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Sensory Cues Mediating Mating-Induced Potentiation of Sexual Receptivity in Female Rats

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Repeated mating of estradiol-primed female rats increases sexual receptivity. Two studies were conducted to determine the contribution of vaginal–cervical stimulation (VCS) to this increase. In the first study, female rats were repeatedly mated for 165 min. The vaginas of half of the females were covered with tape (masked) to prevent intromissions by the males. The remaining females were unmasked. Only females receiving intromissions (unmasked) showed a significant increase in sexual receptivity during repeated mating, suggesting that VCS from intromissions is necessary for repeated mating to increase sexual receptivity. In the second experiment, female rats received either experimentally administered VCS or control scapular stimulation administered with a plastic probe 1 h prior to testing for sexual receptivity. VCS applied in this manner significantly increased sexual receptivity. Together, these findings suggest that VCS from intromissions is one of the primary factors responsible for increases in sexual receptivity following repeated mating.

In estrous-cycling female rats, a gradual increase in estrogens followed by a peak in progesterone induces sexual behavior (Boling and Blandau, 1939; Powers, 1970). Ovariectomy abolishes spontaneous estrus by removing the main source of these hormones; however, sexual behavior can be reinstated by sequential injections of estradiol and progesterone (Boling and Blandau, 1939). Although a high dose of estradiol alone can also induce sexual behavior, both estradiol and progesterone are required for the predictable onset and termination of sexual receptivity (Wallen and Thornton, 1979) and for the complete display of proceptive behaviors (Whalen, 1974; Tennent, Smith, and Davidson, 1980).

Sexual receptivity can also be enhanced over the course of a few hours in the absence of progesterone by exposing female rats to a low dose of estradiol and repeatedly mating them with male rats (Auger, Moffatt, and Blaustein, 1997; Dudley and Moss, 1994; Foreman and Moss, 1977; Rajendren, Dudley, and Moss, 1990; 1991; Rajendren and Moss, 1993, 1994). The exact method of repeated mating varies among studies, but in general, a female rat is placed with a male for 15 min and then returned to the home cage for 15 min. This cycle is repeated every 30 min for 2 to 5 h, generally producing significant increases in lordosis quotients between 1 and 2 h after the start of mating.

These increases in sexual receptivity appear to result from ligand-independent activation of progestin receptors (PRs), because the facilitation is blocked by administration of progestin receptor antagonists even in the absence of progesterone (Auger *et al.*, 1997). It is likely that one or more of the sensory cues received by the female during mating leads to activation of PRs which, in turn, leads to increases in sexual receptivity; however, it is unclear which sensory cue(s) is responsible.

During mating, a female rat is exposed to a wide array of sensory cues which could mediate mating-induced potentiation of sexual receptivity. In particular, previous studies suggest that pheromonal cues from male rats are important for mating-induced increases in sexual behavior. Although vomeronasal organ lesions suppress mating-induced potentiation of sexual receptivity (Rajendren *et al.*, 1990; Rajendren and Moss, 1994), lesioned females still show an increase in lordosis quotient following repeated mating (Rajendren and Moss, 1994). This finding suggests that

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other sensory cues also contribute to the increase. In addition, pheromonal cues do not appear to cause ligand-independent activation of PRs (Bennett, Greco, and Blaustein, 2000), further supporting the hypothesis that there are other sensory cues responsible for the increases in sexual receptivity following repeated mating.

Vaginal–cervical stimulation (VCS) is another sensory cue that could contribute to mating-induced potentiation of sexual receptivity. VCS is produced by the receipt of intromissions or ejaculations and is particularly important to the display of female sexual behavior. VCS induces temporary analgesia (Gómora, Beyer, Gonzàlez-Mariscal, and Komisaruk, 1994), increases female return latencies during paced mating (Yang and Clemens, 1997), accelerates estrous termination (Lodder and Zeilmaker, 1976; Reading and Blaustein, 1984), induces pseudopregnancy (Everett, 1964), and increases production of immediate early genes (e.g., Fos; Tetel, Getzinger, and Blaustein, 1993; Pfaus, Kleopoulos, Mobbs, Gibbs, and Pfaff, 1993; Erskine, 1993).

