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The effects of stress on social preferences are sexually dimorphic in prairie voles

(monogamy/partner preference/social behavior/corticosterone/adrenalectomy)

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ABSTRACT **Prairie voles (*Microtus ochrogaster*) are monogamous rodents that form pair bonds characterized by a preference for a familiar social partner. In male prairie voles, exposure to either the stress of swimming or exogenous injections of corticosterone facilitate the development of a social preference for a female with which the male was paired after injection or swimming. Conversely, adrenalectomy inhibits partner preference formation in males and the behavioral effects of adrenalectomy are reversed by corticosterone replacement. In female prairie voles, swim stress interferes with the development of social preferences and corticosterone treatments inhibit the formation of partner preferences, while adrenalectomized females form preferences more quickly than adrenally intact controls. Because sex differences in both behavior and physiology are typically reduced in monogamous species, we initially predicted that male and female prairie voles would exhibit similar behavioral responses to corticosterone. However, our findings suggest an unanticipated sexual dimorphism in the physiological processes modulating social preferences. This dimorphic involvement of stress hormones in pair bonding provides a proximate mechanism for regulating social organization, while permitting males and females to adapt their reproductive strategies in response to environmental challenges.**

Social bonds are critical to the establishment and maintenance of mammalian and avian social systems, and heterosexual pair bonds are particularly important in mammalian monogamy, where they provide the core of the family unit. However, both monogamy and pair bonding are comparatively rare in mammals and especially uncommon in rodents (1–3).

Prairie voles, *Microtus ochrogaster,* are small rodents that exhibit many characteristics of monogamy, including the formation of long-term pair bonds (4). In both male and female prairie voles, pair bonds are characterized by social preferences for the familiar partner, and, after mating, selective aggression toward unfamiliar conspecifics (5, 6). In the laboratory, the social preference for a familiar partner is used as an index of pair bonding, and reliable preferences for a familiar partner are exhibited after both sexual and nonsexual cohabitation (7). Because the field biology of this species also has been studied (4), research with prairie voles provides an opportunity to examine the proximate determinants of pair bonding in the context of natural history.

Socially naive male and female prairie voles usually leave their natal nest to breed and may form pair bonds during an initial encounter with an unfamiliar animal of the opposite sex. The tendency of prairie voles to abandon their family and form new pair bonds can be influenced by stress, probably through the action of hormones of the hypothalamic–pituitary–adrenal (HPA) axis. The primary adrenal steroid released during stress in prairie voles is corticosterone (B). However, even under basal conditions the HPA axis in prairie voles is exceptionally active; basal corticosterone levels are 5–10 times higher than those measured in rats or nonmonogamous montane voles (8). Serum corticosterone levels rapidly decline in naive female prairie voles exposed to an unfamiliar male (9). When this decline is prevented, females no longer form new pair bonds. For example, in female prairie voles, treatment with corticosterone immediately prior to cohabitation inhibited the formation, but not the expression, of a preference for the familiar partner. In contrast, in adrenalectomized females, new partner preferences were formed within 1 h or less, while adrenally intact or corticosterone-treated adrenalectomized females did not form preferences under comparable conditions (9). Thus, stimulation of the HPA axis inhibits the development of partner preferences in female prairie voles.

Monogamous mammals are characterized by a relative absence of sexually dimorphic traits (1, 2), and the behaviors associated with pair bonding appear similar in both sexes. Therefore, we initially hypothesized that stress or activation of the HPA axis also would inhibit pair bonding in male prairie voles. We have examined herein the effects of manipulations of hormones of the HPA axis, including corticosterone, on the development of partner preference behavior in male and female prairie voles. Experiment 1 compares the effect of swim stress and exogenous corticosterone on the development of social preferences in male and female prairie voles. Experiment 2 tests the hypothesis that exogenous corticosterone treatment modulates the development of partner preferences in male prairie voles. Experiment 3 examines the hypothesis that a reduction in the production of corticosterone, produced herein by removal of the adrenal gland, inhibits pair bonding in males.

