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Bicuculline Infused Into the Hamster Ventral Tegmentum Inhibits, While Sodium Valproate Facilitates, Sexual Receptivity

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FRYE, C. A., P. G. MERMELSTEIN AND J. F. DEBOLD. *Bicuculline infused into the hamster ventral tegmentum inhibits, while sodium valproate facilitates, sexual receptivity.* PHARMACOL BIOCHEM BEHAV **46**(1) 1–8, 1993.—Progesterone's (P) actions on both the ventral medial nucleus of the hypothalamus (VMH) and the ventral tegmental area (VTA) are essential for sexual receptivity in female hamsters. Evidence suggests that progesterone's actions in the hamster VMH may be genomic while those in the VTA may be mediated nongenomically, via $GABA_A$. Ovariectomized female hamsters were bilaterally implanted with cannulae aimed toward the VTA. One week after surgery, animals were SC injected with 10 μg estradiol benzoate (EB) and 40 h later with 200 or 500 μg P. At hour 43.5, 50 ng bicuculline, a $GABA_A$ antagonist, was infused into each available cannula. Control animals received 0.5 μl sterile saline vehicle, or no infusion. At hour 44, animals were tested for sexual receptivity in an observation arena with a sexually experienced male. Histology revealed that only animals with bicuculline infused into the VTA had reduced lordosis durations compared to controls. Other animals, primed with EB and 200 μg progesterone, showed a facilitation of sexual receptivity after infusion into the VTA of 50 μg sodium valproate, a $GABA_A$ transaminase inhibitor. These results suggest that $GABA_A$ plays a necessary role in the mechanism of progesterone's actions on sexual receptivity in hamster VTA.

Progesterone Steroid Nongenomic GABA antagonist GABA transaminase inhibitor Sexual behavior Lordosis

PROGESTOGENIC stimulation of both the ventromedial hypothalamus (VMH) and the ventral tegmental area (VTA) is critical for normal sexual receptivity in estrogen-primed female hamsters (16,38). While there is a large population of estrogen-induced progesterone receptors in the VMH (5), few such receptors have been localized to the midbrain of hamsters (35), rats (47,48), or guinea pigs (45). Other evidence also indicates that progestins do not have actions in the VTA through an intracellular receptor, as in the VMH. Instead, progestins appear to act on neuronal membranes within the VTA. For example, progesterone 3-CMO: BSA (P-3-BSA), which binds well to neuronal membranes and does not enter cells (22), has actions in the VTA that are sufficient to rapidly facilitate receptivity if progesterone has been applied to the VMH 2 h earlier (15).

A possible mechanism for these actions of progestins in the midbrain may involve $GABA_A$ receptors. This is suggested by a number of findings. $GABA_A$ receptors are known to exist on cell membranes in behaviorally relevant sites such as the VMH (36) and the VTA (2,7). Recently, progestins have been shown to modulate GABA-gated neurotransmission by allosteric action on the $GABA_A$ receptor complex (4,19, 25,29,34,40). Moreover, there appears to be a steroid recognition site on the $GABA_A$ receptor complex with structural specificity (17,18,46).

Behavioral evidence supporting the importance of the interactions of progestins and GABA for sexual receptivity is not as clear cut as the biochemical evidence. For example, in rats GABA infused into the VMH is reported to facilitate (10), inhibit (32), or have no effect (11) on sexual receptivity. Muscimol infusions have similarly been reported to facilitate (33) or have no effect (11) on sexual receptivity. However, in hamsters muscimol facilitates sexual receptivity when infused into the VTA (14). This effect is site specific and only occurs in estrogen-primed hamsters treated with at least a low dose of progesterone. These data suggest that progesterone's modulation of the $GABA_A$ receptor complex may be part of the steroid's mechanism of action in the hamster midbrain. However, the results of muscimol infusions do not clarify whether activation of the $GABA_A$ receptor complex is a necessary part of progestin's action. If bicuculline, a $GABA_A$ antagonist, can block progesterone's action, this would indicate that acti-

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vation of the $GABA_A$ receptor is essential. Thus, the present experiment attempts to further define whether GABAergic actions within the midbrain are integral for normal sexual receptivity in hamsters.