VCS can also be produced manually by an experimenter using a mechanical probe. VCS administered in this manner can induce some of the same physiological outcomes as VCS produced by intromissions from a male rat. For example, experimentally administered VCS induces temporary analgesia (Komisaruk, Ciofalo, and Latranyi, 1976), increases lordosis (Rodriguez-Sierra, Crowley, and Komisaruk, 1975), increases rejection behaviors during mating (Pfaus, Smith, Byrne, and Stephens, 2000), and induces pseudopregnancy (Gorospe and Freeman, 1981). Like intromissions by male rats, manual VCS also increases the production of immediate early gene products (e.g., Fos) in estrogen receptor (Tetel *et al.*, 1993)- and progestin receptor (Auger, Moffatt, and Blaustein, 1996)-containing cells in the preoptic area and ventromedial hypothalamus. Furthermore, VCS-induced Fos is partially blocked in the bed nucleus of the stria terminalis, medial preoptic area, and ventromedial hypothalamus by progesterone antagonists in the absence of progesterone, suggesting that VCS causes ligand-independent activation of PRs (Auger *et al.*, 1997). Therefore, it is possible that VCS received during repeated mating causes ligand-independent activation of PRs, which, in turn, causes increases in sexual receptivity.

Two experiments were conducted to determine the role of VCS in mating-induced increases in sexual receptivity. The first experiment contrasted the effect of repeated mating on sexual receptivity in the presence or the absence of VCS from intromissions and ejaculations. The second experiment determined the effect of experimentally administered VCS on sexual receptivity in the absence of most other reproductively relevant cues from male rats.

METHODS

General

Female Sprague–Dawley rats (175–200 g) obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA) were group housed in a 14:10 h light/dark cycle. They received Purina LabDiet No. 5001 and water *ad libitum* prior to surgery. At least 1 week after arrival, the rats were bilaterally ovariectomized and adrenalectomized under 2.5 mg/kg of acepromazine, 10 mg/kg of xylazine, and 50 mg/kg of ketamine. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Massachusetts, Amherst. Ovariectomized/adrenalectomized rats were used in the present experiments to ensure the removal of all circulating progesterone. Following surgery, the rats received Purina LabDiet No. 5015, water, and a sodium chloride spool *ad libitum* for the remainder of the study. In addition, the rats were handled daily to reduce the effects of handling during testing. One week after surgery, the rats were injected subcutaneously with 2 μg of estradiol benzoate (EB; dissolved in 0.1 ml of sesame oil), and 48 h later, they were injected subcutaneously with 500 μg of progesterone (dissolved in 0.1 ml of sesame oil containing 5% benzyl alcohol and 15% benzyl benzoate). Four hours after the progesterone injection, the rats were pretested for sexual receptivity with sexually active male rats, and lordosis quotients (number of lordosis responses divided by the number of mounts by the male, multiplied by 100) were recorded. Each female was left with a male until 10 mounts were received. All behavior tests took place during the dark phase of the light/dark cycle in cylindrical Plexiglas arenas lined with wood chips. Two females displayed low levels of sexual receptivity (lordosis quotients $\leq$70) at the time of the pretest and were not included in the studies.

Experiment 1

Ten days after the pretest, females were injected subcutaneously with 2 μg of EB (dissolved in 0.1 ml of sesame oil). Forty-eight or 72 h later, each female was placed in a testing arena with a sexually active male

rat for 15 min (or until 10 mounts were received) followed by 15 min in the home cage. This mating paradigm was repeated six times. During the repeated mating procedure, the vaginas of half of the females ($n = 6$) were covered with tape (masked) to prevent intromissions by the males. Masking tape was used to cover the vaginal and perineal region, and the tape was then secured to the base of the tail. The remaining rats ($n = 7$) had tape covering part of the perineal area, but the vagina was left exposed. The tape was removed at the end of each mating test and replaced at the beginning of the next mating test. Control and experimental animals were included at both the 48- and 72-h test times. The display of lordosis by the females and the display of mounts, intromissions, and ejaculations by the males were recorded during each mating session. One female showed a lordosis quotient greater than 30 during the first mating session and was excluded from the study.