METHODS

Animals. Prairie voles of the F_3 generation from a stock originally captured near Urbana, IL, were used as subjects. Animals were born and maintained in long-day conditions (14-h light/10-h dark; lights on at 0700 h Eastern Standard Time). They were weaned at 21 days of age and housed in same-sex sibling groups until 2 weeks before the start of the study, when they were individually housed. Animals had ad libitum access to tap water and Purina rabbit chow. All experimental animals were gonadally intact. To prevent changes in ovarian hormones and possible mating during cohabitation or testing, female stimulus animals were ovariectomized at least 2 weeks prior to behavioral testing.

Surgical Procedures. All procedures were performed in accordance with the guidelines for sterile surgery set by the University of Maryland Animal Care and Use Committee. A dorsomedial incision provided a clear view of the adrenal gland. During adrenal removal, gentle suction was applied to

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Abbreviation: HPA, hypothalamic–pituitary–adrenal.

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the adrenal while it was teased carefully away from the kidney capsule. The adrenal glands of the sham-adrenalectomized animals were located but not disturbed. After surgery, both adrenalectomized and sham-adrenalectomized animals were provided with a bottle containing a 3% NaCl solution, as well as a separate bottle of tap water. Adrenal surgeries were conducted 48 h prior to testing to allow serum levels of corticosterone to decline, while avoiding the potential for adrenal regeneration. Completeness of the adrenalectomies was assessed by examining the adrenal glands under a dissecting microscope to determine whether the adrenal was removed with the capsule intact. Also, corticosterone blood levels were measured at the end of the preference test. Data from adrenalectomized animals were included in the analysis only if the adrenal was removed with the capsule intact and if corticosterone levels were less than 5% of basal levels. Procedures for the analysis of corticosterone are described elsewhere (9). Bilateral ovariectomies of stimulus females followed similar procedures and were conducted 2 weeks prior to testing.

Corticosterone Injections. All injections were administered intraperitoneally (i.p.) 30 min prior to pairing the experimental animal with its partner. The vehicle used was 20% propylene glycol in PBS. The doses of corticosterone selected produce circulating corticosterone levels that are within the physiological range of prairie voles that have experienced a 3-min swim test (9).

Corticosterone Replacement Pellets. A 250-mg pellet containing 40% corticosterone (60% cholesterol) was used to maintain serum corticosterone (B) (1000–1200 ng/ml) within the physiological range in one group of adrenalectomized male prairie voles (ADX + B). At the time of surgery, the pellets were cut in half to facilitate implantation. Both halves were implanted subcutaneously, between the scapulae, while the animals were still under anesthesia for the adrenalectomy.

Swim Stress. The 3-min swim tests were conducted in polycarbonate tanks (20 × 25 × 45 cm) filled with tap water to a depth of 15 cm. At this depth the voles could neither touch the bottom of the tank nor climb out. The water was maintained at 32 ± 1°C and the tanks were emptied and cleaned between each animal. After 3 min of swimming, the animals were removed from the tank using a small net and returned to their home cages. Swimming for 3 min is followed by an approximate doubling of serum corticosterone levels (9).

Behavioral Testing. Social preferences of experimental animals were assessed through the use of a three-chambered test apparatus (7). This apparatus consisted of two parallel stimulus chambers (12 × 18 × 28 cm) each of which was adjoined to a third, neutral chamber (12 × 18 × 28 cm) by a hollow tube (17.5 × 16 cm). The partner of the experimental animal was tethered loosely in one of the parallel chambers and the stranger was tethered in the other parallel chamber to restrict their movement to within their own chamber. The experimental animal was able to move freely among all three chambers. The partner was operationally defined as the animal with which the experimental animal had cohabitated prior to the preference test. The stranger had not previously encountered the experimental animal and was otherwise matched to the partner in terms of sex, age, size, and reproductive status. The 3-h preference tests were monitored using time-lapse video taping, with a 12:1 temporal reduction and scored by an experimentally uninformed observer, for the following points: (*i*) duration of physical contact between the experimental subject and the partner or stranger, (*ii*) activity, measured as the frequency of entry into the neutral cage, and (*iii*) frequency of aggression, including the incidence of threats, attacks, or fights.

