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# Sex differences and developmental effects of oxytocin on aggression and social behavior in prairie voles (*Microtus ochrogaster*)

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**Abstract**

Various hormones, including sex steroids and neuropeptides, have been implicated in aggression. In this study we examined (1) sex differences in intrasexual aggression in naïve prairie voles; (2) the effects of developmental manipulations of oxytocin on intrasexual aggression; and (3) changes in patterns of intrasexual aggression after brief exposure to an animal of the opposite sex. Within 24 h of birth, infants were randomly assigned to receive either an injection of oxytocin (OT) or oxytocin antagonist (OTA) or to one of two control (CTL) groups receiving either isotonic saline or handling without injection. As adults, animals were tested twice in a neutral arena; before (Test 1) and 24 h after (Test 2) a 4-h exposure to an animal of the opposite sex. In Test 1, CTL males were more likely to show aggressive and less likely to show social behavior than CTL females. No significant treatment differences were observed within either sex in Test 1. In Test 2, after brief exposure to a male, females treated with OT became more aggressive and less social than OTA or CTL females. Male aggressive behavior did not change after exposure to a female. An increase in aggression and decline in social behavior toward other females, seen here in OT-treated females, is typically observed only following several days of female–male cohabitation. These findings demonstrate a sex difference in intrasexual aggression and suggest that neonatal exposure to OT may facilitate the onset of the mate-guarding component of pair bonding in female prairie voles.


*Keywords:* Oxytocin; Prairie voles; Pair bonding; Aggression; Sex differences

## Introduction

Aggression can play a major role in the determination of mating systems and social organization. For example, in polygynous species intrasexual aggression, especially among males, is associated with competition for mating opportunities (Trivers, 1972). However, among monogamous species aggression is less common or less intense in reproductively naïve animals and often appears during or after the formation of a partner preference; aggression under these circumstances may serve to guard the pair bond or mate from competitors of the same sex. Mammalian monogamy has been defined by the capacity to form heterosexual pair bonds, including selective social preferences for a familiar partner and by aggression toward strangers, especially those of the same sex (Kleiman, 1977). In at least some socially monogamous species, sexually active animals may fight or harass to the point of death same-sex conspecifics (prairie voles, Gavish et al., 1981; Firestone et al., 1991; marmosets and tamarins (family Callitrichidae), Kleiman, 1979; French and Inglett, 1989; Saltzman et al., 1996; Snowdon and Pickhard, 1999).

Most research on aggression is conducted in males, and a number of studies recently have implicated androgen-dependent neural circuits that rely on vasopressin in male aggression (Compaan et al., 1993; De Vries and Villalba, 1997; De Vries and Miller, 1998; Ferris and Delville, 1994; Nelson and Chiavegatto, 2001). A sex difference in the incidence of aggression is often taken as evidence for a role for sexually dimorphic mechanisms. However, direct comparisons between males and females are not common and

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studies examining the mechanisms of sex differences in aggression are rare.

Prairie voles (*Microtus ochrogaster*) are small arvicoline rodents that display a monogamous social system, forming pair bonds and showing mate guarding in both the field and the laboratory (Getz et al., 1981; Winslow et al., 1993; Carter et al., 1995). This species offers an opportunity to examine possible mechanisms through which hormones, present in either early life or adulthood, may regulate social behaviors, including aggression. Prairie voles lack sexual dimorphism in body size and there is evidence that gonadal steroids are comparatively low (Klein and Nelson, 1998). In contrast, oxytocin in prairie vole serum is over twice as high as that in rats (Kramer et al., 2002). Pair bonding in prairie voles may be particularly sensitive to or dependent on neuropeptides, including oxytocin and arginine vasopressin (reviewed Carter and Keverne, 2002; Cho et al., 1999; Insel and Young, 2001). Both male and female prairie voles are capable of forming pair bonds even without mating and in the absence of gonadal hormones in adulthood (Williams et al., 1992; DeVries et al., 1995, 1996; Demas et al., 1999; Cho et al., 1999). In males (Winslow et al., 1993), but not females (Bowler et al., 2002), copulatory experience is necessary for the most dramatic increase in aggression.