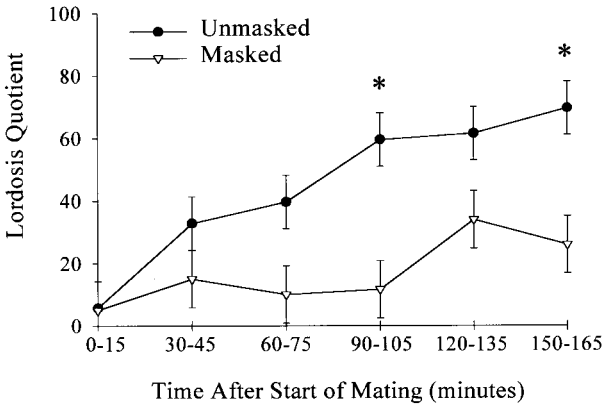

FIG. 1. "Masked" indicates rat that was vaginally masked to prevent intromission ($n = 6$), and "unmasked" a control group able to receive intromissions ($n = 7$). An asterisk indicates a significant difference between masked and unmasked females on a given test number.

Experiment 2

Ten days after the pretest, females were injected with 2 μg of EB (dissolved in 0.1 ml of sesame oil). Forty-eight hours later, each female was vaginally masked and placed with a sexually active male rat until 3 mounts were received in order to screen for progesterone-independent sexual behavior. Fifteen females showed lordosis during this pretest and were removed from the study. The remaining females were then placed in a clean testing arena and given either 300 g of VCS ($n = 9$) or 300 g of control scapular stimulation ($n = 10$) for 2 s every 30 s for 15 min. Stimulations were administered with a 1-cc plastic syringe plunger attached to a force gauge (as described previously; Tetel, Getzinger, and Blaustein, 1994). The control stimulation was applied to the back, rather than the perineum as described previously (Tetel *et al.*, 1994), because either cervical or perineal stimulation may activate the pelvic nerve (Peters, Kristal, and Komisaruk, 1987). Therefore, perineal stimulation may induce some of the same effects as VCS. The pressure and pattern of stimulation were chosen because they were shown previously to induce Fos expression in many of the brain areas associated with female sexual behavior (Moffatt, Baez, Kaplan, and Blaustein, unpublished). Following stimulation, each female was returned to the home cage for 45 min. One hour after the start of treatment, each female was placed with a sexually active male rat until 10 mounts were received. Females were not vaginally masked during this mating test. Lordosis was scored by an observer unaware of the treatment conditions. After the test, all females were injected with 500 μg of progesterone (dissolved in 0.1 ml of sesame oil containing 5% benzyl alcohol and 15% benzyl benzoate), and 4 h later, they were retested for sexual behavior to verify a behavioral response to the hormones. One female showed a lordosis quotient less than 70 during this test and was excluded from the analysis.

RESULTS

Experiment 1

Repeated mating caused an increase in lordosis quotients in females receiving intromissions (unmasked); however, preventing intromissions by placing tape over the vagina prevented the increase (Fig. 1). A 2×6 repeated measures ANOVA revealed significant main effects for treatment (F (1, 11) = 9.41, $P < .05$) and for time (F (5, 53) = 11.12, $P < .01$), as well as a significant interaction (F (5, 53)= 3.58, $P < .01$). The significant effects were probed with Newman–Keuls posthoc comparisons. Unmasked females had significantly higher lordosis quotients during the tests at 90 min ($P < .05$) and 150 min ($P < .05$) than did masked females. In addition, unmasked females had significantly higher lordosis quotients during the tests at 90 min ($P < .05$), 120 min ($P < .05$), and 150 min ($P < .05$) than during the tests at 0, 30, and 60 min. Masked females did not show a significant change in lordosis quotients during the six tests. Unmasked females received an average of 2.08 ($\pm$ 0.29) intromissions and

