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Central and Peripheral Effects of Oxytocin Administration in Prairie Voles (*Microtus ochrogaster*)

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WITT, D. M., C. S. CARTER AND D. M. WALTON. *Central and peripheral effects of oxytocin administration in prairie voles (*Microtus ochrogaster*)*. PHARMACOL BIOCHEM BEHAV **37**(1) 63–69, 1990.—The present study examined the hypothesis that oxytocin (OT) may influence female sexual behavior in prairie voles (*Microtus ochrogaster*). The effectiveness of OT to induce sexual behavior was tested in ovariectomized females that were injected daily with estradiol benzoate (EB, 0.02 μg, twice), a dose insufficient for estrus induction. On the third day females received intracerebroventricular (ICV) injections of OT (1, 300, or 1000 ng) or saline vehicle. In the presence of minimal estrogen stimulation, OT did not induce sexual receptivity, or influence autogrooming or other social interactions. The behavioral effects of OT were examined in another group of ovariectomized females that received daily oil or EB injections (10 μg, twice) followed on the third day by either ICV (1, 300, or 1000 ng) or intraperitoneal (IP) (1, 3, or 10 μg) injections of OT. Among EB-treated females, only those in confirmed estrus, prior to ICV or IP injection, were included in these studies. There was a dose-related decrease in the percentage of females that remained in behavioral estrus after ICV OT. In those females that continued to show sexual behavior, lordosis frequencies and durations were unaffected by ICV OT. Nonsexual behavior did not differ between mated females and those exhibiting OT-inhibited sexual behavior. In females that were EB-treated, autogrooming and side-by-side behavior increased after ICV OT, while there was a decline in aggression. Female sexual and nonsexual behaviors were not significantly affected by IP OT. However, males paired with IP-OT females showed reductions in anogenital investigation and aggression toward IP-OT injected females; male autogrooming increased if females were EB-treated and received IP OT. OT did not induce sexual behavior or affect other social behaviors or autogrooming in oil-treated female prairie voles. These results suggest that centrally active OT may inhibit sexual receptivity and promote social behavior and autogrooming in female prairie voles, while peripheral OT may alter the stimulus properties of the female.

Oxytocin Sexual behavior Social interactions Voles Autogrooming

THE neuropeptide oxytocin (OT) is synthesized in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus, and is released into the peripheral circulation from the posterior pituitary. OT has long been recognized for its peripheral effects on uterine contractions and milk ejection. However, recent studies indicate that there is also intracerebral release of OT from both hypothalamic and extrahypothalamic sites (6, 7, 29, 30, 40). Sexual behavior is one of the most potent stimuli for the release of OT (10, 34, 39, 42). Moreover, OT administration facilitates sexual receptivity in female rats that are estrogen-primed (8) or estrogen- plus progesterone-primed (1,22).

The present study examines the effects of OT on sexual and social behavior in prairie voles (*Microtus ochrogaster*). This species' reproductive physiology and social behavior differs significantly from that observed in laboratory rats. In contrast to rats, prairie voles do not exhibit spontaneous estrous cycles. Estrus is induced by urinary chemosignals from males (14,19). Female autogrooming may facilitate the delivery of chemosignals to the olfactory apparatus (45). In male-induced estrus, copulatory interactions last for 24–30 hours with numerous mating bouts. In contrast, postpartum estrus typically is characterized by a reduction in copulatory interactions with mating continuing for 1–10 hours. The period of female sexual receptivity during postpartum estrus can be lengthened significantly if the pups are removed immediately after birth (46). These findings suggest that, in the intact female, the cumulative release of OT during copulation, birth, and lactation may abbreviate sexual receptivity.

The purpose of the present studies was to investigate the dose-related effects of OT on sexual behavior following either central or peripheral administration. The specific goals of this experiment were a) to assess the ability of OT to induce sexual receptivity in female prairie voles receiving estradiol benzoate (EB) priming at a dose insufficient for the induction of lordosis; b) to test the hypothesis that OT may have inhibitory effects on sexual behavior in estrous females (as observed during postpartum estrus); c) to test the hypothesis that OT may influence female sexual behavior through effects on peripheral systems, such as the contractile actions of OT on smooth muscle (41).