EXPERIMENT 1

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 SC 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 (31). 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). The coordinates for these cannulae were based upon a stereotaxic atlas of the hamster forebrain (30) and upon experiments showing the most effective sites for facilitating (9,37) and inhibiting (12,20,26,39) 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 200 or 500 μg progesterone. At hour 43.5, each animal had 50 ng bicuculline, dissolved in 0.5 μl sterile saline, infused into each available cannula with a Hamilton microsyringe (Hamilton Co., Reno, NV) attached by intramedic tubing to a 30-ga insert. Bicuculline 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. (Note: All animals had gained weight since the original surgery and their postoperative neurological evaluations were not different from their earlier evaluations.) After infusion and neurological evaluation, animals were observed for sexual receptivity at hour 44 by an investigator 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, latency to first lordosis, the total time spent in lordosis (TLD), and mean lordotic bout duration (MLD) were derived. The following week, animals received similar testing except the alternate dose of progesterone was given. Whether the animal initially received 200 or 500 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.

Two factors were taken into account when assigning animals to groups for statistical analysis: histological localization of infusion sites and whether animals received bilateral, unilateral, or no infusions. Although all animals received bilateral cannulae, some cannulae became blocked and were unavailable for infusions. Thus, based upon histology and infusion records animals were assigned as having infusions of bicuculline or vehicle to one of six sites: the VTA, interpeduncular nucleus (IPN), substantia nigra (SN), red nucleus (RN), central grey/central tegmentum (CG), or medial lemniscus (ML). In addition, implanted animals that received no infusion were added to the control group. Multiple analysis of variance (ANOVA) with repeated measures (SAS, SAS Institute, Cary, NC) was used to determine whether behavior varied as a function of what was infused intracranially (vehicle vs. bicuculline), bicuculline dose (50 or 100 ng), progesterone dose (200 or 500 μg), and infusion site. The general linear model ANOVA was followed by Newman-Keuls tests for differences among the means of various groups.

TABLE 1

MEANS ± SEM FOR MEASURES OF LATENCY AND MLD AFTER INTRACRANIAL INFUSION OF BICUCULLINE

Site (*n*)	Dose P (μg)	Lordosis Latency	MLD
VTA	500	313.9 ± 48.5	75.1 ± 26.6
	200	485.4 ± 33.6	7.7 ± 4.3
CG	500	183.9 ± 49.1	97.4 ± 16.7
	200	299.4 ± 49 8	76.8 ± 26.4
RN	500	28.6 ± 10.1	72.6 ± 29.7
	200	457.7 ± 142.0	35.0 ± 35.0
ML	500	88.5 ± 78.7	321.5 ± 263.8
	200	2.0 ± 2.0	175.0 ± 175.7
IPN	500	111.8 ± 50.9	90.6 ± 23.1
	200	329.4 ± 125.6	43.8 ± 34.3
SN	500	74.0 ± 74.0	155.0 ± 155.0
	200	130.0 ± 130.0	22.0 ± 22.0
Control*	500	418.4 ± 36.2	35.6 ± 10.2
	200	557.3 ± 25.4	10.7 ± 1.1

*Because the control values were not different across infusion sites, they have been pooled.

