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Role of glutamate receptors in the ventromedial hypothalamus in the regulation of female rat sexual behaviors II. Behavioral effects of selective glutamate receptor antagonists AP-5, CNQX, and DNQX

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Abstract

Bilateral infusions of glutamate or its selective ionotrophic receptor agonists to the ventromedial hypothalamus (VMH) produce a rapid inhibition of both appetitive and consummatory sexual behavior in hormone-primed female rats. The present study examined whether infusion of selective ionotrophic glutamate receptor antagonists to the VMH can facilitate female sexual behavior in females treated with estradiol benzoate (EB) and progesterone (P), or EB alone. Ovariectomized, sexually experienced female rats were implanted bilaterally with guide cannulae aimed at the ventrolateral VMH. After recovery from surgery, females were primed either with EB + P or EB alone, and infused with saline, or one of two doses each of AP-5 (to target NMDA receptors), CNQX, or DNQX (to target AMPA/kainate receptors), immediately before tests with sexually vigorous male rats in bilevel chambers. In general, the drug infusions had a more powerful effect in females primed with EB alone compared to females primed with EB + P. AP-5 increased lordosis in females primed with EB alone. CNQX had a similar facilitative effect on lordosis, and also increased solicitations. DNQX increased solicitations in both hormone-priming conditions, increased lordosis quotients and magnitudes, and decreased pacing and defensive responses in the EB-alone condition. These results indicate that antagonism of glutamate receptors in the VMH resembles the effect of P, and that the addition of P to an EB baseline eliminates most of the effects of glutamate receptor antagonists. These data support the notion that glutamate receptors in the VMH contribute a strong inhibitory influence in the control of female sexual behavior.

Keywords: Glutamate; Antagonists; VMH; Lordosis; Appetitive; Copulation; Estrogen; Progesterone

1. Introduction

The sexual responses of female rats includes both appetitive (attractive, proceptive), and consummatory (e.g., proceptive, receptive) behaviors that are regulated by the sequential actions of estrogen (E) and progesterone (P) (Beach, 1976; Erskine, 1989; Pfaus et al., 1999; Whalen, 1974). These behaviors include solicitations and hops and darts that stimulate males to mount, pacing behaviors that regulate the initiation and timing of sexual interaction, lordosis, the arching of the back that denotes sexual receptivity to vaginal penetration, and defensive rejection responses used to pace copulation or terminate sexual interaction altogether. Hormonal priming with E is necessary for the activation of lordosis in response to flank or perineum stimulation by the male, whereas the addition of P activates lordosis to maximal levels while also stimulating appetitive responses, such as solicitation and hops and darts. Priming with P also reduces rates of pacing and rejection responses.

The ventromedial hypothalamus (VMH) is critical for the hormonal modulation of the female receptive reflex lordosis, in addition to other appetitive and consummatory female sexual behaviors. Cells in the VMH, and particularly the ventrolateral (vl) region, concentrate both E and P (Pfaff and Keiner, 1973; Rubin and Barfield, 1983a). Although collective evidence from lesion, electrical stimulation, and neurochemical studies indicates that the VMH contains neural mechanisms that facilitate sexual behavior (Dörner et al., 1968; Pfaff, 1980;

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Rubin and Barfield, 1983b), there is also evidence that the neuronal excitatory agent glutamate, or its receptor agonists, inhibits both appetitive and consummatory sexual behaviors (Kow et al., 1985; Georgescu and Pfaus, in press; McCarthy et al., 1991). In those studies, different doses of glutamate or its receptor agonists kainate, AMPA, or NMDA, were infused to the vlVMH of animals primed acutely with estradiol benzoate (EB) and P (Georgescu and Pfaus; McCarthy et al.) or chronic EB alone (Kow et al.). The overall pattern of inhibition included decreases in lordosis, solicitation, and hops and darts, with concomitant increases in pacing and rejection responses. This is reminiscent of the pattern displayed when female rats drop out of sexual heat, during estrous termination. Estrous termination is facilitated by vaginocervical stimulation (VCS) provided either by multiple intromissions by the male, or by manual stimulation with a lubricated glass rod (Lodder and Zeilmaker, 1976; Pfaus et al., 2000), and we have recently found that VCS activates Fos protein selectively in glutamate cells of the vlVMH (Georgescu et al., submitted for publication), an action that is *inhibited* by treatment with EB and P (see also Pfaus et al., 1996). This finding suggests that ovarian steroids blunt the ability of VCS to activate glutamate neurons in the VMH. This action could serve to assure that a requisite amount of VCS is achieved in order to stimulate neuroendocrine changes that support pregnancy. It may also be the case that for ovarian steroids to induce a full complement of appetitive and consummatory sexual behavior in female rats, this system needs to be inhibited.