The neural effects of OT may be modulated by steroid hormones, and in particular by estrogen (16, 41, 44). In addition,

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estrogen is essential for estrus induction in mammals, including prairie voles (5, 13, 20). In female prairie voles estrogen alone induces female sexual behavior and progesterone does not further enhance sexual receptivity (13,20). Moreover, OT has been implicated in ovarian function (44). Therefore, to control for indirect actions of injected OT on ovarian estrogen secretion and to examine possible interactions between estrogen and OT, the behavioral effects of OT were examined in the present study in ovariectomized females that were treated with either EB or oil.

OT has a short half-life (4–5 min) in the peripheral circulation of domestic rats (36) and there is evidence of only limited penetration of the blood-brain barrier with peripherally administered OT (48). Therefore, groups of females receiving IP injections were tested to control for possible effects arising from the peripheral actions of OT. Also, in all groups male behavior in response to peptide-injected females was monitored to evaluate the female's stimulus value to the male and to assess other social interactions elicited by OT injection.

METHOD

Subjects

Prairie voles used in these experiments were derived from wild caught stock which had been randomly bred and reared in captivity for several years. The original animals were trapped by L. L. Getz near Urbana, IL. Animals were maintained routinely under a 14:10-hr light:dark cycle with lights on at 0500 hours. Housing consisted of $20 \times 25 \times 45$ cm polycarbonate cages with pine chip bedding. Purina rabbit chow and tap water were provided ad lib. Weaning took place at 21 days of age when animals were segregated into unisex sibling groups.

At 50–75 days of age females were ovariectomized under pentobarbital anesthesia (0.18 mg, IP). After a two-week recovery period females were assigned randomly to a treatment group. The estrus induction groups were generated to assess the ability of OT to induce sexual receptivity in females that received EB-priming at a level just below that which induces lordosis. In these groups, ovariectomized females were treated for two consecutive days with EB (0.02 μg, SC). On day 3 females were screened briefly with a sexually experienced male and only nonreceptive females were included in these groups. All tests were conducted using sexually experienced males. To maintain sexual experience all males were screened (approximately two to three times per week) with nonexperimental estrous females to maintain high levels of sexual activity. Screening prior to behavioral testing was followed by ICV injections (as described below) of saline (1 μl), or 1, 300, or 1000 ng of OT in 1 μl saline (N = 9 subjects per injection dose). All experimental testing began 10 minutes after peptide or vehicle injection and lasted 30 minutes.

The behavioral effects of OT also were examined in ovariectomized females receiving either high levels of EB (10 μg, SC, twice) or oil (0.05 cc, SC, twice) followed on day 3 by either ICV or IP OT injection. EB-treated females in these groups were used only if they were in confirmed behavioral estrus. The effects of OT were examined in oil-treated females, permitting a second assessment of possible facilitating effects of OT in nonestrous females.

In the ICV groups, oil- or EB-treated females received either 1 μl saline or 1, 300, or 1000 ng of OT in 1 μl saline (N = 10 subjects per injection dose). In the IP groups, EB-treated females were given either IP (0.05 ml) saline, or 1, 3, or 10 μg of OT in 0.05 ml saline vehicle (N = 10 subjects per injection dose). The oil-treated female groups received either IP injections of 0.05 ml saline (N = 10), or 1 μg (N = 8), 3 μg (N = 8), 10 μg (N = 6) of OT in 0.05 ml saline. Saline:India ink vehicle was used to make IP injections comparable with ICV injections. Females were tested with a sexually experienced male approximately 10 minutes after ICV or IP injection and testing lasted for 30 minutes. The ICV and IP groups were monitored concurrently, but results are presented here separately to facilitate analysis because of differences in doses of OT.

Oxytocin Injections

OT doses used in the present study included those which reportedly enhance sexually receptivity in EB-primed rats (1,8) as well as lower doses. OT doses for ICV administration were 1, 300, or 1000 ng; IP injections were 1, 3, or 10 μg. ICV injections were used because this is a reliable method for administering OT which avoids impedance by the blood-brain barrier. OT (Peninsula Laboratory, Belmont, CA) was suspended in a 2:1, saline:India ink vehicle. ICV injections were administered to animals that were anesthetized using inhalant Metofane (methoxyflurane). A removable cranial band was used as an injection guide. This procedure for ICV injection, developed for rats by Popick (35) and modified for voles, avoids surgical trauma and the excessive weight associated with more permanent cannula guides. After behavioral testing females were sacrificed by decapitation and gross coronal dissections were made at the injection site. Brain sections were examined under a 10-power dissecting microscope and data are presented for females with injections in the lateral ventricles, as verified by the presence of India ink.