Vasopressin has been implicated in the development of aggression in prairie voles (Stribley and Carter, 1999). Studies of mice with selective deletions of the gene for oxytocin (DeVries et al., 1997b; Winslow et al., 2000) as well as studies in rats of the mechanisms of early experience also may indirectly implicate oxytocin in aggression. However, studies directly examining the effects of neonatal peptide manipulations on the later expression of aggressive and social behaviors are uncommon.

In the present study we examined (1) sex differences in intrasexual aggression in naïve prairie voles; (2) the effects of developmental manipulations of oxytocin on intrasexual aggression in naive males and females; and (3) changes in patterns of intrasexual aggression after brief exposure to an animal of the opposite sex.

## Methods

Subjects were laboratory-bred male and female prairie voles, descendants of a wild stock originally caught near Champaign, Illinois. Stock was systematically outbred. Animals were maintained on a 14-h light:10-h dark cycle and allowed food (Purina rabbit chow) and water *ad libitum*. Breeding pairs were maintained in large polycarbonate cages (44 × 22 × 16 cm) and provided with cotton for nesting material. At 21 days of age offspring were removed and housed in same-sexed sibling pairs in smaller (27 × 16 × 13 cm) cages. The same-sex sibling pairs were then kept in single-sexed colony rooms.

Within 24 h of birth, test subjects randomly received either a single 3-$\mu$g injection of oxytocin (Peninsula Laboratories, San Carlos, CA) or a single 0.3-$\mu$g injection of oxytocin antagonist (OTA) or were assigned to one of two control groups receiving either an injection of isotonic saline (SAL) or handling without injection (HAN). The OT receptor antagonist [(d($CH_2$)$_5$, Tyr(Me)$^2$, Om$^8$)-Vasotocin] used here was selected from the compounds designed by Bankowski et al. (1980) and is commercially available from Peninsula Laboratories. This compound has been tested extensively in behavioral studies, including those of sexual (Argiolas et al., 1987) and feeding behavior (Arletti et al., 1989; Olson et al., 1991). A lower dose of OTA than OT was used because in studies in rats, the OTA has been shown to be approximately 10–100 times more effective in receptor binding than the natural ligand (Barberis and Tribollet, 1996). All groups consisted of 9 to 13 animals. All injections were 50 $\mu$l in volume and administered intraperitoneally in 250-$\mu$l gas-tight Hamilton syringes. Infants were weighed and toe-clipped for identification on the day of birth. Although litters were not matched for pup number, infants were only used in the study if at least 1 control and 1 treatment animal of a given sex were available in the litter, and litters of more than six pups at birth were culled to six.

Animals were studied as part of a larger project on the developmental effects of oxytocin or OTA, in which subjects also received two tests for alloparental behavior (methods as described in Roberts et al., 1998) and one test for activity in an elevated plus-maze (Insel et al., 1995) prior to their first aggression test. The results from those tests are presented elsewhere.

The aggression test consisted of being placed for 5 min in a neutral arena (27 × 16 × 13 cm mouse cage) with an unfamiliar stimulus animal of the same sex and the same approximate age and size. Stimulus animals were prescreened for aggressive behavior and only nonaggressive animals were used. Each stimulus animal was identified by a small plastic collar. Despite the pretest screening, a few stimulus animals were aggressive toward the test animal; tests in which the stimulus animals were initially aggressive were eliminated from the data set. Only animals for which we had two tests, in neither of which the stimulus animal was initially aggressive, are reported here. Tests that were not included were evenly distributed across the four treatment conditions. Stimulus animals were placed in the arena first and test animals placed immediately afterward.