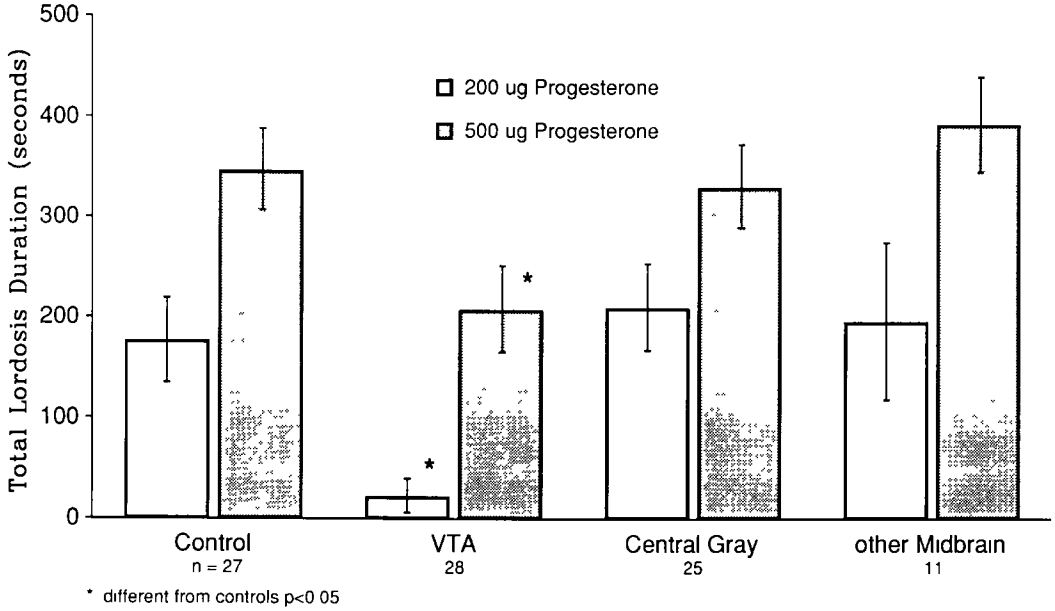

FIG. 1. Total lordosis duration in seconds, ± SE, by estrogen-primed female hamsters treated with either 200 or 500 μg progesterone after bicuculline infusion or vehicle. *Significantly reduced compared to other groups at the same dose of progesterone, $p < 0.05$.

RESULTS

The overall statistical analyses revealed that there was a significant effect of bicuculline on TLD, $F(3, 181) = 11.14$, $p < 0.01$, MLD, $F(3, 181) = 5.62$, $p < 0.01$, and latency to first lordosis, $F(3, 181) = 9.03$, $p < 0.01$. Posthoc comparisons indicated that bicuculline infusions significantly inhibited receptivity. As the purpose of this study was to assess whether bicuculline might inhibit suprathreshold progesterone-facilitated receptivity when infused specifically within the VTA, infusion records and histology were also considered. Animals were subcategorized based upon whether they received unilateral or bilateral bicuculline in addition to progesterone dose.

There were 27 control animals and 64 experimental animals each tested after EB plus 200 μg progesterone and EB plus 500 μg progesterone. Six control animals had no infusion, 5 had sterile saline infused unilaterally, and 16 had sterile saline infused bilaterally. There were no statistical differences among these control groups; therefore, they were combined. Thirty-six of the experimental animals had bicuculline infused unilaterally while 28 had bicuculline infused bilaterally. Analyses revealed that there were hormone and drug dose differences that affected TLD, $F(9, 181) = 4.71$, $p < 0.01$, MLD, $F(9, 181) = 4.49$, $p < 0.01$, and latency to first lordosis, $F(9, 181) = 3.56$, $p < 0.01$. Posthoc tests revealed that animals were more receptive after 500 μg progesterone than 200 μg progesterone: Animals with control infusions had TLDs of 347 ± 42 and 176 ± 42 s, respectively. Unilateral (mean = 35 ± 32 s) and bilateral (mean = 9 ± 5 s) bicuculline infusions attenuated receptivity almost completely in 200 μg progesterone-treated animals. With 500 μg progesterone, only those animals with bilateral (mean = 169 ± 40 s) infusions of bicuculline had significantly reduced receptivity compared to controls (mean = 347 ± 42 s). At this progesterone dose, there was an apparent, but nonsignificant, decrease in receptivity in those animals with unilateral infusions (mean = 241 ± 45 s).

All animals had either control infusions or infusions of bicuculline into the VTA ($n = 28$), CG ($n = 25$), RN ($n = 3$), ML ($n = 2$), IPN ($n = 5$), or SN ($n = 1$). Because few animals had bicuculline infusions into the RN, ML, IPN, or SN and because these infusions were uniformly ineffective (see Table 1), these sites were combined to comprise an "other" ventral midbrain group (oMes). When all animals treated with 500 μg progesterone were assigned to either the control infusion, VTA infusion, CG infusion, or other ventral midbrain group, significant differences existed for both the TLD, $F(3, 90) = 3.23$, $p < 0.02$, and the lordosis latency, $F(3, 90) = 3.98$, $p < 0.01$. Posthoc tests indicated that with 500 μg progesterone the TLD was reduced and the latency increased only when bicuculline was infused into the VTA. Infusion into the CG and other ventral midbrain sites were no more effective than control infusions.