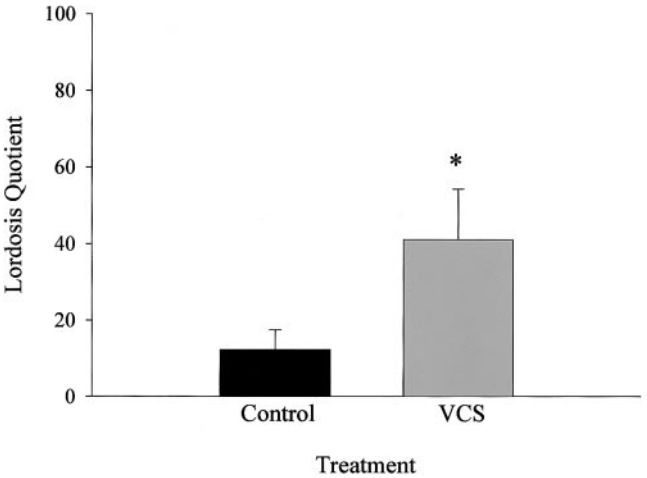

FIG. 2. Controls were given 300 g of scapular stimulation with a plastic probe for 2 s every 30 s for 15 min ($n = 10$), and VCS 300 g of cervical stimulation with a plastic probe for 2 s every 30 s for 15 min ($n = 9$). An asterisk indicates a significant difference between the VCS and control groups.

0.45 ($\pm$ 0.09) ejaculations during each testing session. Masked females did not receive any intromissions or ejaculations.

Experiment 2

Females receiving experimentally administered VCS had significantly higher lordosis quotients than did control females (Fig. 2; t (8) = 2.03 ; $P < .05$, one-tailed test).

DISCUSSION

In Experiment 1, females receiving intromissions and ejaculations (i.e., unmasked) showed an increase in sexual receptivity during repeated mating, but masked females did not. These results suggest that VCS from intromissions and ejaculations is necessary for increased sexual receptivity following repeated mating. Although a previous study found that VCS was not necessary for repeated mating or repeated handling to increase sexual behavior (Hardy and DeBold, 1973), there are several methodological differences between the previous and current studies that may account for the differing results. For example, the rats in the previous study were not adrenalectomized, allowing for the possible effects of adrenal progesterone. In addition, the rats were hysterectomized and received higher doses of EB, increasing the possibility of progesterone-independent sexual behavior. Therefore, it appears that VCS is not necessary to increase sexual receptivity under some experimental conditions; however, under the conditions in the current experiment, VCS was necessary for repeated mating to increase sexual receptivity.

In Experiment 2, rats receiving VCS administered via a plastic probe had significantly higher lordosis quotients than did control females, suggesting that VCS alone is sufficient to induce increases in sexual receptivity in estradiol-primed female rats. This finding is consistent with a previous study showing that experimentally administered VCS alone or in combination with flank stimulation causes a prolonged increase in sexual receptivity in ovariectomized rats (Rodriquez-Sierra, Crowley, and Komisaruk, 1975). The current study adds to these findings by showing that experimentally administered VCS causes an increase in sexual receptivity in ovariectomized / adrenalectomized rats. Thus, the increase does not appear to result from the release of adrenal progesterone.

Although VCS appears to be sufficient to induce increases in sexual receptivity, it is likely that VCS in combination with other sensory cues would induce a greater increase in sexual behavior. Female rats with vomeronasal organ lesions show an increase in sexual receptivity following repeated mating; however, sham-operated controls show greater increases in sexual behavior (Rajendren and Moss, 1994). These results suggest that the combination of pheromonal cues and VCS would induce a greater level of sexual behavior than does VCS alone.