Each test was video-taped and scored later by an experimentally blind rater, using Noldus Observer 3.0 software. Aggressive behaviors observed included lunges (frequency only) and chases (frequency and duration). No actual physical attacks were observed. Defensive behaviors, scored separately from aggression, included an upright rearing posture (frequency and duration). Social contact was defined as sitting in physical contact (frequency and duration). Other behaviors, here collectively called displacement behaviors, included digging (frequency and duration), autogrooming (frequency and duration), and rearing (frequency only). The dyadic encounter test has been used extensively in this

Table 1
Means (±standard errors) for the frequency and durations (in seconds) of behaviors by CTL animals in Test 1

| | Female | Male |
|---|---|---|
| Aggression | | |
| Frequency* | 1.71 ± 1.15 | 2.79 ± 1.01 |
| Duration* | 0.17 ± 0.17 | 1.65 ± 0.74 |
| Social | | |
| Frequency* | 0.71 ± 0.23 | 0.04 ± 0.04 |
| Duration* | 3.54 ± 2.02 | 0.04 ± 0.04 |
| Defensive | | |
| Frequency | 0.67 ± 0.42 | 1.12 ± 0.62 |
| Duration | 1.13 ± 0.54 | 1.62 ± 0.42 |
| Displacement | | |
| Frequency | 15.0 ± 2.08 | 20.12 ± 2.91 |
| Duration | 5.12 ± 1.30 | 11.54 ± 4.02 |

Behaviors included in each category are described under Methods.
* Significant sex differences.

laboratory and in others (Winslow et al., 1993; Harper and Batzli 1997; Bowler et al., 2002) and has been shown to be sensitive to the social and hormonal history of the animal.

The day after the first aggression test (Test 1), the test animal received a 1-h exposure to an adult animal of the opposite sex (here designated the "partner"), followed by a 3-h partner preference test in which animals could elect to spend time with the partner or a comparable opposite-sexed stranger (methods in Williams et al., 1992). Experimental animals were returned to the home cage with their sibling following this test.

Prior research suggests that this procedure does not usually produce a selective partner preference in untreated animals (DeVries et al., 1996, 1997a; Williams et al. 1992). All animals used as stimulus animals were reproductively naïve. Stimulus females were vaginally lavaged before the preference procedure; the vaginal smear was checked for cornified cells, to confirm the female's reproductive status. Tapes were also examined to assure that no mating took place during the test. On the day following the partner preference test, a second aggression test (Test 2) was conducted as described above. Although we did not necessarily use the same stimulus animal in both tests for a given subject, these stimulus animals also were prescreened to eliminate aggressive animals. This research complies with NIH standards and was approved by the University of Maryland Animal Care and Use Committee.

### *Data analysis—sex differences*

At the beginning of data analysis, data from the two control groups (HAN and SAL) were analyzed. HAN and SAL groups did not show significant differences and were therefore combined into one control group (CTL) for the remaining analysis. Data from CTL males ($n = 22$) and females ($n = 20$) in Test 1 were examined for possible sex differences in the tendency to show social and aggressive behavior. Although both frequency and duration data were obtained, these data were not normally distributed; many animals showed no aggression, while a few showed very high levels of aggression. To simplify these data, the percentages of animals displaying at least one instance of a given class of behaviors (aggressive, social, defensive, or displacement) were analyzed using Fisher's exact test, with a level of significance assigned at $P < 0.05$. Means are presented in Table 1 to allow comparison with previously published papers; however, these were not statistically analyzed.

### *Data analysis—treatment differences and effects of exposure to an animal of the opposite sex*

Treatment group differences were examined using nonparametric Kruskal–Wallis tests. Once again, HAN and SAL groups did not differ significantly and were therefore combined. To examine the effects of treatment on behavior during the second test, a change score for each category of behavior was calculated. If an individual animal's frequency of a given behavior increased from Test 1, it was assigned a +1, if decreased it was assigned a −1, and if the level of behavior remained the same it was assigned a 0. This scale was chosen in order to standardize the data and eliminate results that appeared significant but were based on one or two very aggressive animals. Differences between treatments in this change score were then examined nonparametrically in a Kruskal–Wallis test. All statistics were performed in SAS 8.0 (SAS Institute, Cary, NC).