The present study examined the effects of infusions of selective competitive antagonists of NMDA, AMPA and kainate receptors (2-amino-5-phosphonopentanoic acid (AP-5) for the NMDA receptor, 6,7-dinitroquinoxaline-2,3-dione (DNQX) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) for the AMPA/kainate receptors) to the vlVMH on appetitive and consummatory sexual behaviors in ovariectomized (OVX) females primed with either EB+P or EB alone. Given the effects of glutamate and its selective receptor agonists in our previous study, we hypothesized that glutamate receptor antagonists may facilitate sexual behaviors in a manner similar to P.

2. Methods

2.1. Subjects

Twenty sexually naive female Long–Evans rats, weighing 200 to 250 g, were purchased from Charles River Canada, Inc., St-Constant, QC. Females were housed in groups of four in hanging wire gang cages, but following cannula implantation the females were housed individually in Plexiglas cages with wood-chip bedding. The colony rooms were maintained on a reversed 12:12 h light/dark cycle (lights off at 08:00 h) at approximately 21 °C with food and water continuously available.

Twenty Long–Evans males from the same breeder were used as conspecific stimuli. The males received a minimum of 10 prior sexual experiences with receptive females before use, and all were sexually vigorous copulators. The males were housed in groups of 4 in hanging wire-mesh cages in the same colony room.

All animal procedures conformed to the guidelines of the Canadian Council for Animal Care and were approved by the Concordia University Animal Research Ethics Committee.

2.2. Surgery

2.2.1. Ovariectomy

Females were OVX bilaterally through lumbar incisions following anesthesia induced by ketamine hydrochloride (50 mg/ml) and xylazine hydrochloride (4 mg/ml), mixed in a ratio of 4:3 respectively and injected intraperitoneally in a volume of 0.8 ml/kg. All OVX rats were given a week of post-surgical recovery before behavioral testing.

2.2.2. Cannula implantation

Females were anesthetized with sodium pentobarbital (65 mg/kg) injected i.p. Females were then implanted bilaterally with double 26-gauge guide cannulae aimed at the vlVMH using a Kopf stereotaxic instrument. Stereotaxic coordinates were relative to Bregma and implants were made with the head tilted upward at a 5° angle: A-P: 0 mm; M-L: ±1 mm; and D-V: −8.5 mm ventral to dura. The tips of the guide cannulae ended 1 mm above the desired target area. Cannula blockers were cut so that they would protrude 0.5 mm from the guide cannula. The 33-gauge infusion cannulae were cut 1 mm longer than the guide cannulae. Guide cannulae, cannulae blockers, injection cannulae, and dust caps were obtained from Plastics One (Roanoke, VA). Females were given 7 days of post-surgical recovery before testing.

2.3. Hormone and drug administrations

Full sexual receptivity was induced in females by subcutaneous injections of EB (10 μg/0.1 ml reagent grade sesame oil) 48 h, and P (500 μg/0.1 ml of sesame oil) 4 h before each test. Steroids were obtained from Steraloids (Hanover, NH). Partial receptivity was induced by injections of the same dose of estradiol benzoate alone, 48 h before each test.

Drugs were infused bilaterally in a volume of 1 μl/side using an infusion pump (Harvard apparatus, Pump 22) set at a rate of 1 μl/2 min as in Kow et al. (1985). Infusion cannulae were left in place for another 1.5 min to promote absorption. Desired concentrations of AP-5 (50 or 100 mM; DiCiano and Everitt, 2001; Park et al., 2002), CNQX (2.17 or 5.0 mM; Alvarez and Ruarte, 2001; Park et al., 2002), and DNQX (20 or 100 nM; Roullet et al., 2001) were obtained by diluting the drugs in 0.1 M phosphate buffer (pH=7.0). Physiological saline was used as a control, and was made in 0.1 M phosphate buffer (pH=7.0) and infused in a volume of 1 μl/side. All drugs were obtained from Sigma (St. Louis, MO).

2.4. Behavioral testing

All females were primed with EB+P and received 10 sexual training tests with sexually experienced males at 4-day

intervals prior to the study. All training tests were 30 min in duration and were conducted in bilevel chambers (Pfaus et al., 1999) during the middle third of the rats' dark cycle so that females would have stable baselines of sexual responding prior to drug infusions. After the 10th training trial, females were implanted with guide cannulae and allowed 8 days of surgical recovery. However, females were primed with either EB alone ($n=10$) or EB+P ($n=10$) twice during this period prior to the resumption of behavioral testing. Four hours after the second P priming for the EB+P group, females in both the EB-alone, and EB+P groups received an infusion of saline, after which they were transferred to the bilevel chambers for a 30-min infusion baseline test of sexual behavior with a sexually vigorous male. This test served as the baseline infusion control for all drug tests. During the next 3 tests run at 4-day intervals, females were assigned randomly to one of two doses of each of the three drugs, ($n=10$/group). Assignment to drug and dose groups was done using a Latinized block design so that rats would not receive one type of drug or dose after another.