Statistics. Social preferences in each treatment group were assessed by a paired *t* test comparing the mean time spent in physical contact with the partner versus the stranger. Differences were considered statistically significant at $P < 0.05$. Total time spent in physical contact with the stimulus animals (partner + stranger) and activity were compared among treatment groups using an ANOVA. Agonistic behaviors also were monitored but were too infrequent to allow statistical analysis.

Experiment 1. The effects of exposure to the stress of swimming or exogenous corticosterone treatment on the subsequent formation of social preferences were compared in male and female prairie voles. Because pilot studies indicated that male and female prairie voles respond differently to these treatments, 6 h of cohabitation was chosen. This time period normally leads to a preference for the familiar partner in females but not males. Thirty minutes after either 3 min of swimming or receiving an i.p. injection of corticosterone (20 μg), the experimental animals were paired with a stimulus animal of the opposite sex for 6 h. Additional groups of males and females that were adrenalectomized also experienced the swim stress. At the end of the 6-h cohabitation period, social preferences of the experimental animals were assessed during a 3-h preference test as described above. Males and females were assigned to the following groups: 1, no stress control (n = 8 males and n = 8 females); 2, swim stress (n = 10 males and n = 15 females); 3, adrenalectomized + swim stress (n = 11 males and n = 12 females); 4, vehicle-injected controls (n = 7 males and n = 11 females); 5, corticosterone B (20 μg)-treated animals (n = 10 males and n = 11 females).

Experiment 2. The results of Experiment 1 indicated that either the stress of swimming or a single injection of corticosterone could facilitate partner preference development in male prairie voles. A previous study in females (9) revealed a dose-dependent reduction in partner preferences after corticosterone injections. Experiment 2 was designed to examine the dose–response characteristics of an acute increase in corticosterone (B) in male prairie voles. Adrenally intact males received an i.p. injection of corticosterone (2 μg of B, n = 12; 20 μg of B, n = 12; or 200 μg of B, n = 12) or the vehicle (n = 12) or remained as noninjected controls (CTL, n = 12). Other procedures were identical to those in Experiment 1.

Experiment 3. Based on the outcome of Experiments 1 and 2, we hypothesized that adrenalectomy, which eliminates the major endogenous source of corticosterone, would inhibit pair bonding in male prairie voles. One group of males was adrenalectomized (ADX; n = 12), preventing an increase in adrenal steroids in the presence of stressful stimuli. A second group (ADX + B; n = 8) underwent adrenalectomy and immediately received a corticosterone pellet (250 mg) that maintained serum corticosterone within the physiological range. Control animals were either untreated (CTL; n = 11) or sham-adrenalectomized (SHAM; n = 14) prior to pairing. Socially naive male prairie voles that had received these treatments were paired in their home cage with a female partner for 24 h. In adrenally intact males this produces a reliable preference for the familiar partner. Partner preferences then were tested as in Experiment 1.

RESULTS

Experiment 1. Males do not usually form partner preferences after 6 h of nonsexual cohabitation (Fig. 1) (Control "no stress," n = 8, t = 0.89, not significant; vehicle, n = 7, t = 0.36, not significant). However, males that were either given 3 min of swimming (n = 10, t=2.46, $P < 0.05$) or a 20-μg corticosterone (B) injection (n = 10, t=2.30, $P < 0.05$) 30 min prior to cohabitation exhibited significant partner preferences. In addition, adrenalectomy inhibited the formation of preferences for the familiar partner and was associated with a preference for the unfamiliar female (stranger) in males that swam (n = 11, t = 4.06, $P < 0.01$). In untreated females, significant preferences for the familiar partner develop after 6 h of cohabitation (Control "no stress," n = 8, t = 3.20, $P <$

