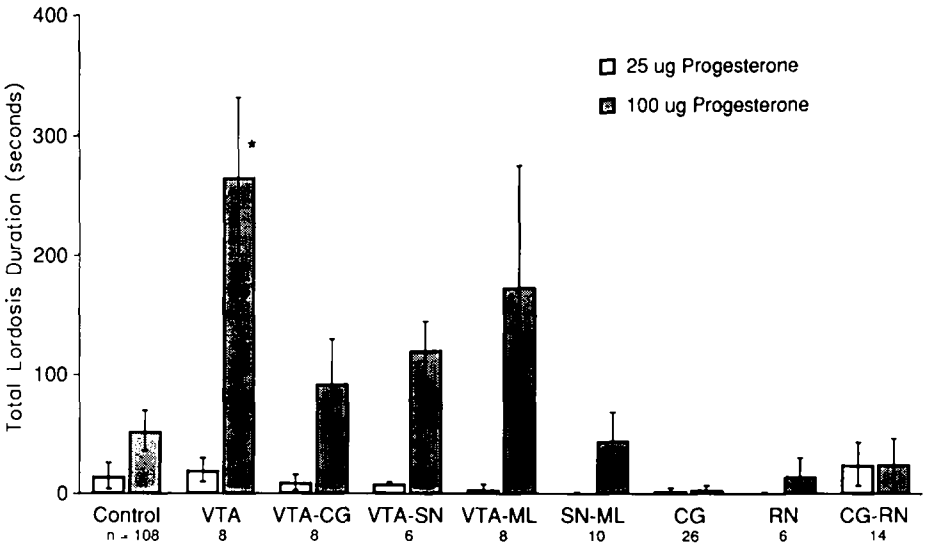

FIG. 2. Total lordosis duration in seconds by female hamsters during a 10-min test with a sexually active male after bilateral muscimol infusion or vehicle with either 25 or 100 μg progesterone. *significantly greater than all other groups at the same dose of progesterone, $p < 0.01$.