Behavioral Testing

Mount-lordosis was recorded when a female assumed a concave arched-back posture in direct response to a male placing his forelimbs on the female's back, while directing pelvic thrust towards her genital region. Unlike domestic rats, it is essentially impossible for a male vole to mount a nonreceptive female. Therefore, in the present experiments, only lordosis frequencies and durations are presented. Side-by-side behavior was recorded when pairs were observed in direct lateral contact. Autogrooming was recorded when animals were observed rhythmically passing their forepaws over the face and body. Anogenital sniffing was recorded when individual animals investigated their partner's anogenital region. Aggression was recorded when individuals directed rearing and/or lunging behavior toward their partner. All behavioral testing was begun approximately 10 minutes after injection procedures, as described above, and lasted for 30 minutes.

Statistical Analysis

Data were analyzed separately, as determined by dose of EB treatment and appropriate oil controls. Differences among ICV or IP injection groups were analyzed within oil or EB treatments using the nonparametric Kruskal-Wallis analysis of variance. Where overall differences were significant within injection groups (ICV or IP), between group comparisons (based on injection dose) were made individually using the Mann-Whitney U-test. An alpha$<$0.05 was required for significance.

RESULTS

Estrus Induction and OT (ICV)

OT did not induce sexual receptivity in female prairie voles that had subthreshold levels of estrogen priming. Sexual behavior was not observed in any of these females. Also, autogrooming and other social interactions were not altered significantly by ICV OT.

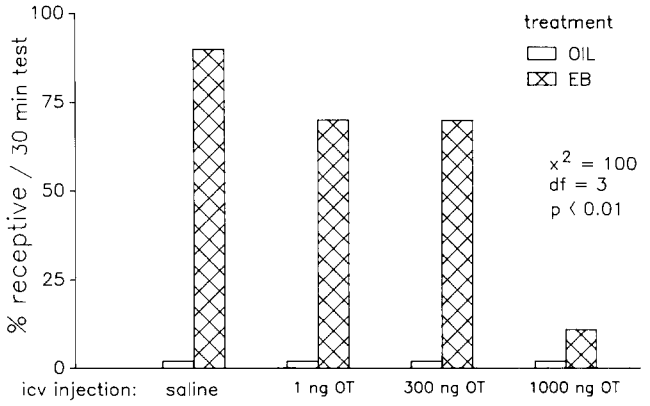

FIG. 1. Percent receptive females after ICV injection. Chi-square statistic indicates that groups differ significantly from expected values.

ICV OT in Estrous and Nonestrous Females

Copulatory interactions. ICV OT did not induce sexual behavior in oil-treated females. OT produced a dose-related decrease in the percentage of EB-treated females that remained in behavioral estrus after ICV injection (Fig. 1) with the 1000 ng OT dose having the greatest effect on sexual receptivity, $\chi^2(3) = 100$, $p<0.01$. Lordosis frequencies and durations did not differ from saline controls in EB-treated females that remained receptive after ICV injection. Nonsexual behavior did not differ among females that mated versus those experiencing OT-inhibited sexual behavior.

Autogrooming. Autogrooming durations were significantly elevated in EB-treated females that received either 1 ng (U-87, $p<0.005$) or 1000 ng of OT (U = 87, $p<0.001$) when compared to saline controls (Fig. 2). Female autogrooming was slightly elevated but did not differ significantly between EB-treated females that received 300 ng OT versus saline controls. Female autogrooming durations did not differ significantly as a function of OT injections in females that were oil-treated. The durations of autogrooming in males paired with oil- or EB-treated females that received OT injections also did not differ significantly among groups.