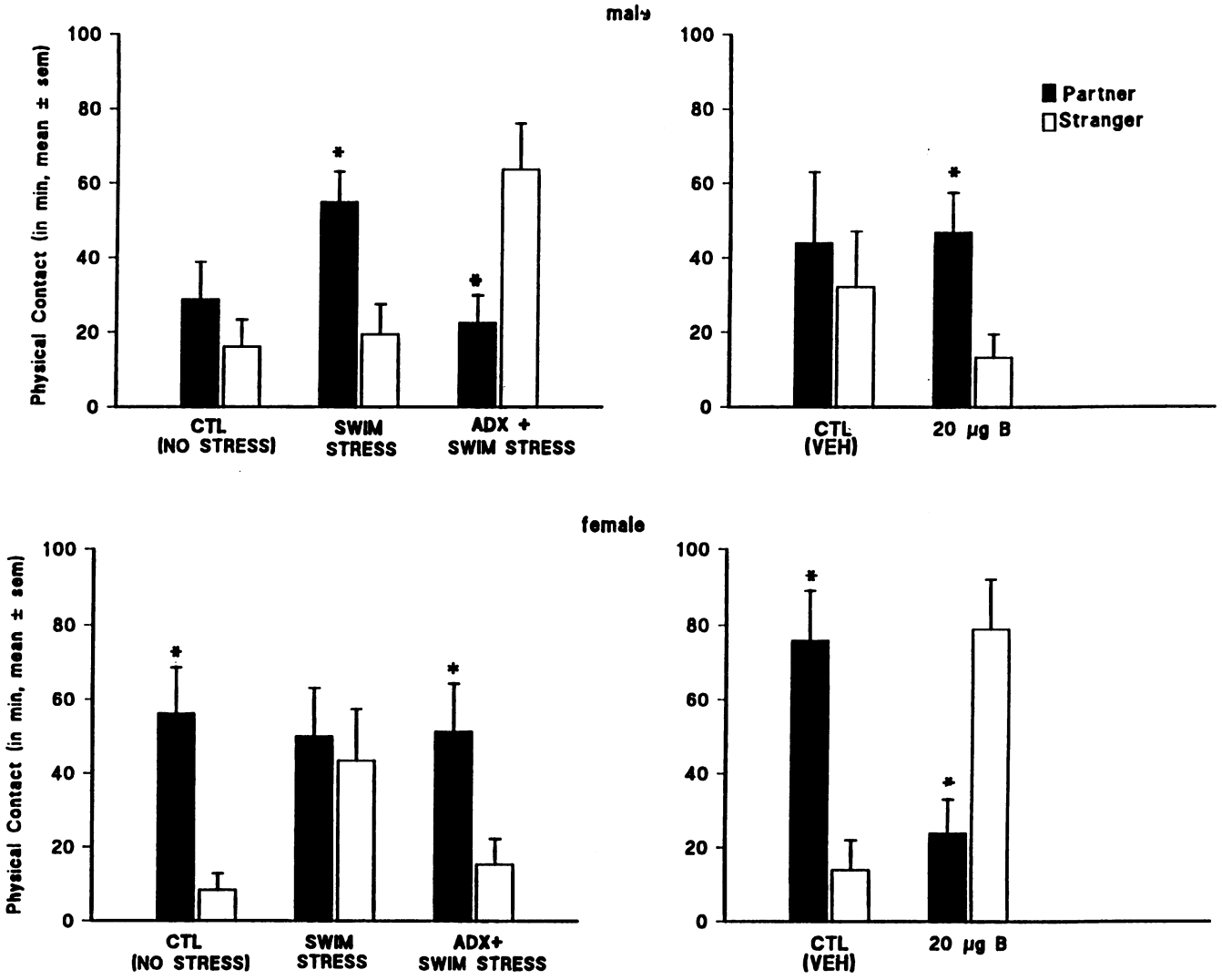

FIG. 1. Data are presented as time spent in physical contact (in min, mean ± SEM) in a 3-h social preference test. Male prairie voles usually do not form a preference for a female made familiar by 6 h of nonsexual cohabitation [no stress or vehicle (VEH) controls (CTL)]. However, significant preferences for the familiar partner were measured in males that experienced 3 min of swimming or received corticosterone (20 μg of B) prior to cohabitation. Adrenalectomy (ADX) inhibited the formation of preferences for the familiar partner and was associated with a preference for the unfamiliar female (stranger) in males that swam. In untreated females, significant preferences for the familiar partner did develop after 6 h of cohabitation (CTL no stress and VEH), but exposure to 3 min of swimming blocked the development of partner preferences. Adrenalectomy counteracted the inhibitory effect of swim stress on the formation of partner preferences in females. An asterisk indicates significance at $P < 0.05$.