Animals injected with 200 μg progesterone and with bicuculline infused into the VTA also showed reductions in TLD, along with increases in latency (see Table 1 and Fig. 1). Group differences (control, VTA, CG, or other ventral midbrain site) in TLD, $F(3, 90) = 5.44$, $p < 0.01$, and latency, $F(3, 90) = 3.31$, $p < 0.02$, were noted after 200 μg progesterone. The location and behavioral efficacy of all infusion sites after 200 and 500 μg progesterone doses are schematically illustrated in Figures 2 and 3.

DISCUSSION

The present findings show that bicuculline, when infused into the ventral tegmental area, can inhibit lordosis in hamsters primed with EB and 200 or 500 μg progesterone. Infu-

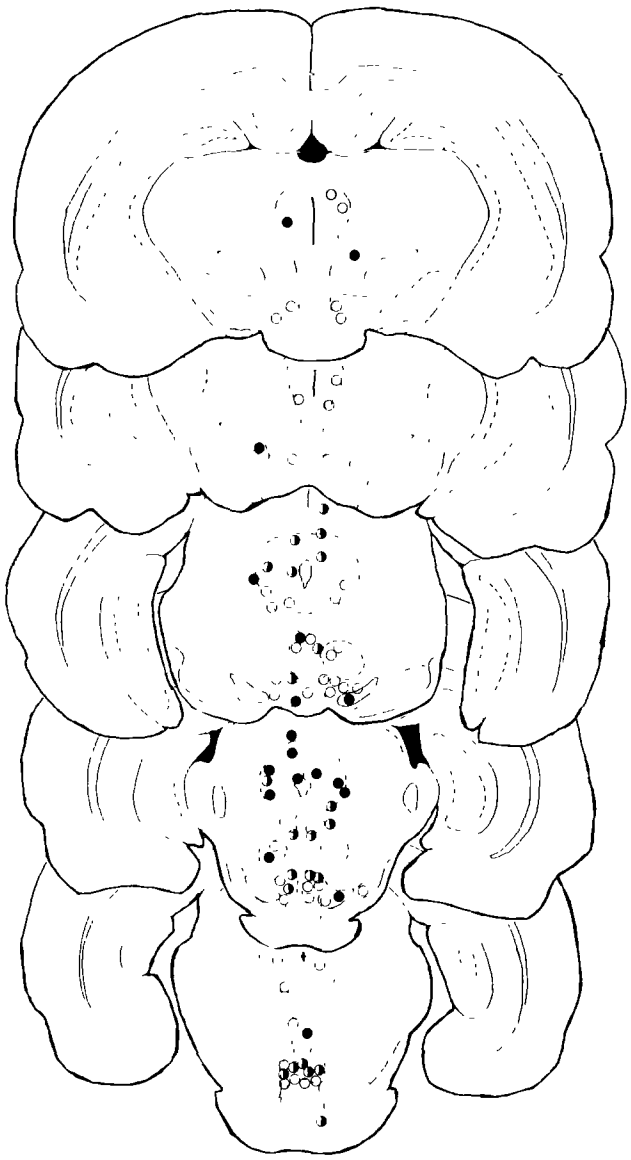

FIG. 2. Coronal sections depicting the location of bicuculline infusion sites in unilaterally and bilaterally infused estrogen-primed female hamsters with 200 μg progesterone. (●), infusion sites associated with total lordosis duration (TLD) over 250 s; (◑), sites with TLD > 0 but < 250 s; (○), sites in animals that showed no lordosis.

sions of bicuculline into other ventral midbrain sites did not significantly alter receptivity. A comparison of the effects of unilateral vs. bilateral bicuculline infusions into the VTA suggests that more bicuculline is necessary to reduce the effect of greater amounts of progesterone. These results further suggest that $GABA_A$ receptors in the VTA play a necessary role in the behavioral effects of progesterone in female hamsters.

EXPERIMENT 2: VALPROIC ACID

Because the GABAergic antagonist bicuculline was effective at inhibiting lordosis duration, it is of interest to assess the effects of another GABAergic manipulation. The purpose of the following experiment is to determine whether sodium valproate, a GABA-transaminase inhibitor, will facilitate lordosis when infused into the VTA. Valproate is an indirect agonist (8,27) that increases endogenous GABA concentrations within the synaptic cleft by blocking GABA metabolism. It is expected that if progestins work via the GABAergic system valproic acid should facilitate low-dose progesterone receptivity.