All behavioral tests were videotaped and scored subsequently using a computerized event recorder customized for female sexual behavior (Cabilio, 1996). Behavioral data from the first ejaculatory series (from the introduction of the female into the bilevel chamber to the first ejaculation of the male, or the entire 30-min testing period if ejaculation did not occur) were scored, along with the total number of ejaculations received by females during each 30-min test, as in our previous study (Georgescu and Pfaus, 2006-this issue). Behaviors included the frequency of solicitations (characterized by a head-wise orientation of the female towards the male followed by a quick runaway), hops and darts, pacing (frequency of level changes), and rejection responses (boxing, fighting, kicking and prone defensiveness). Lordosis (the dorsoflexion of the back that characterizes sexual receptivity) was analyzed as a lordosis-to-mount quotient (LQ) and a reflex magnitude (LM, on a 1 to 3 scale, as in Hardy and Debold, 1971), along with the frequency of each magnitude. Finally, the total number of ejaculations received by females during each 30-min test was scored and used as a measure of male reactivity to the females (Landau and Madden, 1983).

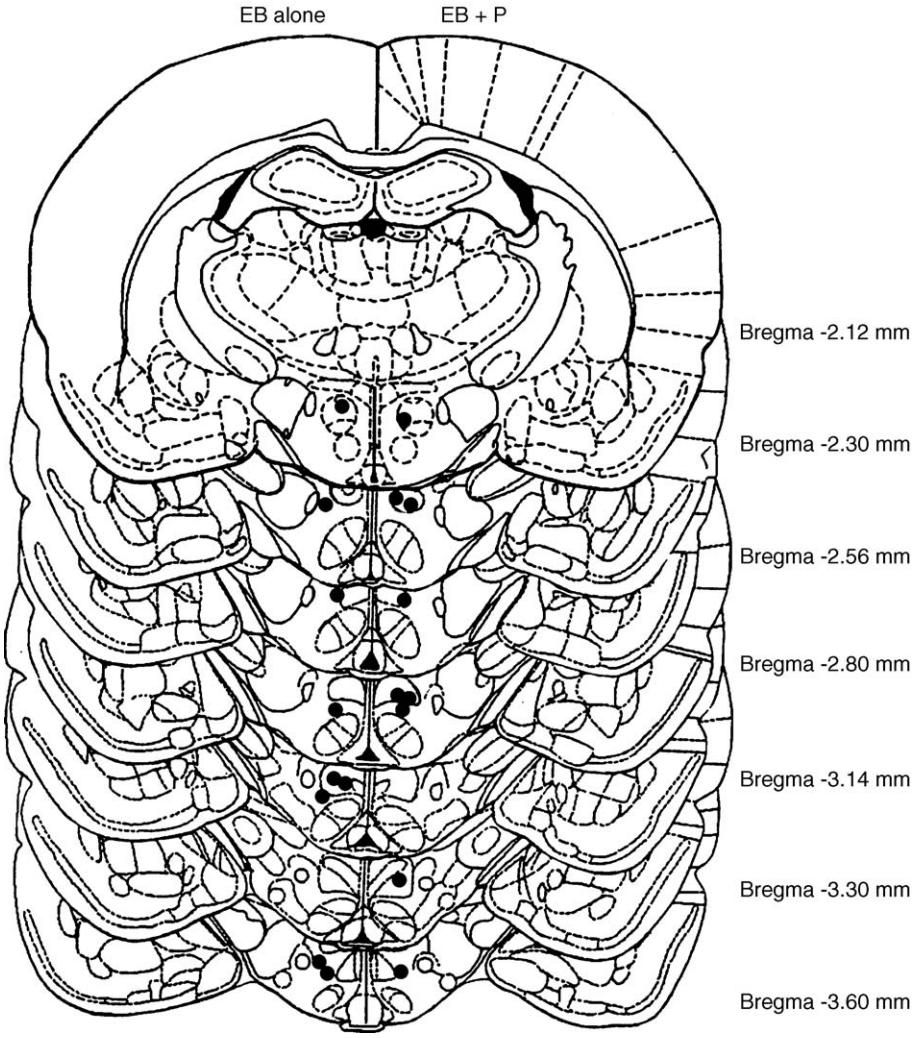

Fig. 1. Guide cannula placements in the present experiments according to the atlas of Paxinos and Watson (1998). Placements for animals primed with EB alone are depicted on the left and EB+P on the right. Dots depict the end of the guide cannula. Injection cannula extended 1 mm below the tip of the guides.