## Results

### *Sex differences*

Female and male controls differed in both aggressive and social behaviors (Fig. 1). A significantly higher proportion

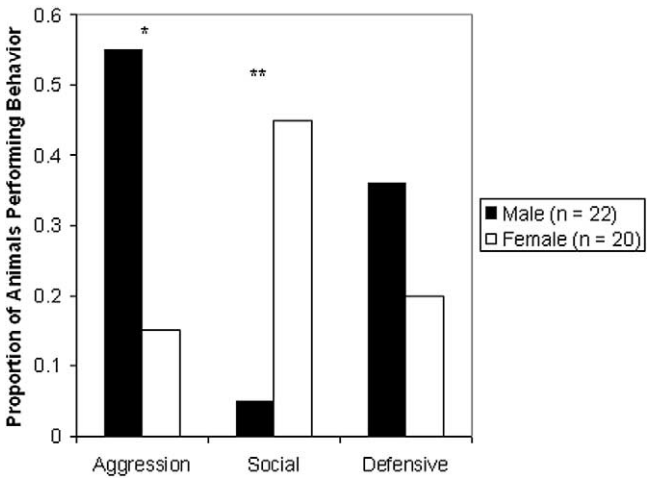


Fig. 1. Proportion of control males and females displaying different categories of behavior in Test 1. *$P < 0.05$. **$P < 0.01$.

Table 2
Comparison of the proportion of females receiving different neonatal treatments performing different categories of behaviors—Test 1

| | OT ($n$ = 11) | OTA ($n$ = 12) | CTL ($n$ = 20) | Statistics and $P$ values |
|---|---|---|---|---|
| Aggression | | | | |
| Proportion | 0.18 | 0.08 | 0.15 | $P = 0.123$<br>$p = 0.864$ |
| Social | | | | |
| Proportion | 0.36 | 0.42 | 0.45 | $P = 0.072$<br>$p = 0.924$ |
| Defensive | | | | |
| Proportion | 0 | 0.08 | 0.20 | $P = 0.068$<br>$p = 0.413$ |
| Displacement | | | | |
| Mean ± SEM | 19.55 ± 4.68 | 16.17 ± 2.26 | 15.9 ± 2.23 | $\chi^2 = 0.592$<br>$p = 0.744$ |

of males behaved aggressively ($P = 0.008$, $p = 0.011$), while a significantly higher proportion of females behaved socially ($P = 0.003$, $p = 0.003$). Sex differences in defensive behaviors were not significant ($P = 0.169$, $p = 0.50$). Because all but one CTL animal displayed at least one displacement behavior, a nonparametric comparison of the proportions of the males and females displaying these behaviors was not made. Frequencies of displacement behaviors did not differ between males and females (Kruskal–Wallis test; $\chi^2 = 0.31$, $p = 0.579$). Means and standard errors for all behavioral categories are in Table 1.

*Treatment effects—Test 1 only*

There were no significant treatment differences in either females or males in Test 1 (Tables 2 and 3).

*Treatment effects after exposure to an animal of the opposite sex*

*Females*

After exposure to a male, oxytocin-treated females showed a greater increase in aggression than either OTA or CTL females ($\chi^2 = 6.85$, $p = 0.033$; Fig. 2). Oxytocin-treated females also showed reduced social behavior, although this change was not significant ($\chi^2 = 2.87$, $p = 0.238$; Fig. 2). However, an examination of proportions of animals displaying social behavior in Test 2 shows that oxytocin-treated females were less social than the other two groups ($P < 0.0001$, $p = 0.01$; Fig. 3). CTL and OTA females did not show a significant change in either aggressive or social behavior after exposure to a male. Defensive and displacement behaviors did not change significantly for any treatment after exposure to a male.

*Males*

Exposure to a female did not significantly change male aggressive, social, defensive, or displacement behavior for any treatment group.

## Discussion

*Sex differences in aggression*

In the present study levels of intrasexual aggression were higher and social contact was lower in sexually naive males versus females. The results of this study are consistent with

Table 3
Comparison of the proportion of males receiving different neonatal treatments performing different categories of behaviors—Test 1

| | OT ($n$ = 9) | OTA ($n$ = 13) | CTL ($n$ = 22) | Statistics and $P$ values |
|---|---|---|---|---|
| Aggression | | | | |
| Proportion | 0.56 | 0.23 | 0.55 | $P = 0.013$<br>$p = 0.165$ |
| Social | | | | |
| Proportion | 0.11 | 0 | 0.05 | $P = 0.209$<br>$p = 0.453$ |
| Defensive | | | | |
| Proportion | 0.56 | 0.46 | 0.36 | $P = 0.038$<br>$p = 0.490$ |
| Displacement | | | | |
| Mean ± SEM | 15.78 ± 2.88 | 14.54 ± 3.38 | 18.95 ± 3.08 | $\chi^2 = 1.700$<br>$p = 0.427$ |