METHOD

The same method as in the previous experiment was followed with the following modifications. One week after unilateral cannula implantation (AP = −2.8, ML = 0.3, DV

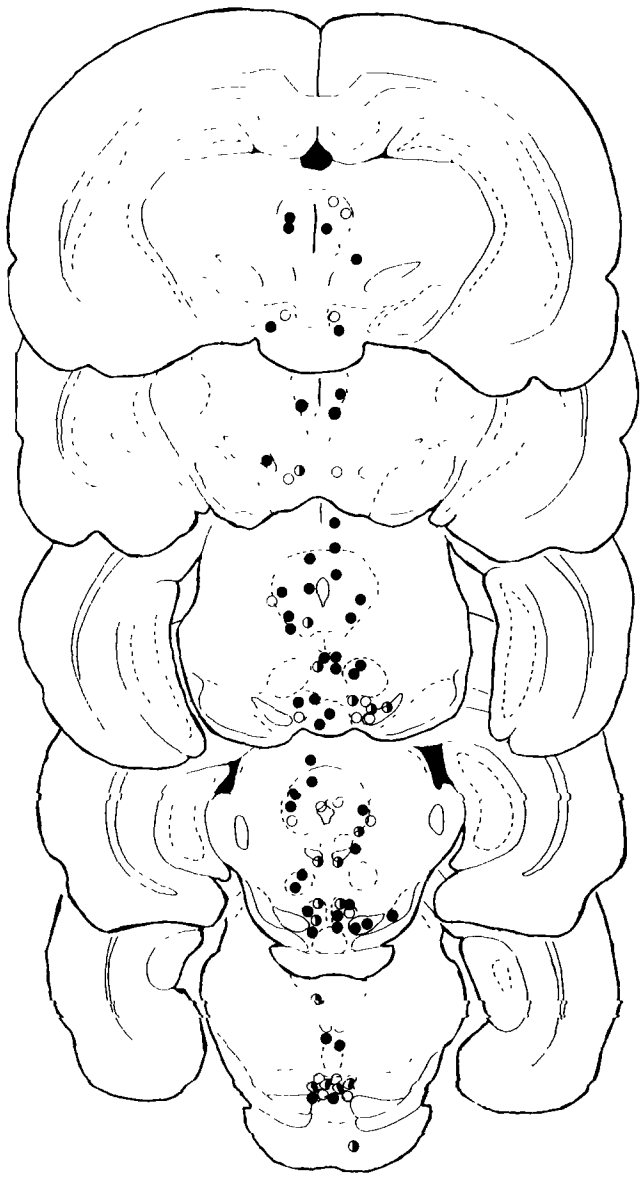

FIG. 3. Coronal sections depicting the location of infusion sites in unilaterally and bilaterally bicuculline infused estrogen-primed female hamsters with 500 μg progesterone. (●), infusion sites associated with total lordosis duration (TLD) over 250 s; (◑), sites with TLD > 0 but < 250 s; (○), sites in animals that showed no lordosis.

= −7.8), animals were injected with 10 μg EB and then, 44 h later, with 200 μg progesterone. Subjects were neurologically examined before progesterone injection as in Experiment 1. Four hours after progesterone, the insert was removed and 0.5 μl 0.9% saline infused into the cannula at 0.1 μl/10 s through an injection needle the same length and thickness as the insert. The test for sexual receptivity began 10 min after infusion. The following week, this protocol was repeated, except that 50 μg/0.5 μl valproate was infused into the cannula. The order of saline and valproate infusions was not counterbalanced because valproate can have long-lasting effects.

After the second week of testing, animals were perfused intracardially with 0.9% saline solution followed by 10% formalin. A multiple ANOVA model, taking into account repeated measures, was used to analyze TLD, latency, and MLD. Significant differences between subjects were further evaluated with Duncan's multiple-range tests (SAS). Within-subjects *t*-tests on infusion site determined quantitative differences between administration of saline and valproate. Qualitative trends were determined using the sign test (42).

