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Physiology & Behavior 87 (2006) 424 – 429

PHYSIOLOGY & BEHAVIOR

Effects of stress on parental care are sexually dimorphic in prairie voles

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Received 6 May 2005; received in revised form 30 July 2005; accepted 7 November 2005

Abstract

The effects of stress on parental care are poorly understood, especially in biparental species where males also display care. Data from previous studies in prairie voles, as well as parallels with pair-bonding behavior, suggest the hypothesis that a stressful experience might facilitate parental care in males but not in females. In the present study, male and female prairie voles were exposed to either a 3-min swim stressor or no stressor; 45 min later each animal was tested in a parental care paradigm. Following the parental care test, blood samples were collected and assayed for corticosterone (CORT). After the stressor males, but not females, showed significant changes in parental behavior including significantly more time in kyphosis (arched-back huddling), and a tendency to spend more time licking and grooming pups. In males, CORT levels measured following the parental care test were inversely related to licking and grooming but positively correlated with retrievals. These findings support earlier studies suggesting that the neuroendocrine substrates of parental behavior, as well as the effects of stressors, are sexually dimorphic in this species.

Keywords: Stress; Parental care; Corticosterone; Sex differences

The effects of stress and hormones of the hypothalamic-pituitary-adrenal (HPA) axis on parental behavior are not well understood. For, example, injection of corticotropin-releasing factor (CRF) reduced maternal aggression, although not other maternal behaviors, in mice [1]. In contrast, lactating female rats exposed to a noise stress showed an increase in both locomotor activity and licking and grooming of the pups. In this same study, virgin females also showed a stress-related increase in activity, including rearing and locomotion around the home cage [2]. It also has been reported that a tail pinch can facilitate maternal behavior in virgin female rats [3]. Human mothers with higher postpartum cortisol were more attracted to, and better able to discriminate, their own infant's odors [4]; however in captive gorillas [5] and baboons [6] high levels of postpartum cortisol were associated with lower levels of maternal behavior. Thus in female mammals, activation of the HPA axis can either disrupt or facilitate maternal behavior, depending on the reproductive status of the female and the measure of maternal behavior used. The effects of stressful experiences on male parental care have not to our knowledge been previously examined.

Male parental care is most commonly observed in socially monogamous species, which make up a small minority (3%) of mammals [7]. The physiological conditions underlying paternal care have only recently become the subject of analysis. Cortisol in parental males varies across the mate's pregnancy [8–11]. In male black tufted-ear marmosets, males with higher CORT carried infants less [12]. The neuropeptides oxytocin (OT) and arginine vasopressin (AVP), hormones associated with stress in rats and mice [13,14] also have been linked to male paternal care [15–18].

Prairie voles are socially monogamous rodents that typically show spontaneous male parental behavior [19,20]. This species also forms pair bonds, indexed by partner preference behavior. In prairie voles the effects of stress are sexually dimorphic, with stress facilitating the formation of a partner preference in males and inhibiting the development of a partner preference in females [21–23].

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0031-9384/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.physbeh.2005.11.002

In a previous study, we observed that males that had undergone a surgical stressor spent more time in kyphosis (arched-back huddling over pups) than males that had not undergone surgery [18]. Kyphosis is a major component of parental behavior [24] and we therefore hypothesized that administration of a mild stressor (3 min of forced swimming) would facilitate parental care in males. In contrast, because stress can be disruptive to certain aspects of female social behavior, we hypothesized that a prior stress would disrupt parental care in females. The forced swim test has also been used to measure "depressive-like behavior" in voles and other rodents [25]. We also examined plasma levels of the "stress hormone" corticosterone (CORT) for its relationship to parental behavior. To avoid disrupting behavior, blood samples were taken after the parental care test. We have recently observed that exposure to a pup is associated with a rapid (15 min) reduction in CORT in males, but not in females [26]. For this reason we hypothesized that CORT might be related to behavior, either causally or as a consequence of the behavioral experience of the animal. Finally, we also examined the behaviors displayed during the swim test/stressor (swimming, struggling, and floating) for correlations with parental behavior or CORT.