0.05; vehicle, $n = 11, t = 3.19, P < 0.01$), but exposure to 3 min of swimming ($n = 15, t = 0.27$, not significant) 30 min prior to cohabitation blocked the development of partner preferences while exogenous corticosterone (20 μg) treatment resulted in the development of a preference for the stranger ($n = 11, t = 2.64, P < 0.5$). In addition, adrenalectomy counteracted the inhibitory effect of stress on the formation of partner preferences in females that swam ($n = 12, t = 2.29, P < 0.05$). The total time spent in physical contact with the stimulus animals (partner + stranger) did not vary across male [$F_{(4, 41)} = 2.11$, not significant] or female treatment groups [$F_{(4, 52)} = 1.59$, not significant]. Activity levels were similar among the three treatment groups in males [$F_{(4, 41)} = 1.72$, not signficant] and females [$F_{(4, 52)} = 1.86$, not significant].

Experiment 2. An acute injection of corticosterone (B) facilitated the formation of partner preferences in male prairie voles in a dose-dependent manner (Fig. 2). After 6 h of cohabitation, preferences for the familiar partner were displayed by male voles that received 20 μg of corticosterone (20 μg of B, $t = 2.26, P < 0.05$) and 200 μg of corticosterone (200 μg B, $t = 3.14, P < 0.01$) but not in the males that received 2 μg of corticosterone (2 μg of B, $t = 1.04$, not significant) or the vehicle (VEH, $t = 0.13$, not significant) or in the untreated controls (CTL, $t = 0.82$, not significant) (Fig. 2). The total time spent in physical contact with the stimulus animals [$F_{(4, 55)} = 2.4$, not significant] and general activity levels [$F_{(4, 55)} = 0.99$, not significant] did not vary significantly across treatment groups during the 3-h preference tests.

Experiment 3. Adrenalectomy inhibited the development of partner preferences in male prairie voles (Fig. 3). After 24 h of cohabitation, the control and sham-adrenalectomized male prairie voles exhibited significant preferences for the familiar partner (CTL, $t = 2.32, P < 0.05$; sham, $t = 4.41, P < 0.01$, respectively). Adrenalectomized males did not exhibit partner preferences under these conditions (ADX; $t = 1.11$, not significant), although adrenalectomized animals that received a corticosterone replacement pellet (ADX + B; $t = 3.64, P < 0.01$) continued to show preferences for the familiar partner. The total time spent in physical contact with the stimulus animals did not vary significantly across treatment [$F_{(3, 41)} = 0.29$, not significant]. Activity levels also were similar among the four treatment groups [$F_{(3, 41)} = 1.25$, not significant].

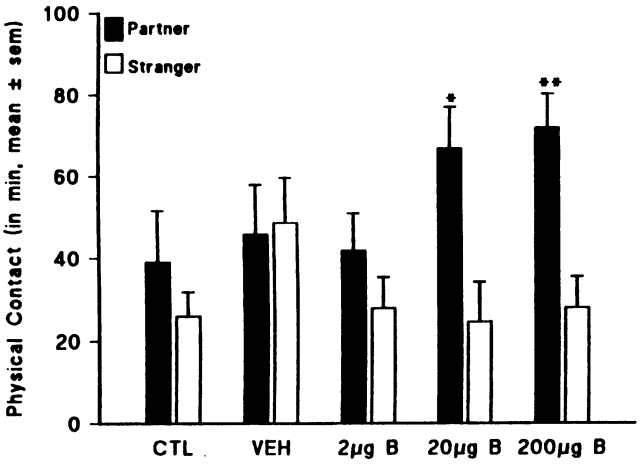

FIG. 2. Data are shown as minutes of physical contact (mean ± SEM) during a 3-h social preference test. Male prairie voles that had received 20 or 200 μg of corticosterone (B) 30 min prior to 6 h of cohabitation exhibited a significant preference for the familiar partner (*, $P < 0.05$; **, $P < 0.01$). Males that did not receive an injection (CTL) or that received an injection of the vehicle (VEH) or 2 μg of B did not exhibit a significant preference for either stimulus animal.