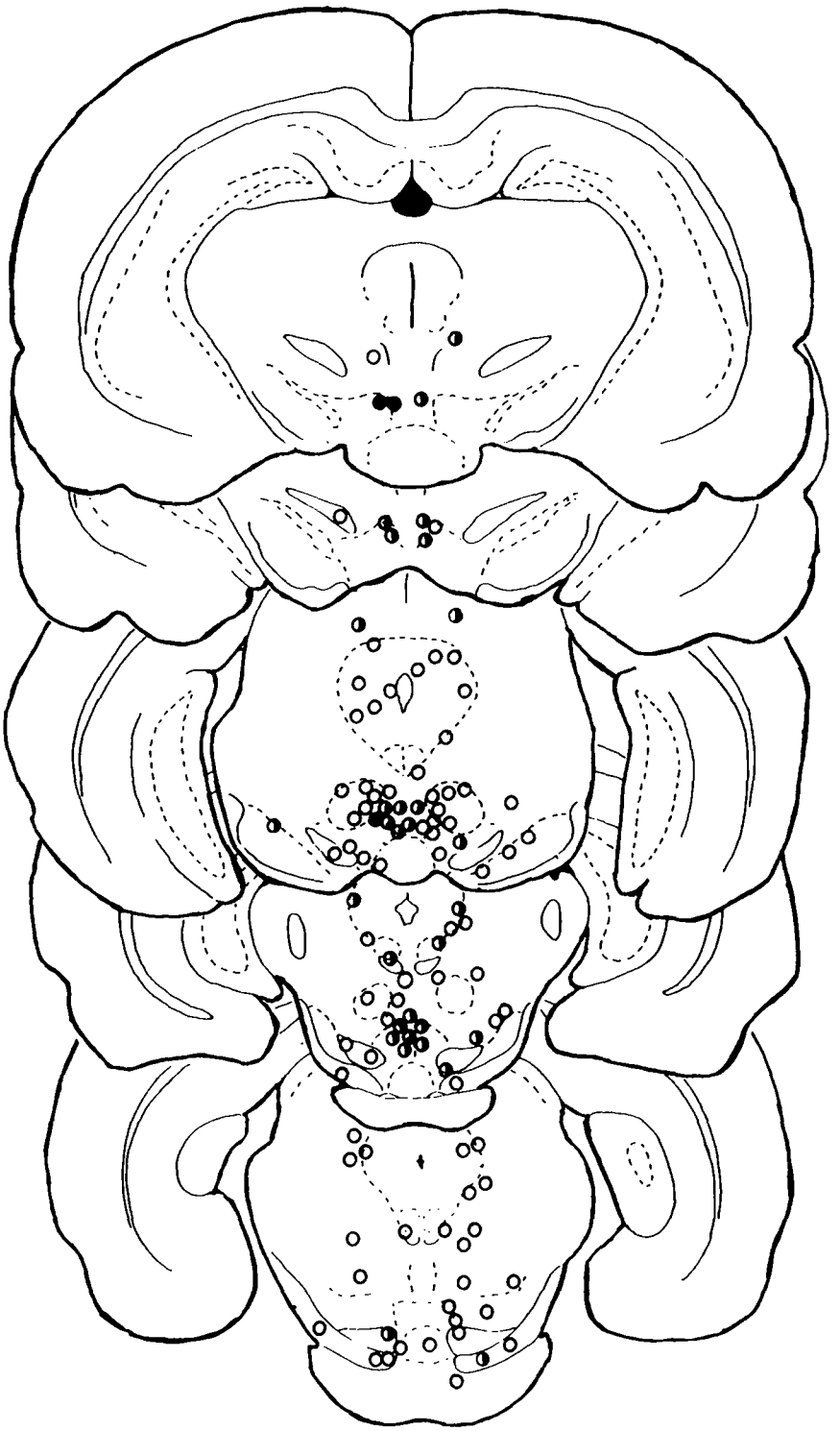

FIG. 3. Coronal sections depicting the location of infusion sites in unilateral and bilaterally infused estrogen-primed female hamsters with 25 μg progesterone. (●) infusion sites associated with total lordosis duration over 250 s; (◑) sites in animals with TLD >0 but <250 s; (○), sites in animals that showed no lordosis.