1. Methods

Subjects were laboratory-bred male and female prairie voles (*Microtus ochrogaster*), descendants of a wild stock originally caught near Champaign, Illinois. Prairie voles were maintained on a 14 : 10 light : dark cycle and allowed food (Purina high-fiber rabbit chow) and water ad libitum. Breeding pairs were maintained in large polycarbonate cages (44 cm long × 22 cm wide × 16 cm high) and provided with cotton for nesting material. At 21 days of age, voles were weaned and housed in same-sex sibling pairs in standard mouse cages (27 cm long × 16 cm wide × 13 cm high). The same-sex sibling pairs were then kept in a single-sex colony room. All test subjects were sexually naïve, had never been exposed to pups, and had not been used in any previous experiments. Females do not experience a spontaneous estrus cycle [27], and therefore stage of estrus is not an issue in this species.

At approximately 60 days of age, voles underwent a parental care test, preceded either by a swim stressor or by no stress. The swim stressor consisted of 3 min of swimming in lukewarm water in a large plastic cage (20 × 25 × 45 cm). At this depth the voles can neither touch the bottom nor climb out. The parameters of the response to this stressor in voles have been previously characterized [21,23,28]. Normal animals show approximately a doubling of corticosterone (CORT) with a maximum increase within approximately 45 min following swimming [23], and levels remain elevated for several hours. In a previous study performed by the first author on this paper, control animals showed an average of an 82% rise in CORT following a swim stressor. Swim tests were scored for three behaviors: swim (vole is quietly swimming); struggle (vole is violently swimming against the side and trying to get out of the cage) and float/immobility (vole is not paddling at all). Scoring was performed using Behavior Tracker 1.0 (www.behaviortracker.com).

Immediately following the swim stressor voles were placed into an alloparental care testing arena. Unstressed voles were placed directly into the arena. Procedures for testing parental behavior were modeled on previous work from this lab [29,30]. Voles were given 45 min following introduction to acclimate to the empty testing arena; this time period also allowed maximal changes in CORT to occur. The arena consisted of two standard mouse cages connected by a short, clear tube. At the end of the acclimation period, the subject was removed from the testing arena and an unrelated 1–3 day old pup placed in the front cage. Each pup was used as a stimulus no more than twice. The subject then was placed into the arena, and pup-directed behavior was recorded for 10 min on videotape. If the test subject displayed aggression towards the pup, the test was stopped immediately, and the pup was removed and returned to its parents. The incidence of pup-directed aggression was higher in females, as has been previously shown [29,31], but was not affected by stress. In most cases, the pup was not injured, and this protocol resulted in a full recovery for the pup. Tapes were scored by an experimentally blind observer using Behavior Tracker 1.0 software. Subjects were initially categorized as either parental or nonparental. A subject was said to be parental if it displayed kyphosis over or retrieved an pup (without later attacking it; in about 50% of attacks, an extremely short retrieval was a prelude to immediate attack [29]). The term "parental" therefore only refers to those animals that displayed full parental behavior (i.e. in this characterization, those that just investigated the infant were not categorized as parental).

Individual components of behavior were then further analyzed, including location in the testing arena (cage with pup, far cage, or the connecting tube), huddling or "kyphosis" which consisted of sitting over the pup with an arched-back posture [32]; licking/grooming; sniffing; non-kyphotic contact (sitting flat on a pup or next to it, while touching, but without an arched back); and retrievals. These parental behaviors as scored were mutually exclusive.

Following the alloparental care test, voles were anesthetized using a combination of Ketamine (67 mg/kg) and Xylazine (13 mg/kg) and a blood sample taken via a heparinized capillary tube from the supraorbital sinus. Blood samples were centrifuged and serum stored at −20 °C until assay.

One week later, voles underwent an alloparental care test preceded by the opposite condition (i.e. if they were stressed in week 1, they were not stressed in week 2). Following the second test, another blood sample was collected.

1.1. Corticosterone assay

Corticosterone was assayed using a commercially available radioimmunoassay (MP Biomedicals, Irvine, CA) previously validated for the prairie vole [28]. Samples were assayed following a dilution of 1 : 2000. Intra-assay CV's averaged 2.19%. No interassay CV is applicable because all samples were assayed at once.