DISCUSSION

Both male and female prairie voles form pair bonds, characterized by selective partner preferences and aggression toward strangers (3, 5–8). The behavioral processes associated with the formation of partner preferences in prairie voles appear superficially similar in both sexes (5). Both males and females develop partner preferences after cohabitation, and mating can hasten the formation of such preferences (7). However, gender differences exist in several behavioral parameters of pair bond formation. For example, although stranger-directed aggression is seen in sexually experienced prairie voles of both sexes, males become aggressive more quickly after mating than do females (6). In contrast, unmated female prairie voles form partner preferences more rapidly and retain those preferences

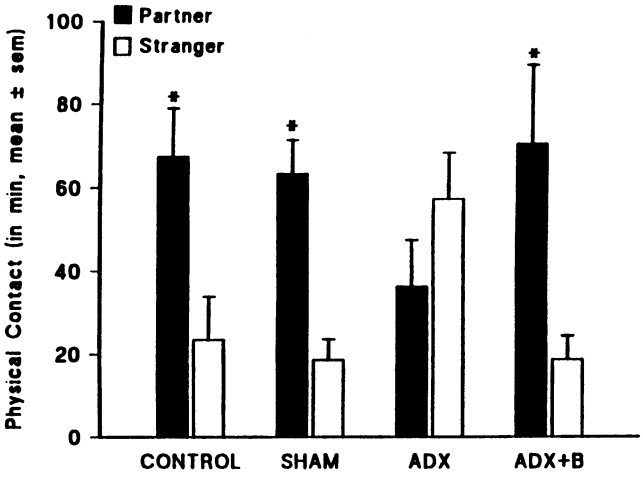

FIG. 3. Data are shown as minutes of physical contact (mean ± SEM) during a 3-h social preference test. After 24 h of cohabitation with an ovariectomized stimulus female, male prairie voles were tested for social preferences. Males that had not received any treatment prior to the cohabitation (CTL), sham-adrenalectomized males (SHAM), and adrenalectomized males that received a 250-mg corticosterone replacement at the time of surgery (ADX + B) exhibited significant social preferences (*, $P < 0.05$) for the familiar partner. Adrenalectomized (ADX) males did not display a social preference for either stimulus animal.

longer than do comparably treated males (A.C.D., C.S.C., unpublished results).

The present study offers support for the hypothesis that the physiological substrates for pair bonding are sexually dimorphic and, in conjunction with earlier work, indicates that male and female prairie voles react differently to hormones of the HPA axis. In male prairie voles, exposure to exogenous corticosterone treatment (Figs. 1 and 2) and swim stress (Fig. 1) facilitated the development of partner preferences. In contrast, adrenalectomized males did not show a preference for a familiar partner, even after a full day of cohabitation, although adrenalectomized males that were maintained with high levels of corticosterone (B) did form partner preferences during the same period (Fig. 3).

We have found (9) in female prairie voles (in studies employing comparable doses and methods) that corticosterone treatments inhibited the development of a preference for a partner that was present after corticosterone injection. In contrast, partner preferences formed very quickly in adrenalectomized female prairie voles, an effect that was reversed by corticosterone replacement (9). Additional support for a gender difference in the behavioral effects of adrenal hormones comes from Experiment 1 in which exposure to stress had opposite effects on pair bonding in male and female prairie voles.

Despite what appears to be a striking sex difference, there is no indication that gonadal hormones in adulthood regulate the partner preference component of pair bonding. Gonadectomized male and female prairie voles are capable of developing partner preferences. In addition, the gonadal condition of a stimulus animal does not influence its attractiveness as a partner (A.C.D., C.S.C., unpublished results). Prairie voles are reproductively inhibited within the family and may remain gonadally quiescent prior to exposure to a novel animal of the opposite sex. Thus, initial partner preferences may form in the relative absence of gonadal activity.