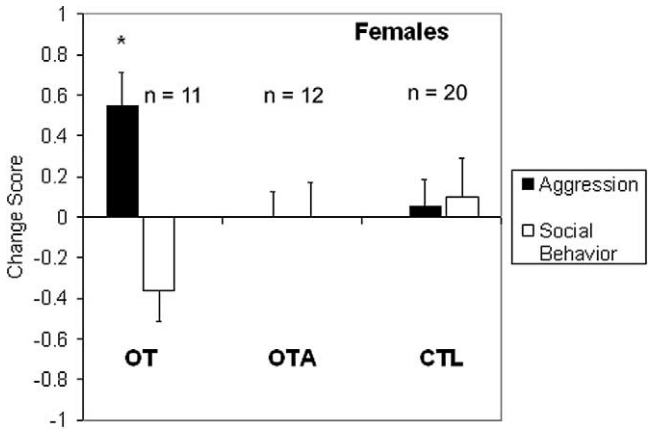


Fig. 2. Change scores for female aggression and social behavior after exposure to a male (score = +1 if frequency of given behavior increases, −1 if given behavior decreases, and 0 if no change). *$P < 0.05$.

sex differences in wounding rates for prairie voles from one field study (Rose and Gaines, 1976). However, in other studies of sexually naive prairie voles sex differences in aggression have been minimal (Getz, 1962; Harper and Batzli, 1997; Stribley and Carter, 1999). The levels of male aggression measured in control animals in the present study were high when compared to those of nontreated, sexually inexperienced animals in other studies from this same laboratory (Stribley and Carter, 1999). However, it may be important to note that the control animals that were used in the present study were handled and toe-clipped as infants. Separations from the mother or other early manipulations have been shown to increase aggression in other rodents (Levine, 1959; Boccia and Pedersen, 2001); it is possible that male prairie voles are especially sensitive to early experience.

Neither castration (Demas et al., 1999) nor ovariectomy (Bowler et al., 2002) reduces aggression in prairie voles, suggesting that gonadal steroids in adulthood are not essential for the expression of aggression. However, peptide hormones, and especially vasopressin, have been implicated in male aggression in several species, including prairie voles (Winslow et al., 1993; Stribley and Carter, 1999; Albers and Bamshad, 1998). It is possible that vasopressin, which is more prevalent in males (Bamshad et al., 1993) plays a role in the observed sex differences.

Cohabitation-induced aggression in females does not require mating and is not dependent on ovarian hormones (Bowler et al., 2002). Preliminary attempts to induce aggression with a single centrally administered vasopressin injection in adult female prairie voles were not successful (Bowler and Carter, unpublished). However, we cannot discount a role for vasopressin in the development of female aggression, since a subset of females exposed to vasopressin during the first week of life were markedly more aggressive, while females treated with a vasopressin (V1a) antagonist rarely showed aggression (Stribley and Carter, 1999).

Although aggression in female prairie voles is less common and less well understood than that in males, the consequences of female–female interactions can be significant. When two females in estrus are paired with a male over a period of time, one of the females usually dies (Gavish et al., 1981; Firestone et al., 1991). Thus, same-sex aggression and social harassment may be biologically relevant in both males and females of this species.