Table 1
Behavioral results for females (means ± standard errors)

Variable	Non-stressed	Stressed
Kyphosis	6.5 ± 5.73 (s)	8.65 ± 5.25
Non-kyphotic contact	73.0 ± 25.83 (s)	46.45 ± 15.93
Licking and grooming	102.15 ± 32.01 (s)	92.55 ± 32.60
Sniffing	25.95 ± 4.51 (s)	24.0 ± 5.15
Retrievals	4.0 ± 0.82	3.95 ± 1.26

1.2. Data analysis

Exposure to an pup has been shown to affect behavior during a subsequent encounter [33]. In the present data set, not only were males more likely to display huddling behavior in the second test, but the effect was sexually dimorphic, with females not showing this order effect (see Results section). Therefore, for the analysis of stress effects on parental care only the first parental care test was used. Logistic regression calculated using a likelihood ratio χ^2 was used to predict parental behavior based on whether or not the test animal was stressed. Individual components of parental behavior were analyzed according to treatment by non-parametric Kruskal–Wallis tests [34] because residuals in many cases were non-transformable to normality.

Correlations between swim test, parental care test, and hormonal variables were performed using Spearman correlations on the entire dataset (both parental care tests for each animal) so that each animal would have a swim test represented in the dataset. All statistical tests were performed in SAS 8.2 (SAS Institute, Cary, NC). Tests for effects of treatment on parental behavior were one-tailed due to a priori predictions of direction, while correlations with swim test and hormonal variables were two-tailed. Values of $p < 0.05$ were considered significant.

2. Results

2.1. Effects of testing order

During the second parental care test, males spent more time engaged in kyphosis ($n = 20$, Wilcoxon signed-rank (paired) test, $S = 19.5$, $p = 0.019$; two-tailed) than during the first test, while females did not show an order effect ($n = 20$, Wilcoxon signed-rank test, $S = 2.5$, $p = 0.625$). Data for females are presented in Table 1. There were no test order differences in males or females in non-kyphotic contact, licking and grooming, retrievals, or CORT values.

2.2. Effects of stress

Males were significantly more likely to display parental behavior following a stressor (Fig. 1; $n = 20$, logistic regression, likelihood ratio $\chi^2 = 3.4522$, $p = 0.032$; one-tailed). However, stress did not significantly affect the proportion of females that displayed parental care towards the pup ($n = 20$, logistic regression, likelihood ratio $\chi^2 = 0.2024$, $p = 0.326$; one-tailed).

Following stress, males spent a significantly longer duration engaged in kyphosis (Fig. 2; $n = 20$, Kruskal–Wallis test, $\chi^2 = 3.327$, $p = 0.034$; one-tailed) and tended to spent more time in licking and grooming ($n = 20$, $\chi^2 = 2.069$, $p = 0.075$; one-tailed). Stressed versus nonstressed males did not differ in non-kyphotic contact ($n = 20$, $\chi^2 = 0.824$, $p = 0.182$; one-tailed) or retrievals ($n = 20$, $\chi^2 = 0.054$, $p = 0.408$; one-tailed). Females showed no significant differences in any of these behaviors following stress.

Following the parental care test, CORT levels were no longer elevated in the stressed groups compared to the non-stressed groups (see Discussion). Female values were 1501.73 ± 133.35 ng/ml for the unstressed group and 1736.82 ± 211.33 ng/ml for the stressed group, while male values were 1030.83 202 ± 61.10 ng/ml for the unstressed group and 1111.17 ± 60.94 ng/ml for the stressed group.