The results of Experiment 2 suggest that experimentally administered VCS can mimic the behavioral effects of intromissions. This finding is interesting, because the experimental probe is smooth and provides pressure directly to the cervix, whereas the rat penis is covered with keratinous spines (Sachs, Glater, and O'Hanlon, 1984; Taylor, Komitowski, and Weiss, 1983) and may not contact the cervix directly during an intromission. Although it is unlikely that experimentally induced VCS provides the same type of vaginal stimulation as an intromission, experimentally administered VCS does cause longitudinal stretching of the vaginal wall which appears to cause sufficient vaginal stimulation to induce immobilization similar to that induced by an intromission (Komisaruk and Larsson, 1971). Therefore, it is possible that experimentally administered VCS induces the same behavioral effects as intromissions, because there is sufficient stretching of the vaginal wall to mimic the vaginal stimulation from an intromission. Alternatively, it is possible that ex-

perimentally administered VCS induces a combination of cervical and vaginal stimulation that is sufficient to mimic the vaginal stimulation following an intromission, as both cervical and vaginal stimulation activate the pelvic nerve (Peters *et al.*, 1987).

Although both intromissions and experimentally administered VCS cause increases in sexual receptivity, it should be noted that the experimentally administered VCS caused a more rapid increase in sexual receptivity than did the repeated mating paradigm. Experimental VCS caused a significant increase in lordosis quotient 1 h after the start of stimulation, whereas repeated mating did not cause a significant increase until 90 min after the start of mating. This difference may have resulted from different amounts of stimulation. Experimental VCS was administered for 2 s every 30 s for 15 min, producing a total of 30 stimulations. In contrast, repeatedly mated females received an average of 2.5 intromissions or ejaculations per mating session. Thus, females receiving experimentally administered VCS may have shown a more rapid increase in sexual receptivity because they receive more stimulations in a shorter period of time. However, as stated above, it is not clear how the stimulation from experimentally administered VCS compares to that of intromissions. Therefore, we cannot be certain that the experimentally administered VCS actually caused more stimulation than did repeated mating.

The results of Experiment 2 also suggest that a pressure and temporal pattern of VCS that induce Fos expression in brain areas associated with female sexual behavior also induce changes in sexual receptivity. Applying 300 g of VCS for 2 s every 30 s for 15 min induces Fos expression in the medial preoptic area, bed nucleus of the stria terminalis, medial amygdala, caudal ventromedial hypothalamus, and rostral ventromedial hypothalamus 1 h after stimulation (Moffatt *et al.*, unpublished). Likewise, this VCS paradigm was sufficient to increase sexual receptivity 1 h after stimulation.

VCS may induce sexual receptivity via ligand-independent activation of PRs. Mating-induced increases in sexual receptivity in the absence of circulating progesterone can be reduced by administration of progesterone antagonists (Auger *et al.*, 1997), suggesting that ligand-independent activation of PRs is, at least partially, responsible for the increase in sexual receptivity following repeated mating. Likewise, VCS-induced Fos expression in some cells is reduced by progesterone antagonists in the absence of progesterone (Auger *et al.*, 1997), suggesting that VCS induces Fos expression in some cells via ligand-independent activation of PRs. Therefore, it is possible that VCS influences neuronal response, as well as sexual receptivity via this progestin receptor-dependent mechanism. In contrast, pheromonal cues do not appear to cause ligand-independent activation of PRs (Bennett *et al.*, 2000). Thus, it is possible that VCS and pheromonal cues contribute to increases in sexual behavior via different mechanisms.