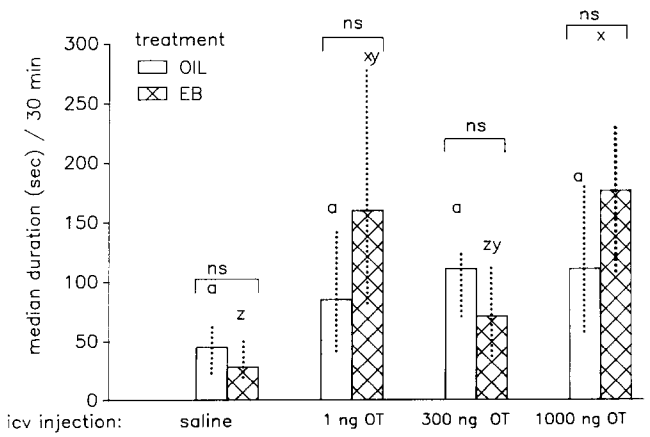

FIG. 2. Median durations (sec) of female autogrooming after ICV oxytocin or saline injection. Dotted lines signify upper and lower hinges of interquartile ranges. N = 10 per group. Groups with different letters differ significantly ($p<0.05$) ns = not significant.

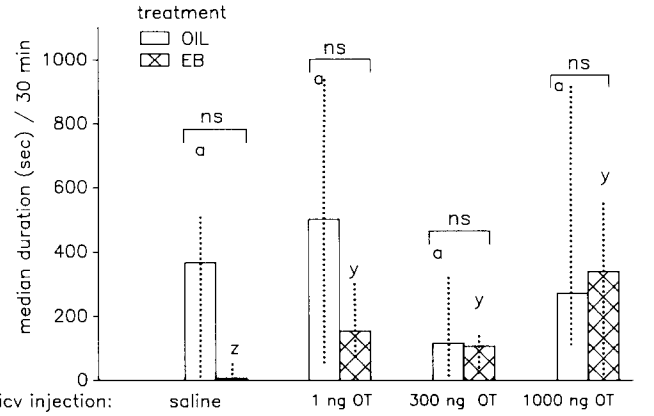

FIG. 3. Median durations (sec) of side-by-side contact after ICV oxytocin or saline injection. Dotted lines signify upper and lower hinges of interquartile ranges. N = 10 per group. Groups with different letters differ significantly ($p<0.05$), ns = not significant.

Anogenital investigation. Anogenital sniffing toward the male by females was not affected significantly by EB treatment or OT injection. However, males paired with EB-treated females (N = 40) exhibited significantly longer durations of anogenital sniffing than did males paired with oil-treated females (N = 40), regardless of ICV injection (U = 981, $p<0.05$). Males directed similar levels of anogenital sniffing toward females that received ICV OT versus saline.

Side-by-side contact. EB-treated females spent significantly more time in contact with the male after receiving either 1 ng (U = 82, $p<0.01$), 300 ng (U = 75, $p<0.05$), or 1000 ng (U = 81, $p<0.01$) of OT versus saline injections (Fig. 3). Oil-treated females were in side-by-side contact with the male for similar periods of time regardless of ICV injection.

Aggression. Female aggression was significantly reduced in EB-treated females that received either 1 ng (U = 17, $p<0.01$), 300 ng (U = 20, $p<0.002$), or 1000 ng (U = 22, $p<0.05$) of OT when compared to saline-injected females (Fig. 4). Oil-treated females exhibited similar levels of aggression regardless of ICV injection. Male aggression was unaffected by being paired with either oil- or EB-treated females that received either OT or saline injection.

IP OT in Estrous and Nonestrous Females

Copulatory interactions. Oil-treated females remained nonreceptive after OT injection. All EB-treated females remained receptive after IP OT injection. Lordosis frequencies and durations in OT-injected females did not differ from saline controls.

Autogrooming. Autogrooming durations in oil- and EB-treated females did not differ from saline controls as a function of OT injection. Male autogrooming was unaffected by pairing with an oil-treated female that had received OT versus saline injections. However, male autogrooming durations were significantly longer when males were paired with an EB-treated female that had received either 3 μg OT (U = 16, $p<0.05$) or 10 μg OT (U = 15, $p<0.05$), than when paired with females that received saline injections (Fig. 5). Autogrooming durations in males paired with EB-treated females that received 1 μg OT did not differ significantly from those in males paired with EB-treated females that were saline-injected.