2.5. Perfusions and histology

Once the final behavioral tests were concluded, females were sacrificed by overdose of sodium pentobarbital (120 mg/kg) in order to verify proper cannulae placement. They were perfused intracardially using a 50 ml syringe filled with ice-cold phosphate-buffered saline followed by 50 ml of 4% paraformaldehyde in 0.1 M phosphate buffer. Brains were removed and placed in a 4% paraformaldehyde solution for 4 h, and then into a 30% sucrose solution overnight. Brains were then blocked around the area of the anterior hypothalamus, mounted on a chuck, and sliced into coronal sections using a cryostat. Sections were mounted on gel-coated slides, stained in cresyl violet, coverslipped, and examined under a microscope to confirm cannulae placements. Animals that had guide cannula tracks ending outside the anterior or posterior boundaries of the VMH or more than 1 mm dorsal to it were excluded from data analysis ($n=1$/hormone treatment group), leaving 9 rats in each hormone treatment condition. Of these, approximately half had cannula tracks that were observed bilaterally, whereas for the other half we could confirm a cannula track only on one side. We retained these animals for data analysis. Cannula placements are depicted in Fig. 1 for animals primed with EB+P or EB alone.

2.6. Statistical analyses

Separate 2 (dose)×2 (treatment: drug vs. saline) analyses of variance (ANOVAs) were conducted with dose as a between-measures variable and treatment as a repeated-measures variable for all sexual behaviors in each hormone condition (EB+P or EB alone). In each case, the saline trial served as the baseline measure to which drug measures were compared. For each significant interaction, Tukey post hoc comparisons of the individual means were conducted, $P<0.05$.

3. Results

3.1. General observations

No unusual behaviors were observed and females did not require any special handling following infusions of AP-5, CNQX, or DNQX.

3.2. Effects of AP-5

Fig. 2 shows the effects of infusions of saline and 2 doses of AP-5 to the VMH on female sexual behaviors and male ejaculatory responses in females primed with EB alone or EB+P. In EB-primed females, the ANOVA detected a significant main effect of treatment only on LQs, $F(1,16)=12.86$, $P<0.01$, relative to saline. Post hoc comparisons revealed that animals displayed significantly greater LQs overall when infused with AP-5 compared to saline. In females primed with EB+P, infusions of AP-5 had no effect on any behavioral measures compared to saline.

3.3. Effects of CNQX

Fig. 3 shows the effects of infusions of saline and 2 different doses of CNQX administered to the VMH on female sexual behaviors and male ejaculatory responses in females primed with EB alone or EB+P. Overall, in EB-primed females, infusions of CNQX increased the number of solicitations (treatment: $F(1,15)=3.67$, $P<0.05$), LQs (treatment: $F(1,15)=5.56$, $P<0.05$; dose: $F(1,15)=29.80$, $P<0.001$; interaction: $F(1,15)=7.49$, $P<0.05$), LMs (treatment: $F(1,12)=11.57$, $P<0.01$), and the number of ejaculations by the males (treatment: $F(1,15)=11.51$, $P<0.01$), but had no effect on other behaviors. In females primed with EB+P, infusions of CNQX increased the number of solicitations (dose: $F(1,16)=5.69$, $P<0.05$), but had no effect on other behaviors.

3.4. Effects of DNQX

Fig. 4 shows the effects of infusions of saline and 2 different doses of DNQX administered to the VMH on female sexual behaviors and male ejaculations in females primed with EB alone or EB+P. In EB-primed females, infusions of DNQX increased the number of solicitations (treatment: $F(1,15)=6.67$, $P<0.05$), hops and darts (dose: $F(1,15)=15.41$; interaction: $F(1,18)=5.2$, $P<0.05$), LQs (treatment: $F(1,14)=57.48$, $P<0.001$), LMs (treatment: $F(1,15)=11.52$, $P<0.01$; interaction: $F(1,13)=13.54$, $F<0.01$), and the number of ejaculations by the males (treatment: $F(1,15)=11.44$, $P<0.01$). DNQX also decreased the frequency of level changes (treatment: $F(1,15)=4.26$, $P<0.05$). In females primed with EB+P, infusions of DNQX increased the number of solicitations (dose: $F(1,15)=4.28$, $P<0.05$), and decreased the frequency of level changes (treatment: $F(1,15)=9.77$, $P<0.01$) and defensive behaviors (treatment: $F(1,15)=4.74$, $P<0.05$). DNQX had no effect on other behaviors in females primed with EB+P.