RESULTS

Subjects were separated into one of six groups following verification of cannula placement (see Fig. 4). These groups consisted of animals with infusions into the VTA (n = 14), SN (n = 11), RN (n = 7), pontine nuclei (PN) (n = 21), central gray/central tegmentum (n = 6), or other mesencephalic sites (n = 16). The last group represents the aggregation of the sites with four or fewer animals and levels of behavior that were not significantly different. Although there was no main effect of valproate on TLD, $F(1, 69) = 2.63$, n.s., or main effect of site, $F(5, 69) = 1.94$, n.s., there was a significant interaction between valproate and site of administration on TLD, $F(5, 69) = 2.72$, $p < 0.05$. Posthoc tests revealed between site differences: Animals with valproate infused into the VTA, PN, and CG all had significantly longer TLDs than those with infusions into the RN ($p < 0.05$). VTA subjects also had significantly longer TLDs compared with subjects with cannulae in the SN. CG subjects exhibited significantly higher TLDs than SN and other mesencephalic (oMes) subjects. There were no site-dependent differences after saline infusion. There were also no significant effects of valproate on lordosis latency or MLD. Means and standard errors for these measures, separated by site, are listed in Table 2.

t-Tests examining the difference between saline and valproate effects on TLD within subjects indicated valproate in the CG significantly enhanced receptivity ($t = 2.63$, $p < 0.05$). Valproate also increased sexual receptivity when infused into the VTA ($t = 2.07$, $p < 0.06$) and PN ($t = 2.02$, $p < 0.06$). No differences were recorded for the SN ($t = 0.04$, n.s.), RN ($t = 1.78$, ns), or oMes ($t = 1.17$, n.s.).

Using nonparametric statistics to examine the direction of effects, valproate within the VTA significantly lengthened TLD (sign test, $p < 0.02$). This is due to valproate increasing TLDs in 12 of 14 VTA animals. The effect of infusions of valproate into any other site were not significantly different from vehicle infusions using this criteria (sign test, n.s.) (see Fig. 5).

Nineteen animals that received infusions of saline but had guide cannulae that had become blocked by the second week served as controls for differences between testing sessions. Within-subjects *t*-test found no evidence for differences in these animals' behavior between test sessions ($t = 0.32$, n.s.). In addition, all animals that were tested for receptivity had normal performance on their neurological evaluations.