Anogenital investigation. Oil- and EB-treated females were

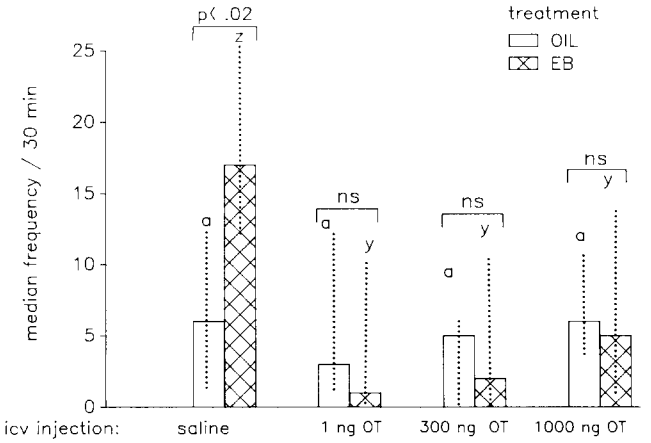

FIG. 4. Median frequencies of female aggression directed toward the male after ICV oxytocin or saline injection. Dotted lines signify upper and lower hinges of interquartile ranges. N = 10 per group. Groups with different letters differ significantly ($p<0.05$), ns = not significant.

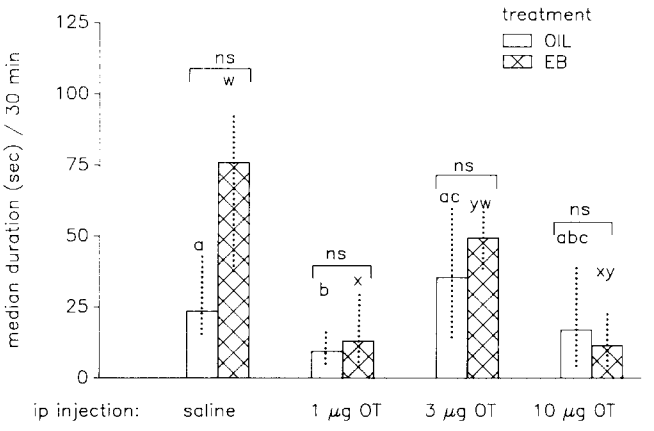

FIG. 6. Median durations (sec) of male anogenital sniffing directed toward the female in pairs with females that received IP injections of oxytocin or saline. Dotted lines signify upper and lower hinges of interquartile ranges. See Fig. 5 for group sizes. Groups with different letters differ significantly ($p<0.05$), ns = not significant.

similar in the durations of anogenital sniffing directed toward the male; IP-OT injections did not significantly influence female anogenital sniffing. Males paired with EB-treated females that received saline injections exhibited significantly more anogenital sniffing than males paired with females that received either 1 μg OT ($U=61$, $p<0.01$) or 10 μg OT ($U=59$, $p<0.05$, Fig. 6). Males paired with EB-treated females that received 3 μg OT did not differ from males paired with saline controls. However, males exhibited significantly shorter durations of anogenital sniffing when paired with oil-treated females that received 1 μg OT than did males paired with either saline-injected females ($U=68$, $p<0.01$) or females receiving 3 μg OT ($U=13$, $p<0.04$, Fig. 6). Males exhibited similar durations of anogenital sniffing when paired with oil-treated females that received either 3 or 10 μg OT, or saline injections.

Side-by-side contact. Durations of side-by-side contact between pairs were unaffected by EB treatment. IP OT injections of the females also did not significantly alter side-by-side contact.

Aggression. The frequency of female aggression did not differ as a function of EB treatment or OT injection of the females. However, males paired with oil-treated females that received saline injections were significantly more aggressive than males paired with females that received either 1 μg ($U=33$, $p<0.01$), or 10 μg ($U=32$, $p<0.01$, Fig. 7) of OT. Aggression in males paired with EB-treated females that received 3 μg of OT did not differ from that observed in males paired with saline-injected females or from those paired with females receiving either 1 or 10 μg OT injections.

DISCUSSION

Several studies in female rats have shown that OT injections can facilitate female sexual receptivity (1, 8, 22). In contrast, the present analysis of the effects of OT in prairie voles offered no