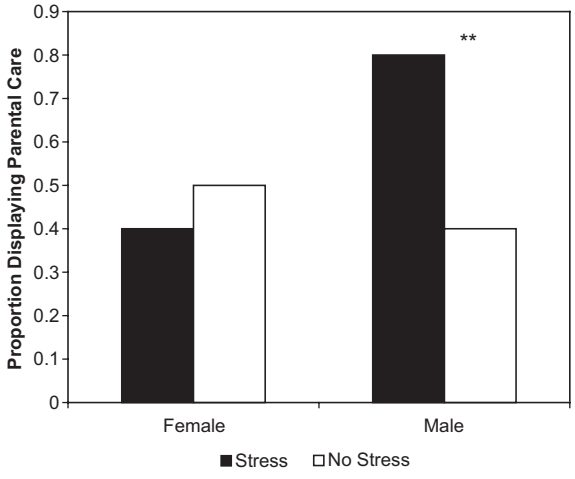

Fig. 1. Proportion of animals displaying parental behavior after a swim stressor or no swim stressor ($n = 10$ animals/group). Males were more likely to display parental behavior following stress (logistic regression, likelihood ratio $\chi^2 = 3.4522$, $p = 0.032$; one-tailed), while females were not.

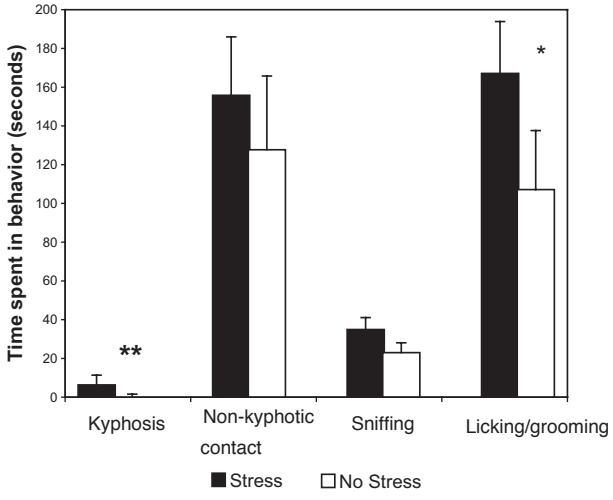

Fig. 2. Time spent (seconds) by males in parental care behaviors. $^{**}p < 0.05$, $^{*}p < 0.1$.

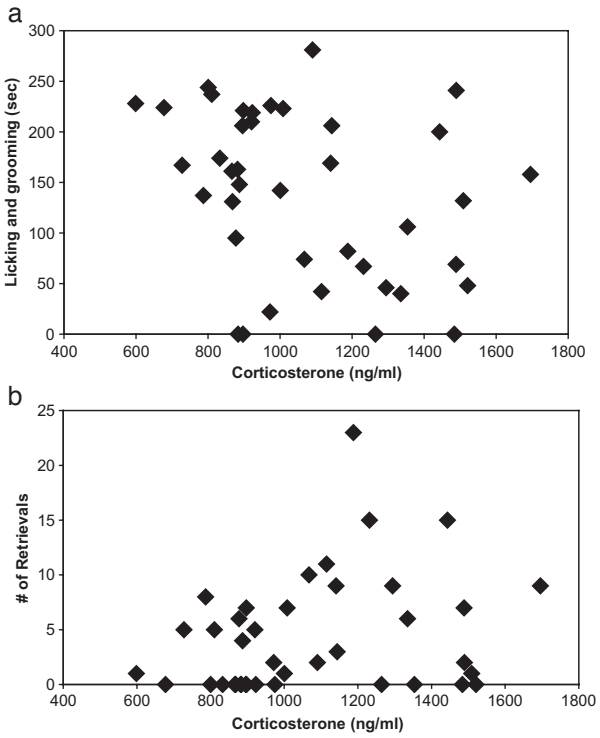

Fig. 3. (a) Negative correlation between licking and grooming and corticosterone in males ($p=0.025$). (b) Positive correlation between retrievals and corticosterone in males ($p=0.071$).