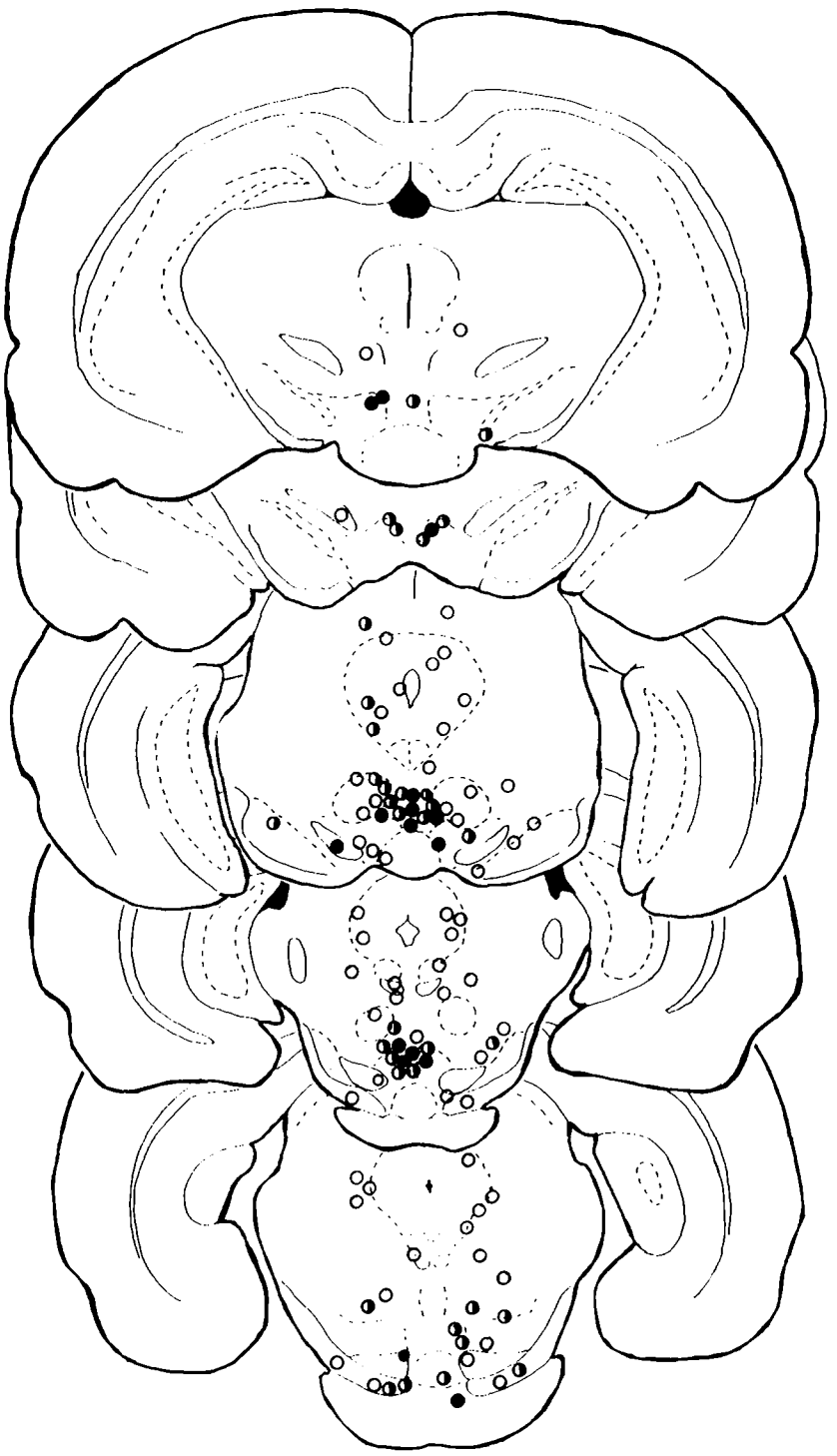

FIG. 4. Coronal sections depicting the location of infusion sites in unilateral and bilaterally infused estrogen-primed female hamsters with 100 μg progesterone. (●), infusion sites associated with total lordosis duration over 250 s; (◑), sites in animals with TLD >0 but <250 s; (○) sites in animals that showed no lordosis.

in hamsters primed with EG and 25 mg progesterone. This lack of facilitation may be due to a variety of reasons. First, animals with bilateral infusions had greater damage due to the additional insert and infusion volume. It is possible that at a lower dose of progesterone animals might not be able to overcome the effect of this additional ventral damage. However, this is unlikely since small, subtotal bilateral electrolytic lesions to the VTA do not significantly impair sexual receptivity (22). Second, it is possible that facilitation of receptivity was not seen with animals bilaterally infused with muscimol to the VTA and given 25 μg progesterone because of the different doses. Animals with bilateral infusions received a total of 100 ng muscimol as opposed to 50 ng after unilateral infusions. It may be that the bilateral muscimol dose (or increased neural tissue stimulated by the muscimol) was excessive in proportion to the smaller (25 μg) dose of progesterone present. These data suggest that the degree of sexual receptivity after muscimol infusion to the VTA and progesterone is dose dependent upon *both* of these factors. Moreover, these behavioral data indicate that it is unlikely that muscimol infusion into the hamster VTA, in the absence of progesterone, would facilitate lordosis. Finally, it is possible that if additional 25-μg-progesterone-treated animals were infused bilaterally into the VTA with muscimol a facilitation of receptivity would have been seen. To ensure that the lack of effect at 25 μg progesterone in these eight animals is not due to variability, behavior from an equal number of unilateral and bilaterally VTA infused animals would need to be considered.