4. Discussion

The present results show that selective glutamate receptor antagonists facilitate appetitive and consummatory measures of sexual behavior following infusions to the VMH. These effects were most pronounced when a low level of sexual functioning was induced by hormonal priming with EB alone, but some appetitive effects were still evident when sexual functioning was high due to full hormonal priming with EB+P. These effects were generally opposite to those induced by infusions of selective glutamate receptor agonists to the VMH in our previous study (Georgescu and Pfaus, in press) and support the idea that glutamate transmission in the VMH, and in particular the activation of AMPA/kainate receptors, inhibits both appetitive and consummatory aspects of sexual behavior in the female rat, while increasing the activation of pacing and defensive behaviors.

The NMDA receptor antagonist AP-5 increased lordosis, but had no significant effect on other measures of sexual behavior.

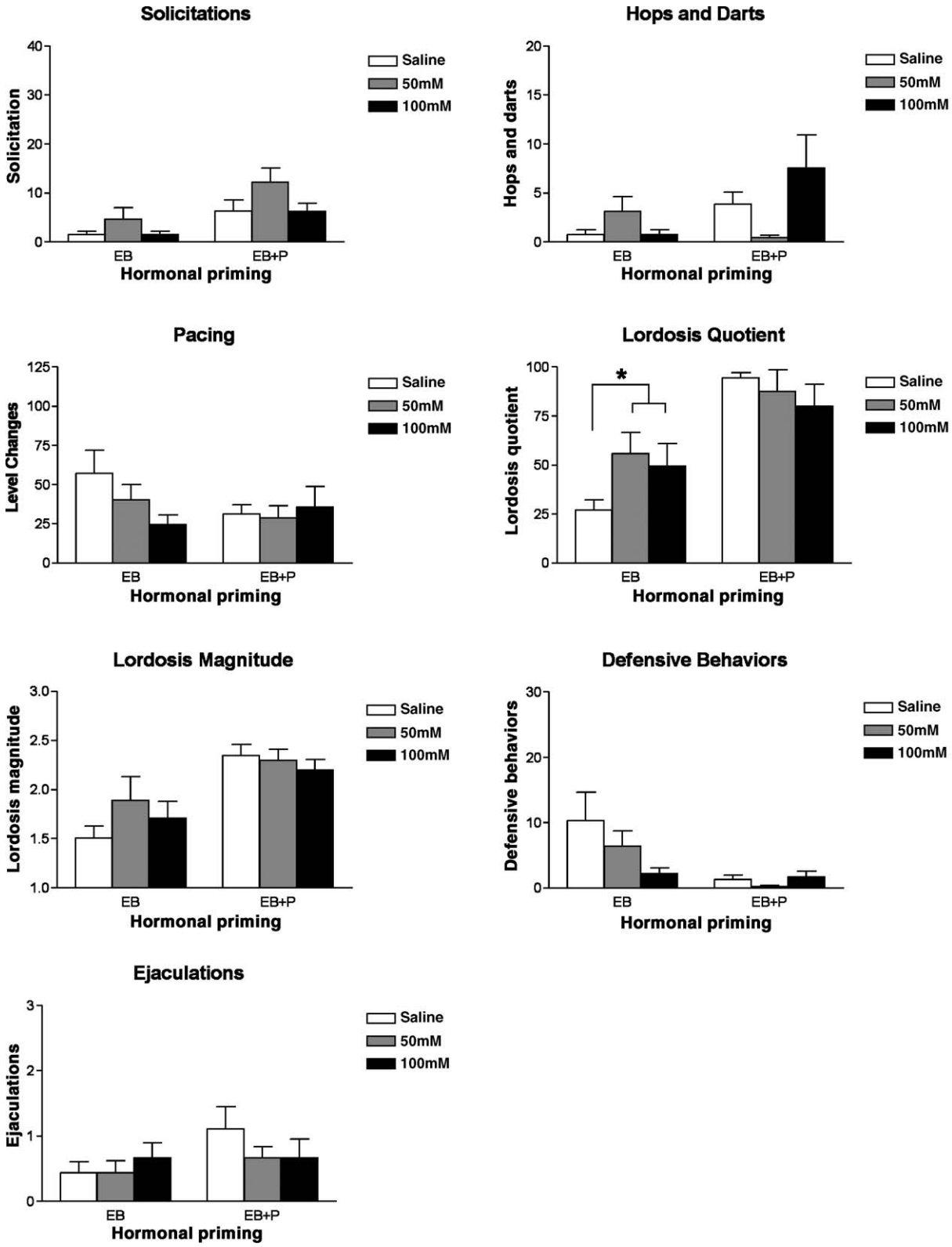

Fig. 2. The effect of AP-5 or saline infusions on the number of solicitations, hops and darts, level changes, lordosis quotient and magnitude, defensive behaviors, and male ejaculations. Data are means+S.E.M. $*P<0.05$, main effect of drug vs. saline.