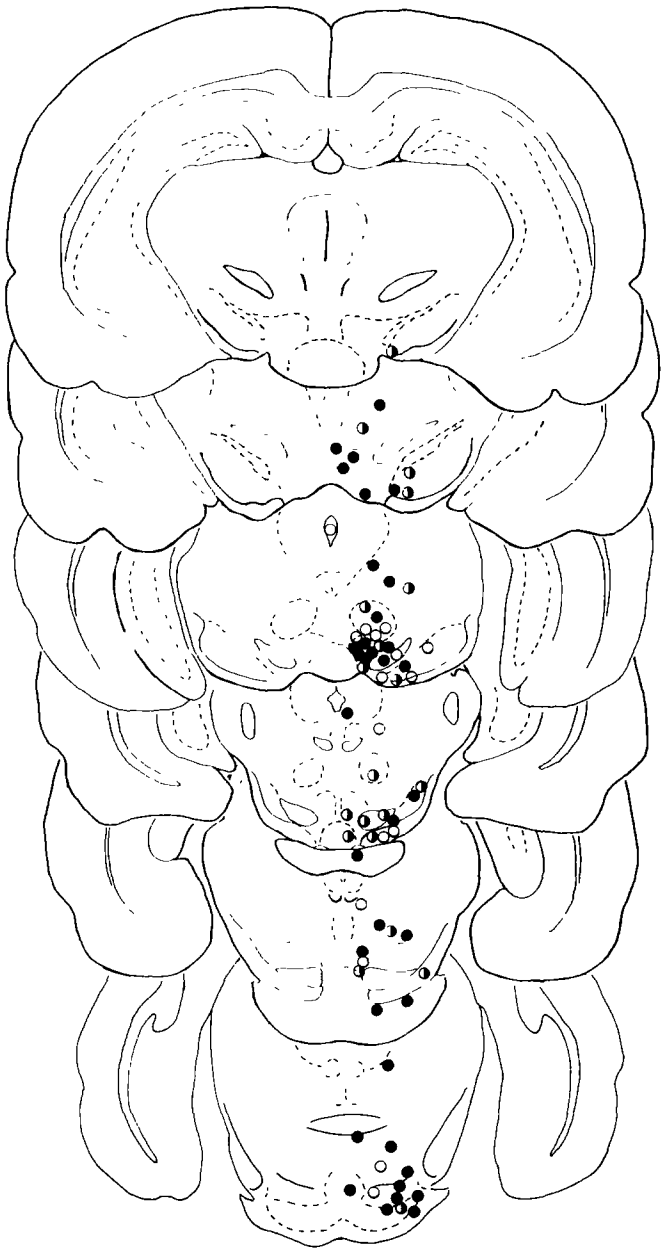

FIG. 4. Analyses of cannula placement using coronal sections of hamster brain. (○), injection sites where sodium valproate lowered the total lordosis duration (TLD) by more than 25 s; (◑), change in TLD of 25 s or less between saline and sodium valproate infusions; (●), injection sites where sodium valproate infusions raised TLDs by more than 25 s.

GENERAL DISCUSSION

Infusion of sodium valproate varied in its ability to modify measures of sexual receptivity, dependent upon site. Results of the two experiments were congruent in that bicuculline infusions into the VTA inhibited lordosis and valproate infusions into the VTA increased receptivity. Valproate's action to increase endogenous GABA activity within the VTA, result-

TABLE 2

MEANS ± SEM FOR MEASURES OF TOTAL LORDOSIS DURATION (TLD), LORDOSIS LATENCY, AND MEAN LORDOSIS DURATION (MLD) AFTER INTRACRANIAL INFUSION OF SALINE AND SODIUM VALPROATE

Infusion Site	Drug	TLD	Lordosis Latency	MLD
VTA	Saline	310.9 ± 67.0	211.0 ± 69.2	111.3 ± 38.8
	Valproate	399.6 ± 55.2	82.4 ± 35.8	143.4 ± 43.6
PN	Saline	201.9 ± 46.9	266.9 ± 59.4	74.7 ± 29.9
	Valproate	311.4 ± 55.5	187.3 ± 52.4	134.3 ± 38.2
SN	Saline	187.0 ± 71.5	326.9 ± 85.3	111.8 ± 66.0
	Valproate	183.2 ± 75.5	299.3 ± 80.2	81.8 ± 50.4
RN	Saline	280.5 ± 98.0	115.0 ± 82.0	50.3 ± 16.6
	Valproate	87.5 ± 67.8	368.6 ± 91.1	14.7 ± 8.7
CG	Saline	267.3 ± 102.2	163.8 ± 90.6	84.2 ± 38.8
	Valproate	512.1 ± 42.4	33.0 ± 13.9	231.7 ± 84.1
oMes	Saline	181.0 ± 55.7	310.4 ± 64.5	71.3 ± 37.0
	Valproate	227.8 ± 55.3	183.7 ± 49.8	85.2 ± 35.8

ing in longer TLDs, is also consistent with muscimol's ability within the VTA to facilitate sexual receptivity (14). Moreover, these data together suggest that changes in GABA in the hamster ventral midbrain may be an integral part of the mechanism of progesterone's actions for facilitating receptivity.

The effect of valproate on sexual receptivity was not as robust as the effects seen in the muscimol and bicuculline studies. For example, valproate infusions into the VTA caused a smaller increase in TLD than did muscimol infusions (14). There are several possible explanations for this outcome. First, 50 μg valproate may not be the ideal dose to maximize endogenous GABA levels when infused into hamster VTA. The choice of this dose was based upon effective intracranial infusion doses of valproate in rats (23,24). Because hamsters are known to differ from rats in their response to, and metabolism of, many drugs (6,21), it is possible that 50 μg was not a sufficient dose to increase GABA activity fully in the hamster VTA. In addition, this experiment did not assess the diffusion of either bicuculline or valproate from the infusion site, nor did it assess whether these two drugs, at two different doses, diffused differentially. Second, the doses of progesterone used in this experiment were higher than those used with muscimol. Muscimol infused into the hamster VTA facilitated sexual receptivity when given with threshold doses of progesterone (25