Adrenal hormones, including corticosterone, can influence exploratory behavior (10, 11) and social interactions (12) in male rats. However, in the present study, overall movement did not differ between experimental animals and controls, suggesting that the observed differences were not secondary to changes in locomotor activity.

A body of research exists in which corticosterone has been studied as an index of HPA activation or "stress." Our results, as well as work by others (10–13), suggest that corticosterone also can be behaviorally active. In the present study the behavioral effects of corticosterone were measured 6.5–9.5 h after injection, therefore, these behavioral effects may be mediated through either genomic actions of corticosterone or perhaps more rapid nongenomic actions, such as effects on cell membranes (13) or on other neurochemical systems.

The centrally active neuropeptides oxytocin and vasopressin have been implicated in both the regulation of the HPA axis and in pair bonding. Evidence thus far indicates that the effects of oxytocin and vasopressin also may be gender specific. In female prairie voles, oxytocin facilitates the development of partner preferences (14) and a selective oxytocin antagonist (OTA) interferes with pair bonding (15); comparable treatments in males were less effective (6). In males, vasopressin was more effective than oxytocin in facilitating partner preferences, and a selective antagonist for the vasopressin V1a receptor inhibited the development of pair bonds in male, but not female, prairie voles.

Vasopressin has a well-documented central role in the stress response and is capable of releasing adrenocorticotropin hormone and thus corticosterone (16). In the prairie vole, as in other mammals, vasopressin content in some areas of the central nervous system is highly sexually dimorphic (17), and vasopressin has been implicated in social memory in male, but not female, rats (18). We are currently examining the hypoth-

esis that corticosterone and vasopressin may interact to modulate pair bonding in male prairie voles.

Because of its role in parturition and lactation, oxytocin often has been described as a "female" hormone. However, in prairie voles, there currently is no evidence for sexual dimorphism in either oxytocin content or receptor density (19, 20). The role of oxytocin in stress responses and the effects of other hormones of the HPA axis on oxytocin are complex and may be gender specific (21) and species specific (20). Oxytocin may facilitate the release of adrenocorticotropin hormone and, thus, corticosterone during acute stress, at least in rats (22). However, stressful experiences also can impede the release of oxytocin during parturition or lactation (23). In female prairie voles, acute stress or exposure to corticosterone may inhibit the release of oxytocin, impeding the development of partner preferences. Whether the behavioral phenomena described here reflect direct behavioral actions of adrenal corticoids or are secondary to changes in other neural systems remains to be determined.

Field and laboratory studies suggest that prairie voles are monogamous mammals, and males and females of this species can develop pair bonds, characterized by selective partner preferences (4, 24). One of the defining characteristics of monogamy is a relative absence of anatomic and behavioral sexual dimorphism (1). However, the present study suggests that hormones of the HPA axis have gender-specific and opposite effects in male and female prairie voles. Sex differences in response to stress have been reported in nonmonogamous species (21, 25). The cytokine interleukin 6, which activates the HPA axis (26), inhibits sexual behavior in female rats but may increase sexual motivation in males (27). Dopamine, which is associated with arousal, also can inhibit female sexual behavior (28) but usually facilitates sexual behavior in males (29). Thus our finding of a sex difference in the effect of corticosterone on pair bonding may be part of a larger pattern in which, even in monogamous species, activation of the HPA axis or "stress" has sexually dimorphic effects on behaviors associated with reproduction.

The involvement of the HPA axis in pair bond formation also provides a mechanism through which environmental challenges may differentially influence patterns of social behavior in male and female prairie voles. Under stressful conditions in nature (i.e., high population density), it may be disadvantageous for young females to leave their natal family and form a new pair bond; female prairie voles may reproduce without leaving the natal nest, probably by mating with nonfamily members (4–6, 30). In contrast, sexually active male prairie voles become highly aggressive toward other males (6) and may be too agonistic to remain at the natal nest (6). For this reason, the capacity to form pair bonds under stressful conditions may be advantageous to male prairie voles. Thus, male, but not female, prairie voles may derive reproductive benefits from forming new heterosexual pair bonds under stressful conditions.

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