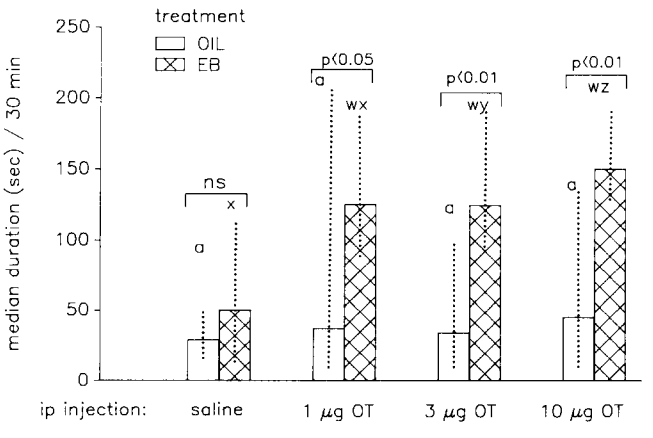

FIG. 5. Median durations (sec) of male autogrooming after females received IP oxytocin or saline injections. Dotted lines signify upper and lower hinges of interquartile ranges. Oil-treated groups received: saline (N = 10) or 1 μg (N = 8), 3 μg (N = 8), 10 μg (N = 6) of oxytocin. EB-treated groups contain 10 females per IP dose injection. Groups with different letters differ significantly ($p<0.05$), ns = not significant.

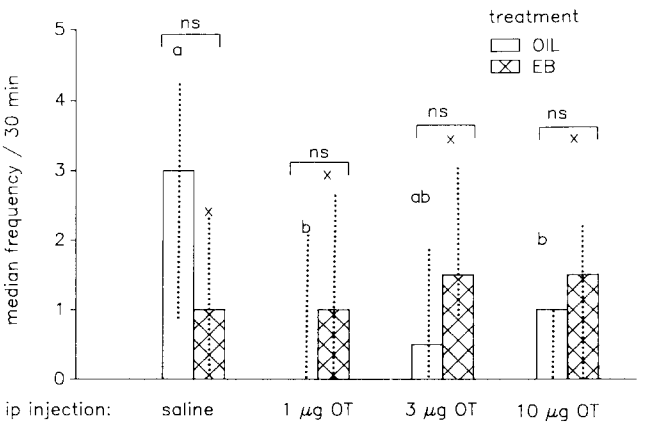

FIG. 7. Median frequencies of male aggression directed toward the female in pairs with females that received IP injections of oxytocin or saline. Dotted lines signify upper and lower hinges of interquartile ranges. See Fig. 5 for group sizes. Groups with different letters differ significantly ($p<0.05$), ns = not significant.

evidence for a facilitation of sexual behavior. Furthermore, centrally, but not peripherally injected OT inhibited sexual behavior in female prairie voles.

It is possible that there are parallels between the behavioral effects of OT and progesterone (22). In rats, both OT and progesterone surge on the night of proestrus (38) and both can facilitate sexual receptivity. In contrast, the effects of progesterone (20) and OT (present study) are primarily inhibitory in prairie voles.

Voles, along with other induced ovulators, rely predominantly on estrogen (3, 4, 23) and social signals from the male (14,15) for estrus induction. Among spontaneous ovulators such as rats hormonal signals, including the release of progesterone, OT, and LHRH (33), may synchronize the onset of sexual behavior and ovarian function. Moreover, recent studies of central OT receptors have indicated that receptor densities levels in the hypothalamus are steroid-dependent in rats (25,26), but not in prairie voles (47).

Mating and maternal behavior, including nursing, contribute to reproductive success. However, these biological events are mutually exclusive and require a mechanism for time-sharing between the two behavioral systems involved in mating and maternal interactions (21). OT may function as a hormone during suckling episodes and as a neuromodulator during mating bouts thus mediating different behavioral responses. The present study, and early evidence that suckling inhibits sexual receptivity in prairie voles (46), supports the assumption that OT could be part of the physiological message associated with sexual satiety. This assumption also could be supported by the absence of steroid regulation of hypothalamic OT receptors in prairie voles (47). Also there is no evidence that postcopulatory sexual satiety is steroid-dependent in males (37) or females (11).

The possibility exists that female prairie voles respond to ICV OT in a manner similar to that reported in males of other species. In male rats and rabbits, infusions of OT into the third ventricle increased latencies to mount and intromit, and lengthened the postejaculatory refractory period (PEI) (24,28). The authors of these studies have proposed that OT mediates sexual satiety in males. In male prairie voles, OT (300 ng, ICV) also produced an immediate cessation in sexual behavior without inhibiting other behavioral patterns (Mahalati, Okanoya and Carter, unpublished observations). A role for OT in sexual satiety also has been proposed in humans. Davidson (17) speculated that OT release in human females may stimulate uterine contractions during orgasm and thereby contribute to either the "subjective and/or physiologic events of orgasm specifically those involved in sexual satiation." The mechanisms of action by which OT exerts behavioral effects are unknown. However, in prairie voles endogenous release of OT may summate to result in eventual sexual satiety. The studies presented here indicate that female prairie voles may show behaviors associated with sexual exhaustion, and support the hypothesis that OT release may signal and/or mediate sexual satiety.