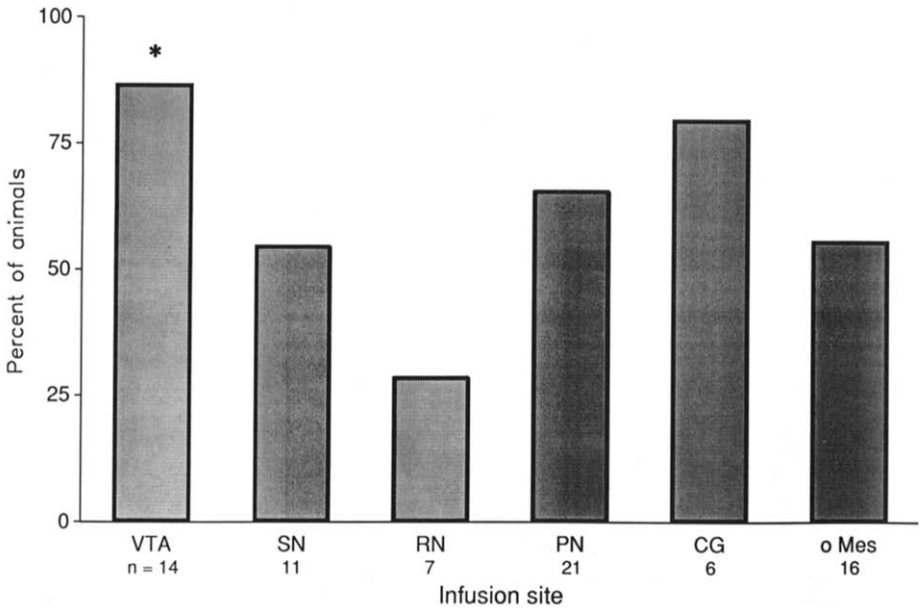

FIG. 5. Enhancement of total lordosis duration (TLD) by intracranial infusion of sodium valproate (50 μg) into specific hamster brain regions. Animals with sodium valproate infused into the VTA more consistently showed an increase in TLD over their saline values than animals with valproate administration to other sites ($p < 0.02$).

and 100 μg) (14). In the present study, 200 μg progesterone was used to be comparable to a dose used for inhibition of receptivity by bicuculline. This 200-μg dose of progesterone facilitated receptivity in the saline condition such that it may have been difficult to achieve a large increase in sexual behavior.

The facilitation of sexual receptivity when valproate was infused into brainstem areas other than the VTA (CG and PN) was unexpected. Infusions of muscimol and bicuculline into the central grey region had no effect on sexual behavior in the hamster (14). However, unlike these $GABA_A$-specific drugs, valproate increases GABA concentrations that can then act at both $GABA_A$ and $GABA_B$ receptors. These two classes of receptor may be, in some cases, associated with different circuitry (44). In addition, $GABA_A$- and $GABA_B$-specific drugs have different effects on sexual behavior (1,28). The effect of valproate in the hamster CG and PN may reflect increased $GABA_B$ activity or the result of simultaneous stimulation of $GABA_A$ and $GABA_B$.

The present study is part of a series of experiments attempting to ascertain whether progestins have behaviorally relevant effects on GABA-sensitive neurons. More specifically, is interaction of progestins with the $GABA_A$ receptor complex in the hamster VTA essential for female sexual behavior? Consistent with our hypothesis, hamsters require at least threshold progestogenic stimulation in the ventral midbrain for GABA facilitation of sexual receptivity (14); GABAergic drugs are not progesterone mimetic. Further, progestins active at the $GABA_A$-benzodiazepine complex, which do not bind to the intracellular progestin receptor, such as 3α-OH-DHP and 5α-THDOC (3,4,41,43), have facilitatory effects on hamster sexual behavior when implanted into the VTA (13), whereas progestins not potent at the GBR, like 5β-THDOC, are ineffective at facilitating sexual behavior.

In sum, infusions of the $GABA_A$ antagonist bicuculline into the VTA inhibit suprathreshold progesterone-induced receptivity, while endogenous increases in GABA with valproate facilitate sexual receptivity. These findings are consistent with the GABAergic neurotransmitter system being an important component of progestin action in the hamster midbrain. The precise manner in which progesterone and GABA interact in the hamster VTA to promote sexual receptivity is currently being investigated.

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