2.3. Relationships between CORT and parental behavior

In males (all tests combined), CORT levels were negatively correlated with time spent licking and grooming the pup (Spearman correlation, $n=40$, $r=-0.354$, $p=0.025$, two-tailed; Fig. 3a) and tended to be positively correlated with the number of retrievals ($r=0.288$, $p=0.071$, two-tailed, Fig. 3b). A median split by CORT level (Fig. 4) also showed differences in male behavior by CORT. Males with high CORT (above the median) tended to lick and groom pups less ($n=40$, Kruskal–Wallis test, $\chi^2=3.142$, $p=0.076$, two-tailed) but

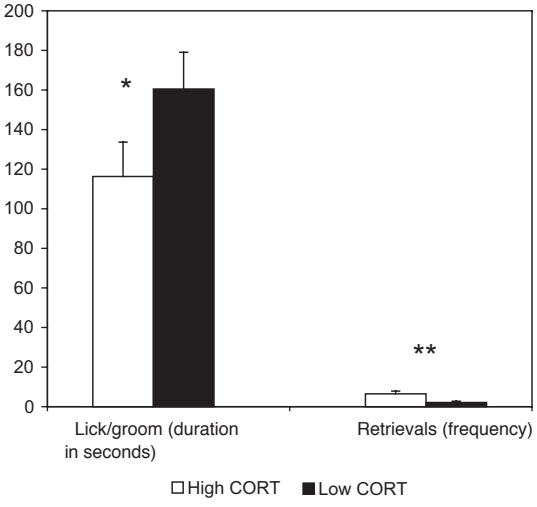

Fig. 4. Parental care behaviors according to whether the subject had high CORT (above the median) or low CORT (below the median). $^{**}p<0.05$, $^{*}p<0.1$.

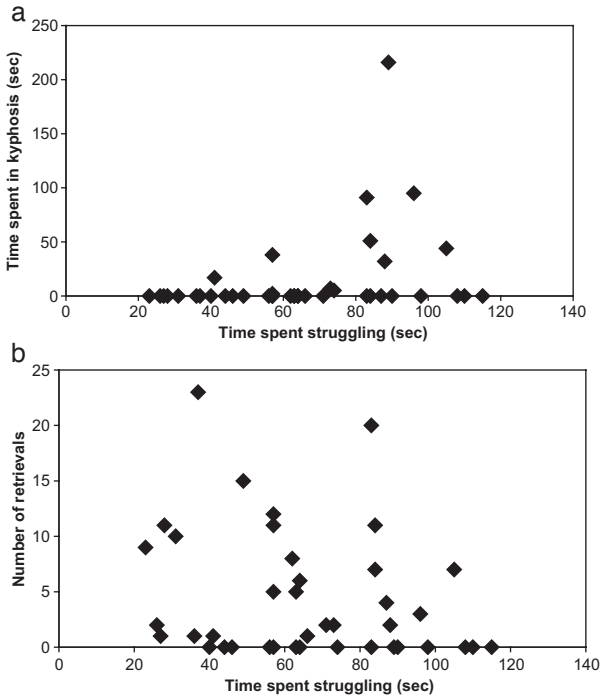

Fig. 5. (a) Positive correlation between time spent struggling and time spent in kyphosis ($p=0.040$). (b) Negative correlation between time spent struggling and retrievals ($p=0.098$).

retrieved pups more ($n=40$, Kruskal–Wallis test, $\chi^2=7.357$, $p=0.007$, two-tailed). In females, no measures of parental care were significantly correlated with CORT.

2.4. Relationships between swim test behavior and other variables

When all tests were combined, time spent struggling during the swim test was positively correlated with time spent in kyphosis in the parental care test (Spearman correlation, $n=40$, $r=0.326$, $p=0.04$; Fig. 5a), while struggling tended to be negatively correlated with retrievals ($n=40$, $r=-0.265$, $p=0.098$; Fig. 5b). Females tended to float more than males (Kruskal–Wallis test, $n=40$, $\chi^2=3.40$, $p=0.065$). CORT was not correlated with any swim test variables.

3. Discussion

In prairie voles, a biparental and relatively monomorphic species, stress affects parental care in reproductively naïve animals in a sexually dimorphic manner. As with pair bond formation, males became more parental following a stressor. In particular, in males the behavior of kyphosis (huddling) was significantly increased following stress. It is also notable that male kyphosis increased during a second parental care test (also potentially a stressor). In females neither a prior stressor nor repeated testing significantly influenced the overall tendency to show parental behavior or kyphosis. Although the swim stressor is a relatively mild stress and the subsequent changes in behavior were not large, we believe that these reflect important sex differences and an area for future research.