### *Developmental consequences of oxytocin*

Under the conditions of the present experiment, developmental administration of oxytocin appeared to affect intrasexual aggression more strongly in female prairie voles than in males. Female prairie voles typically become aggressive toward other females following a period of male cohabitation lasting for several days (Bowler et al., 2002). Thus, the observation in the present study of high levels of female–female aggression after only a few hours of exposure to a male partner in neonatally oxytocin-treated females was unexpected. The mechanisms underlying the increase in female aggression following male exposure, observed here and in other studies (Bowler et al., 2002), remain to be identified. However, a recent analysis of the long-term consequences of neonatal oxytocin suggests that early treatment with this peptide can increase the expression of oxytocin in later life (Yamomoto et al., 2002). Thus it is possible that early exposure to oxytocin enhances the later functions of this peptide. Neonatal treatment with an oxytocin antagonist (OTA) did not significantly influence later patterns of intrasexual aggression in either males or females. However, there was a tendency toward lower levels of aggression in OTA-treated males: 23% compared to 55–56% of males in other groups. Previous studies, including data from a subset of the animals tested here, have revealed that a single exposure to OTA in early life has long-lasting behavioral effects. When tested at 21 days of age, OTA-treated animals showed lower levels of male parental be-

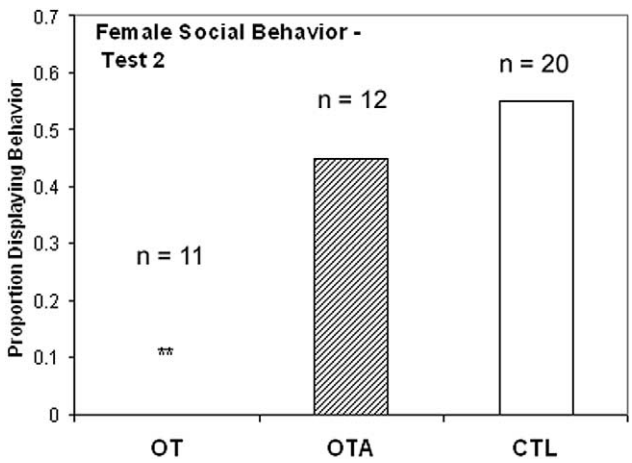


Fig. 3. Proportion of females displaying social behavior in Test 2. **$P < 0.01$.

havior and an increased incidence of pup attacks (Pfeifer et al., 2001).

The absence of a significant effect of neonatal oxytocin on aggression does not allow us to conclude that males are incapable of responding to oxytocin; when injected in prairie voles on postpartum day 1, the doses of oxytocin and OTA and methods of administration used here have been shown to produce a significant increase in cFos expression, measured 1 h after injection in the supraoptic nucleus. The effects of these injections on cFos expression were especially apparent in males, in part because spontaneous cFos expression was higher in females (Cushing et al., 2003). We have also observed that neonatal oxytocin treatment given as described here (and including some animals used in this study) facilitates the onset of a partner preference in male prairie voles (Bales and Carter, 2003); in addition, a single treatment, especially with OTA, may have an inhibitory effect on sperm transport (Bales et al., 2001). Thus, neonatal manipulations of oxytocin can have long-term consequences in males, making the apparent absence of an effect on male aggression particularly interesting. It is possible that the higher baseline levels of aggression in males obscured possible effects of oxytocin. In addition, as described above males may depend more than females on vasopressin to regulate intrasexual aggression.

Oxytocin and vasopressin can influence each other's receptor systems and there is at present no evidence for a sex difference in oxytocin or vasopressin receptors in this species (Insel, personal communication). It is possible that the effects of oxytocin seen here in females were mediated through the vasopressin receptor system. However, if this is the case, one might expect the effects of oxytocin or OTA to be similar in males and females. While developmental administration of vasopressin facilitated adult aggression in female prairie voles in comparison to untreated animals (Stribley and Carter, 1999), the effects of vasopressin were not significantly different from those of a saline control, again suggesting a role for early stress in prairie vole aggression. In addition, in Stribley and Carter (1999) vasopressin was given each day for 7 days, while we administered here only a single injection on the first day of life.

In summary, in the present study intrasexual aggression was higher in untreated males than females. In addition, significant effects of neonatal oxytocin manipulations were observed only in females and only after exposure to a male. Procedural differences preclude a direct comparison of the present results with those of previous studies. However, the present data suggest the hypothesis that female aggressive behavior in prairie voles may be especially sensitive to neonatal manipulations of oxytocin and that such manipulations may enhance the tendency of female prairie voles to begin to show one component of pair bonding, i.e., intrasexual aggression. Mechanisms for these differences are not known, but may include increased availability of (Yamamoto et al., 2002b) or sensitivity to oxytocin.

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