In the present study, muscimol infusions unequivocally facilitated sexual behavior in the estrogen- and progesterone-treated female hamster. In other species such as the rat, findings have not been as clear cut. The majority of these studies have focused on the primary progestin-sensitive site in rats, the VMH. Muscimol or GABA infusions into the VMH have been reported to enhance (7,29), inhibit (28), or have no effect on sexual receptivity (9). Another strategy that has been used to test the possibility that progesterone exerts its effects on receptivity through GABA has been to employ progestins that are particularly potent at the $GABA_A$ receptor complex. However, some of the progestin metabolites that are very effective at altering neuronal firing and enhancing GABAergic activity have no effect on lordosis if applied to the VMH of rats (2). In addition, although the anesthetic actions of progestins are thought to be due to actions at the $GABA_A$ complex (15) there is little correlation between this action and their efficacy in facilitating sexual behavior (31) if administered systemically. These differential behavioral effects may be due to progesterone working genomically in the VMH and after metabolism by working via the $GABA_A$ receptor complex. Thus, the disparate behavioral effects seen in rats treated with GABAergic drugs may be because these drugs only mimic one portion of progesterone's actions. If, in rats, only a portion of progesterone's actions are evoked by the infusion of GABAergic drugs, then one would not expect such manipulations to elicit all the behavioral effects. Hamsters also may have both genomic and nongenomic mechanisms of progestin action in the VMH; however, this species also appears to have a required nongenomic mechanism in the VTA (12).

The effective locations of GABAergic drug infusions in rats may provide information regarding the neural circuitry of progestin-facilitated sexual receptivity in rodents. In the present study, infusions of muscimol to only the VTA were effective in facilitating receptivity. Infusions into any other midbrain site, including the central grey, were ineffective in facilitating sexual behavior in the estrogen- and progesterone-primed hamster. Previous research indicates that infusions of muscimol or GABA into the central grey facilitates lordosis quotients in estrogen-primed rats (30). However, central grey muscimol failed to facilitate sexual receptivity if estrogen-primed rats had also received progesterone. In the present experiment, there was a lack of facilitation after muscimol infusions in the VTA if coupled with muscimol infusion to some other midbrain site. This suggests that some site(s) proximate to the VTA, perhaps the CG, may have opposite, inhibitory effects on progesterone-facilitated sexual behavior in response to GABAergic stimulation. Alternately, it is possible that hamsters without any progesterone treatment would respond to muscimol infused into the central grey. This part of the brain has important connections to and from the VMH (14,30,32) and lesions of the central grey and deep tectum can inhibit lordosis in both rats and hamsters (10,34,46). Moreover, electrophysiological evidence indicates that the central grey is important for the integration of lordosis-relevant sensory stimuli in hamsters (42) and also has connections to the ventral midbrain, which is affected by progesterone administration (17).

The interaction of estrogen and progesterone priming with muscimol in the VTA for facilitation of sexual receptivity suggests two possibilities for mechanisms. It may be that GABAergic neurons are part of the neural circuitry for hormone effects on sexual receptivity and muscimol is stimulating a portion of the circuit. However, since it seems likely that progesterone acts at the membrane in the VTA (12) this interaction could be accounted for by a direct action of progestins on the $GABA_A$ receptor complex. Alternatively, progesterone could be acting via some other membrane protein. For example, progesterone can act directly on *Xenopus oocyte* membrane to induce meiotic maturation through alteration in calcium uptake (1,35). In addition, it has recently been demonstrated that another steroid, corticosterone, exerts its effects on male sexual behavior in rough-skinned newts by acting on a non-$GABA_A$ membrane binding site (36). We cannot rule out the possibility that some similar non-$GABA_A$ binding site exists in hamster VTA. If, however, progesterone exerts its actions directly on the $GABA_A$ receptor complex then it may be acting in a fashion similar to that reported for in vitro neuronal membrane preparations (24). A number of studies agree that there is a steroid recognition site with structural specificity on the $GABA_A$ complex that may be functionally coupled to the $GABA_A$ receptor (13,15,18,21).

In summary, the present research indicates that exogenous administration of muscimol facilitates progesterone-induced sexual receptivity in hamsters if it is infused into the VTA. This suggests that within the hamster midbrain, in the absence of a large population of estrogen-induced progestin receptors, progesterone might have effects on sexual receptivity via the $GABA_A$ receptor complex. Recent research indicates that the effect of the naturally occurring metabolite of progesterone, 3α hydroxy-5α-pregnan-20-one, on gonadotropin secretion is mediated via the $GABA_A$ receptor complex (4). Because our goal is to clarify how progestins normally facilitate sexual receptivity by actions on the hamster midbrain, we are currently investigating the effects of endogenous GABA upregulation and naturally occurring progestin metabolites for their ability to facilitate sexual receptivity in the hamster midbrain.

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