It is possible that the effects of stress on parental care in males are partially mediated by the type of stress; i.e., a swim stressor produces a group of wet animals. In order to dry off, voles subjected to a swim stressor spend significant time auto-grooming, which may induce hormonal changes potentially including changes in both oxytocin [35–37] and dopamine [38] systems. These same hormonal systems have been implicated in parental behavior in both males and females [18,39–41]. However, as many types of stress may induce a rise in auto-grooming, this does not rule out a general effect of stress on parental care that is not dependent on becoming wet.

The relationship between the hormonal measure (CORT) and parental behavior in this study is complicated because this hormone might not only be affected by stress but also by exposure to an pup [26]. Post-hoc measurements, which did not differ between stressed and non-stressed groups, therefore may be reflective of the effects of pup exposure or the parental behavior in which animals engaged [26]. In fact, it appears quite likely that males used the pup to regulate their stress response. Although swim stress reliably increases CORT, and males were more parental following swim stress, male licking and grooming of pups was associated with a lower post-testing level of CORT. We hypothesize that stressed males are more motivated to interact with pups, and therefore are actively engaged in lowering their own stress response and reducing the difference in CORT between stressed and non-stressed groups. It is also possible that the 45-min exposure to the testing arena, which was chosen in order to get the maximal response of CORT resulting from the swim test, partially masked the differences between groups due to the stress of exposure to a novel environment.

Male retrieval of pups, as opposed to licking and grooming, was associated with higher post-testing CORT. These behaviors are also distinguished by the fact that while licking and grooming tended to be affected by prior stress, retrieval behavior was not. In general, the findings of this study are consistent with the hypothesis that male prairie voles may use social contact to modulate stressful experiences; in addition, exposure to a stressor may have different behavioral consequences in males versus females [21,26,42]. It is possible that retrieval, while beneficial to the pup, does not carry the same anti-stress benefit for the adult as a behavior which is less active and more fully engages the olfactory system.

It is quite probable that the effects of stress on parental care, and of pup exposure on CORT, are both mediated by neuropeptides such as oxytocin (OT) and vasopressin (AVP). Both OT and AVP may be released by stress, but the response of OT and AVP to stress appears to vary by species and by stressor [43]. For example, OT is released by stress in rats [43], but not in humans following exercise stress [44]. In contrast, AVP in rats is not released by a swim stressor [14]. In female rats, kyphosis as well as lordosis (a similar arched-back posture) is dependent on OT acting in the periaqueductal gray of the midbrain [45–49]. Both OT and AVP are also involved in male parental care in voles [18,50,51]. Further examination of the effects of stress on neuropeptides in voles, as well as differential effects of neuropeptides on components of parental behavior (kyphosis and licking/grooming vs. more active behaviors such as retrievals), seems indicated.

Behavior during the swim test has not been previously examined in this species. Swim test variables did not correlate with many of the other variables measured; however struggling in the swim test did correlate positively with kyphosis in the parental care test, and negatively with retrievals. This once again suggests possible different hormonal bases for the two behaviors, as well as validating the relevance of swim test measures in this species.

The sexual dimorphism shown here in the effects of stress on parental care parallels that seen in the effects of stress on partner preference in this species. Males that received exogenous CORT, or an optimal dosage of corticotropin-releasing factor, pair-bonded faster than controls [21,52]. On the other hand, females pair-bonded more slowly under stress [21]. The current results suggest that this relationship may be relevant to other forms of social behavior in this species.

Acknowledgments

This research was supported by NIH PO1 HD38490 to C. S. Carter, NIH NRSA F32 HD08702 and NSF 0437523 to K.L. Bales and NIH NRSA F32 HD 41293 to K.M. Kramer. Additional support was provided by IRUL. We thank Tim Hill and Dr. James Artwohl for animal and veterinary care. We also thank Sheryl Katta and Julie Hazelton for research assistance.

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