It is possible that OT's inhibitory effects on sexual behavior were secondary to its effects on general health or the arousal condition of the female. There is some evidence for active transport of vasopressin-like peptides, such as OT, across the blood-brain barrier (2). Arletti and Bertolini (1) demonstrated that peripheral (IP) administration of OT altered sexual receptivity in rats. Arletti and Bertolini (1) concluded that in estrogen- and progesterone-primed rats the site of action for OT was probably in the CNS, and suggested that some peripherally administered OT reached the CNS. In the present study we examine the behavioral effects of relatively large doses of IP-injected OT. However, no evidence was observed of behavioral toxicity after ICV or IP OT. Only specific components of behavior were affected and these effects occurred only in the presence of high levels of steroid priming. Other behavioral measures indicated that OT-injected females were in good health, behaved normally, and pharmacologically induced stereotypies were absent.

IP OT did not affect nonsexual behaviors in female prairie voles. However, male responses (Figs. 5, 6 and 7) to IP OT-injected females were altered significantly, especially in females receiving EB treatment. It is possible that the male's reductions in anogenital investigation and aggression and increased autogrooming reflects a decrease in the stimulus value of the female for the male following peripheral OT. OT may alter the female's odor, body temperature, the production of ultrasonic vocalizations or other subtle behaviors [reviewed in (43)] which could inform the male that the female has been mated or is about to give birth. It is possible that peripherially administered OT may mimic processes that are normally associated with lactation or parturition.

ICV OT also affected nonsexual behaviors, but these effects were independent of OT's effects on sexual receptivity. For example, autogrooming was significantly increased in ICV OT-injected females that were treated with EB despite OT-inhibited sexual behavior. Centrally administered OT enhanced autogrooming in rats (9,18) at doses similar to those used in the current study.

OT increased autogrooming in prairie voles only when estrogen levels were sufficient for the display of sexual receptivity, but OT-enhanced autogrooming did not require the display of sexual behavior. OT-enhanced autogrooming could affect chemosignal reception during mating and/or mediate processes involved in mate recognition or pairbonding in this monogamous rodent (12). Furthermore, the recent discovery of estrogen-regulated OT receptors in the anterior olfactory nucleus of female prairie voles (47) suggests a role for OT in the mediation of olfactory events in this species. These results, in concordance with data on OT-enhanced autogrooming and increased side-by-side contact, suggested that olfactory processing may be altered by estrogen stimulation and OT release. It is possible that OT modulates olfactory responses associated with avoidance or fear of strangers (12).

In sheep, vaginal stimuation and presumably OT release have been implicated in maternal bonding (31). Work on filial bonding in sheep also has implicated the olfactory system in the release of OT following vaginal stimulation (28,30) or during parturition and suckling (28,29) may influence maternal bonding (27,31) or the olfactory recognition of offspring (30). The hypothesis that OT may facilitate social bonding or mate recognition in prairie voles is supported by the observed increases in affiliative behavior and reduced aggression. Affiliative behavior, such as side-by-side contact, increased while female aggressive responses decreased in estrogen-primed and OT-injected female voles. This interaction between estrogen and centrally administered OT suggests that social behavior is encouraged even when sexual behavior is inhibited or has subsided. OT mediation of affiliative contact might facilitate social bond formation during copulation (12).

Current data indicate that in female prairie voles OT enhances the female's willingness to interact socially, but not sexually. These findings suggest a new function for OT in adult social bond formation (12) and support the hypothesis that OT mediates sexual satiety. In addition, OT appears to alter the stimulus value of the female. OT may be involved in a variety of undiscovered "adaptive" behaviors (32). Moreover, OT receptors found throughout the central nervous system, and their patterns of distribution and steroid-sensitivity, vary across species (47). Cross-species comparisons and detailed analyses of behavior are essential in discovering the functions of hormones and neuropeptides.

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