Although it is not yet known which neurotransmitters are involved in mating-induced potentiation of sexual receptivity, there is considerable evidence suggesting that dopamine plays a role in the effect. Mating, particularly intromission, causes release of dopamine in the bed nucleus of the stria terminalis (Kohlert, Rowe, and Meisel, 1997) and ventromedial hypothalamus (Vathy and Etgen, 1989). Furthermore, VCS induces an increase in phosphorylation of dopamine- and cyclic AMP-regulated phosphoprotein (DARPP-32) immunoreactivity in brain areas associated with female sexual behavior (Meredith, Moffatt, Auger, Snyder, Greengard, and Blaustein, 1998). DARPP-32 is a phosphoprotein believed to be involved in mediating the effect of the D1 subtype dopamine receptors on neurons (Greengard, Nairn, Girault, Ouimet, Snyder, Fisone, Allen, Feinberg, and Nishi, 1998). Therefore, these results suggest that the neuronal effects of VCS may result from activation of D1 subtype dopamine receptors (Meredith *et al.*, 1998). Indeed, a D1 dopamine receptor antagonist decreases VCS-induced Fos expression in the brain, adding further support to the hypothesis that D1 dopamine receptor activation is necessary for VCS to induce neuronal effects (Quysner and Blaustein, unpublished). In addition, D1 dopamine receptor agonists (*e.g.*, SKF38393) induce female sexual behavior in the absence of progesterone in estradiol-primed female rats (Foreman and Moss, 1979; Mani, Allen, Clark, Blaustein, and O'Malley, 1994). The fact that this facilitation of sexual behavior can be prevented with a progesterone antagonist or oligonucleotides antisense to progestin receptor mRNA suggests that dopamine facilitates the expression of sexual behavior via ligand-independent activation of PRs (Mani *et al.*, 1994). Therefore, it is possible that VCS causes activation of dopamine receptors and this activation, in turn, causes ligand-independent activation of PRs, which then increases sexual behavior.

There is also evidence that GnRH is involved in the display of female sexual behavior. GnRH can induce sexual behavior in estradiol-primed female rats (Moss and McCann, 1973; Pfaff, 1973). GnRH-enhanced sex-

ual behavior can also be blocked by progesterone antagonists (Beyer, Gonzalez-Flores, and Gonzalez-Mariscal, 1997), suggesting that GnRH may enhance sexual behavior through ligand-independent activation of PRs. However, GnRH antagonists do not block mating-induced increases in sexual behavior (Rajendren *et al.*, 1990), suggesting that GnRH receptor activation is not necessary for the potentiation of sexual receptivity following repeated mating.

There are several limitations to the experiments reported here. First, the observer was not blind to the treatment conditions in Experiment 1, because the placement of the tape was visible during the observations. Second, we cannot exclude the possibility that exposure to male sensory cues during the screening for progesterone-independent sexual behavior or during the test for receptivity contributed to the increase in sexual receptivity in Experiment 2. Although exposure to the males was limited to a few minutes, and the females were vaginally masked during the screening, it is possible that the combination of VCS and sensory cues from the males, rather than VCS alone, caused the increase in sexual receptivity. In addition, females were not vaginally masked during the behavior test. Thus, it is possible that VCS from intromissions contributed to the increase in sexual behavior. However, it is unlikely that stimulation from intromissions could cause significant increases in sexual behavior within a 10-min behavior test. Nevertheless, we cannot completely rule out the possibility that VCS from intromissions contributed to the increase in sexual behavior. Work is under way to investigate the possible interactions among these sensory cues. Third, only one VCS administration paradigm, one which was known to induce Fos expression in the brain, was used. Therefore, the possible effects of a lower or higher pressure of VCS or of a different temporal pattern of VCS on potentiation of sexual behavior are not known. Nevertheless the current findings are sufficient to demonstrate that under certain conditions VCS alone can enhance sexual behavior. In addition, quantities of VCS sufficient to induce changes in Fos expression in the brain are also sufficient to induce changes in behavior. Finally, as discussed above, the type of stimulation provided by experimentally administered VCS may differ from that of intromissions. Therefore, it is unclear how the behavioral effects of experimentally administered VCS compare to the effects of naturally occurring intromissions.

In conclusion, the results of Experiment 1 suggest that VCS from intromissions and ejaculations is necessary for repeated mating to induce increases in sexual behavior. The results of Experiment 2 suggest that levels of experimentally administered VCS that are sufficient to induce Fos expression in brain areas associated with female sexual behavior are also sufficient to induce modest increases in sexual behavior. Together these findings support the hypothesis that VCS is an important factor in mating-induced potentiation of sexual behavior.

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