Infusions of NMDA to the VMH decrease lordosis quotients and reflex magnitudes (Georgescu and Pfaus, in press; McCarthy et al., 1991), and also increase pacing and rejection responses (Georgescu and Pfaus, in press). Similar to the findings reported here, McCarthy et al. did not find a significant effect of AP-5 infusions to the VMH of ovariectomized females primed fully with EB and P, although a significant increase in lordosis was observed in the present study in females primed

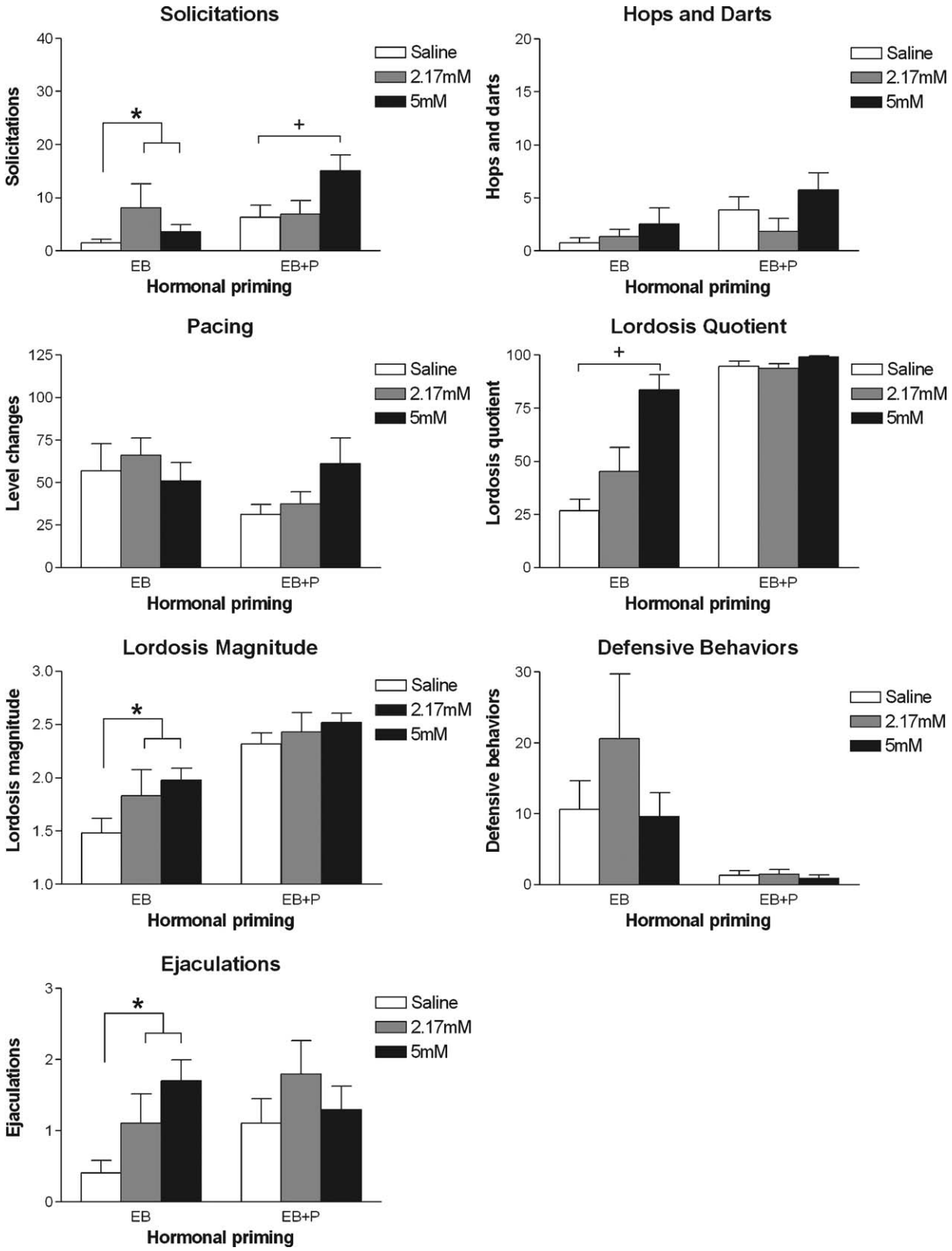

Fig. 3. The effect of CNQX or saline infusions on the number of solicitations, hops and darts, level changes, lordosis quotient and magnitude, defensive behaviors, and male ejaculations. Data are means+S.E.M. *$P<0.05$, main effect of drug vs. saline. $^{+}P<0.05$, post hoc Tukey test of the individual dose vs. saline.

with EB alone. Taken together, these findings suggest that the primary role of NMDA receptors in the VMH is to control lordosis, with secondary effects on the pacing of intromissions.

Infusions of the AMPA/kainate receptor antagonist CNQX produced a progesterone-like effect on lordosis quotients in E-primed females: when infused with the large dose of CNQX,

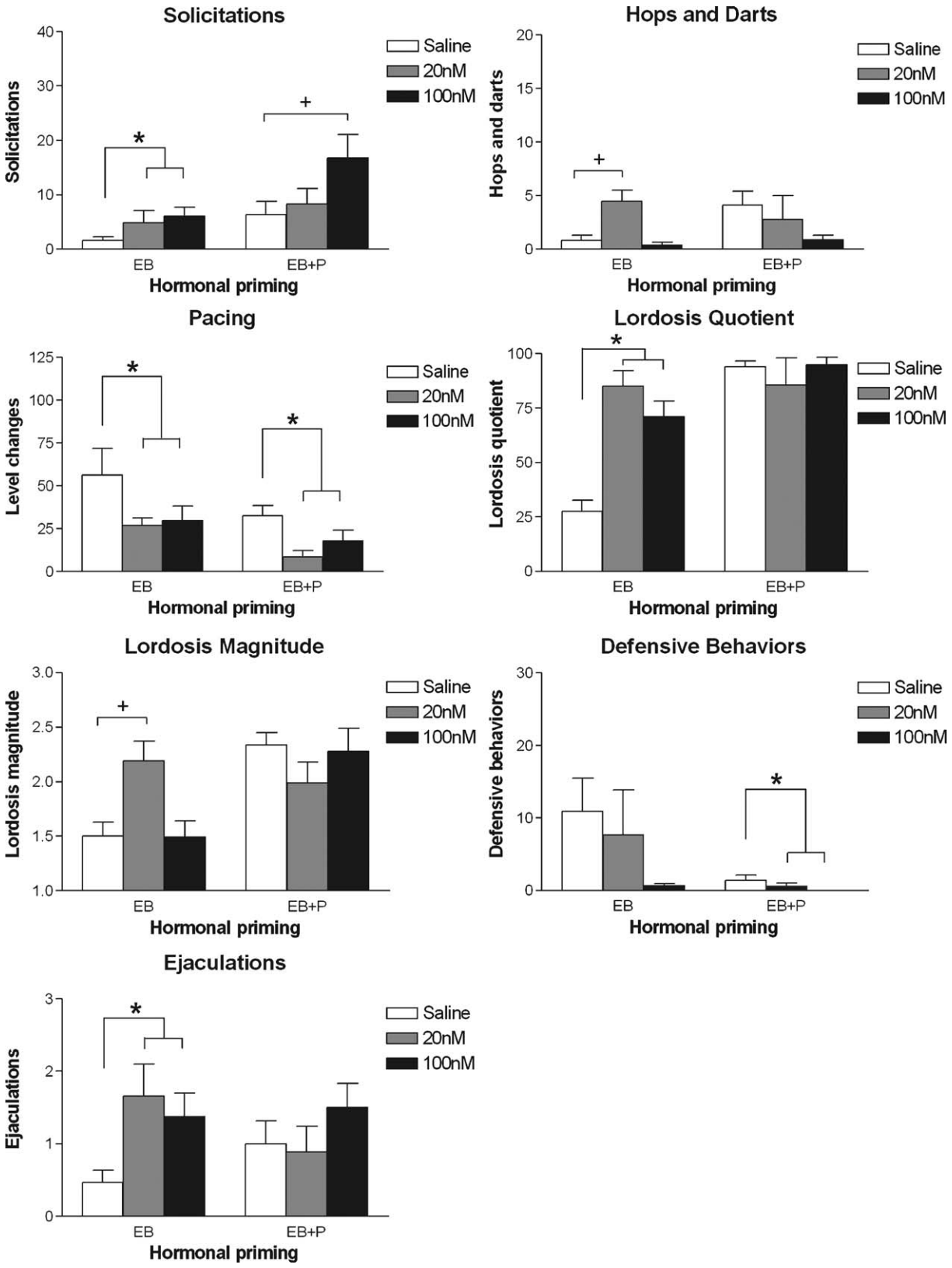

Fig. 4. The effect of DNQX or saline infusions on the number of solicitations, hops and darts, level changes, lordosis quotient and magnitude, defensive behaviors, and male ejaculations. Data are means+S.E.M. *$P<0.05$, main effect of drug vs. saline. $^{+}P<0.05$, post hoc Tukey test of the individual dose vs. saline.

lordosis quotients almost reached the levels observed in females primed with EB+P. Although CNQX also increased lordosis reflex magnitudes significantly, they did not reach the level induced by P. CNQX infusions also increased the number of solicitations in females primed with EB alone and EB+P. Although rates of pacing were not altered by CNQX, the

number of ejaculations achieved by males paired with the EB-alone females was increased in a dose-dependent manner. Solicitations are an important component of the sexual incentive value of female rats (Everitt, 1990; Landau and Madden, 1983; Madlafousek et al., 1976). For example, female rats treated with a dopamine receptor antagonist (e.g., haloperidol or flupenthixol) do not engage in solicitations or display hops and darts. Those females are also slow to disengage from a lordosis posture once the reflex has been stimulated. Castrated male rats, or males with hypofunctional mesolimbic dopamine transmission (induced by 6-OHDA lesions of the nucleus accumbens) are extremely sensitive to the lack of proceptive behaviors, and mount those females at a slower rate (Everitt, 1990). The increased number of ejaculations achieved by males paired with EB-alone females treated with CNQX may have been due to the increased solicitations displayed, which in turn increased the male's arousal and incentive motivation.

The most pronounced effect on female sexual behaviors occurred following infusions of the other AMPA/kainate antagonist, DNQX, to the VMH. This antagonist increased lordosis quotients, magnitudes, hops and darts, and ejaculations, in females primed with E-alone, increased solicitations in females in both hormone-treatment conditions, and decreased rates of pacing and the display of defensive responses in both hormone-treatment conditions. In our previous study, selective activation of kainate receptors decreased lordosis quotients and solicitations, and increased pacing and defensive behaviors, whereas selective activation of AMPA receptors decreased lordosis quotients and magnitudes, solicitations, and hops and darts, and increased pacing and defensive responses (Georgescu and Pfaus, in press). Taken together with the present data, it would appear that activation of all three ionotrophic glutamate receptors in the VMH decreases lordosis and increases defensive responses, whereas activation of AMPA/kainate receptors further increases pacing and decreases appetitive sexual responses used to solicit mounts, including full solicitations and hops and darts.

All of the effects of the glutamate antagonists observed in EB-primed females are reminiscent of the additive effects of P when administered in conjunction with EB. It is possible that one of the actions of P in the VMH is to dampen glutamate transmission or binding. Indeed, the antiprogestin RU486 increases kainate GluR6 subunit mRNA in the mediobasal hypothalamus of gonadally-intact female rats on the afternoon of proestrus, whereas exogenous administration of P reduces it (Brann et al., 2005). Because selective glutamate receptor antagonists also facilitated sexual behavior in females primed with EB+P, it is possible that they accentuate the efficacy with which P activates both appetitive (e.g., solicitation, hops and darts) and consummatory (e.g., lordosis) aspects of sexual behavior while reducing the display of aversive or defensive responses, when administered in conjunction with EB.

Another possibility is that EB and/or P activates pathways that inhibit glutamate interneurons in the VMH. Candidate inhibitory systems could be GABA acting at GABA-A receptors or enkephalins acting at δ-opioid receptors. Treatment with EB is known to increase the synthesis of GAD, thereby increasing endogenous GABA tone (McCarthy et al., 1995), and P can increase the binding efficacy of GABA-A receptors (DeLorey and Olsen, 1994; Majewska et al., 1986). Infusions of GAD antisense to the VMH inhibits lordosis, suggesting that GABA input to this region is critical for its display (McCarthy et al., 1994). A mutually antagonistic role of GABA and glutamate systems is not unprecedented: studies on neuroprotection have shown that NMDA and AMPA receptor antagonists, like GABA-A receptor agonists, limit or prevent ischemia-induced damage in the hippocampus (e.g., Gagliardi, 2000). Low doses of opioid peptides acting at δ-opioid receptors in the VMH also facilitate proceptive and receptive behaviors in females primed with EB alone, whereas treatment with the δ-opioid receptor antagonist naltrindole has the opposite effect in females primed with EB+P (Acosta-Martinez and Etgen, 2002). It remains to be established whether glutamate neurons in the VMH express GABA-A or δ-opioid receptors.

Future studies should investigate the effects of more selective receptor antagonists, such as 2,3-dihydro-6-nitro-7-sulphamoyl-benzo(f)quinoxaline (NBQX), the subtype AMPA selective antagonist, or GYKI 52466, the noncompetitive subtype AMPA selective antagonist, in order to isolate behaviors that AMPA receptors mediate relative to those mediated by kainate receptors. Finally, it would be important to examine glutamate release within the VMH using microdialysis throughout multiple ejaculatory series or during estrus termination. We have found that multiple vaginocervical stimulations produced by intromissive stimulation activate Fos in glutamate neurons of the VMH, an effect that is blunted by ovarian steroid treatment in OVX rats (Georgescu et al., submitted for publication). It may be the case that the degree of EB- and/or P-induced inhibition of glutamate neurons is reduced progressively by increasing amounts of vaginocervical stimulation, leading to the behavioral effects observed during estrous termination, including the early inhibition of solicitations and hops and darts, increases in pacing and defensive responses, and a later inhibition of lordosis (Lodder and Zeilmaker, 1976; Pfaus et al., 2000).

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