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Gonadal hormones modulate the display of submissive behavior in socially defeated female Syrian hamsters

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Abstract

There are striking differences in the behavioral response to social defeat between male and female Syrian hamsters. Whereas males exhibit a prolonged behavioral response to defeat (i.e., conditioned defeat), many females remain aggressive or show only a transient submissive response following defeat. The current study tested the hypothesis that sex steroids underlie this differential behavioral responsivity to social defeat. Female hamsters were ovariectomized and implanted with Silastic capsules containing estradiol (E_2), testosterone (T), progesterone (P), dihydrotestosterone (DHT), or a blank capsule (no hormone replacement). After a 3-week recovery period, each subject was placed inside the home cage of a larger, more aggressive female for four 5-min defeat trials. The following day, each animal was tested for conditioned defeat by testing it in its own home cage in the presence of a smaller, non-aggressive intruder. Submissive, aggressive, social, and nonsocial behaviors were subsequently scored. Hamsters receiving E_2 or T displayed significantly lower levels of submissive behavior than did animals receiving P, DHT, or no hormone replacement. There were no significant differences in aggressive behavior among groups. These data suggest that gonadal hormones can influence submissive behavior in female hamsters. Collectively, these results suggest that the sex differences observed in conditioned defeat may, in part, be explained by sex differences in circulating gonadal hormones.

Keywords: Agonistic behavior; Gonadal hormones; Aggression; Submission; Hormone replacement; Testosterone; Estradiol; Stress; Sex differences

Introduction

Exposure to social stress can produce a variety of physiological and behavioral responses such as reductions in aggression or sexual activity or increases in anxiety, ethanol consumption, and drug self-administration, changes in neurotransmitter and neuropeptide release, and changes in neuronal structure (Albonetti and Farabollini, 1994; Anisman and Zacharko, 1986; Blanchard et al., 1995, 2001; D'Aquila et al., 1994; Friend, 1991; Korte et al., 1990). These responses to stress, however, can vary according to the sex of the subject being studied in both human (Seeman et al., 2001; Wolf et al., 2001) and nonhuman subjects (Duncko et al., 2001; Palanza, 2001; Palanza et al., 2001). It is also well known that sex differences exist in the expression of stress-related psychiatric disorders (Palanza, 2001). The mechanisms underlying these sex differences have not been elucidated fully, however there is evidence supporting a modulatory role for sex hormones in both the onset of psychiatric illness (Earls, 1987; Palanza, 2001) and in response to stressful stimuli (Palanza et al., 2001).

Syrian hamsters (*Mesocricetus auratus*) provide an excellent model for studying social stress and agonistic behavior. Syrian hamsters are solitary animals (Nowack and Paradiso, 1983) that normally display territorial aggression in their home cages. Defeated male hamsters, but not dominant males, show physiological changes such as increased hypothalamo–pituitary–adrenal (HPA) axis activation (measured by increased plasma adrenocorticotropic

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hormone and glucocorticoid concentrations) (Huhman et al., 1990, 1991, 1992) indicating that social defeat is a potent stressor in male hamsters. Significant behavioral changes also occur when a male hamster is defeated by a larger, more aggressive male conspecific in an agonistic encounter. The defeated hamster subsequently fails to exhibit normal territorial aggression in its home cage even when a smaller, non-aggressive intruder is introduced. Instead, a previously defeated male will exhibit defensive and submissive behaviors (e.g., tail lift, leg lift, upright defensive posture, flight) even in the absence of being attacked. This behavior has been termed conditioned defeat (Potegal et al., 1993). Conditioned defeat has been shown to be consistent and long lasting, with submissive behavior being displayed in many subjects up to 33 days post-defeat and maybe longer (Huhman et al., 2003). Conditioned defeat can be induced with either single or multiple defeats (Jasnow and Huhman, 2001; Jasnow et al., 1999; Potegal et al., 1993).

The occurrence of conditioned defeat has recently been investigated in female hamsters, as well, using the same protocol as that used previously in male hamsters (Huhman et al., 2003). Interestingly, whereas most defeated males exhibit conditioned defeat following exposure to social defeat, many defeated females subsequently fail to show defensive behaviors in the presence of non-aggressive intruders and, instead, attack these intruders. It is noteworthy that females and males exhibit a similar HPA axis response to the initial defeat, which suggests that social defeat is stressful for both sexes (Huhman et al., 2003). One possibility for the sex difference in the behavioral response observed in defeated hamsters is that sex hormones may differentially affect mechanisms underlying defeat-induced behavioral changes.

Several studies have investigated the effects of exogenous estrogen and progesterone administration on agonistic behavior in female hamsters (for a review, see Albers et al., 2002). Chronic estradiol treatment after ovariectomy results in levels of aggression similar to that of controls not receiving hormone replacement (Fraile et al., 1987; Meisel et al., 1988; Vandenbergh, 1971), whereas chronic progesterone treatment results in reduced aggression towards other females (Fraile et al., 1987, 1988). Reduced aggression after chronic testosterone treatment in female rats has also been reported (DeBold and Miczek, 1981). However, aggressive profiles of female rats and hamsters differ because, unlike rats or mice, female hamsters are more aggressive than are male hamsters (Beatty, 1979; Brain, 1972; Payne and Swanson, 1970). Studies examining testosterone treatment in ovariectomized female hamsters have observed no effect of testosterone or testosterone propionate on aggressive behavior (Floody and Pfaff, 1977; Grelk et al., 1974; Vandenbergh, 1971).

It is important to note that all of the aforementioned studies have focused on hormonal control of *aggressive* behavior and have not examined other aspects of agonistic behavior, such as submissive behavior. Therefore, the current study tested the hypothesis that differences in sex steroids may underlie the differential behavioral response to social defeat previously observed in male versus female Syrian hamsters (Huhman et al., 2003). Specifically, the striking display of submissive behavior in defeated male hamsters could be due to the presence of androgens, acting either directly on target tissues or indirectly via aromatization to estradiol, whereas the low circulating concentrations of androgens could explain the relatively low levels of submissive behavior in female hamsters. Conversely, female hamsters could display less submissive behavior because of the presence of circulating estradiol or progesterone. In support of this hypothesis, we have observed that intact female hamsters exhibit different durations of submissive behavior across the estrous cycle (Matia B. Solomon and Kim L. Huhman, in preparation). Other studies report varying levels of aggression across the estrous cycle, with most reporting higher aggression on proestrus (Floody and Pfaff, 1977; Takahashi and Lisk, 1983, 1984; Wise, 1974). Exogenous administration of estrogen can have varying effects on aggressive behavior (Meisel et al., 1988; Wise, 1974). These latter investigations have not examined the effect of cycle or hormone manipulations on submissive behaviors. In order to differentiate among the possibilities outlined above, ovariectomized female hamsters were given hormone capsules containing estradiol, testosterone, dihydrotestosterone, or progesterone, and submissive behavior following a previous social defeat was evaluated in the presence of a non-aggressive stimulus hamster.

Materials and methods

Animals and housing conditions

Fifty-nine adult female Syrian hamsters (*M. auratus*), weighing 120–130 g at the beginning of the experiment, were obtained from a breeding colony at Georgia State University (bred from males and females obtained from Charles River Laboratories). Hamsters were housed individually in a temperature-controlled (20 ± 2°C) colony room on a 14:10 light/dark cycle with lights off at 12:00 h. Additional female hamsters were used for defeat training and conditioned defeat testing. Specifically, individually housed hamsters weighing 140–180 g were used as resident aggressors for the initial defeat training, and group-housed hamsters weighing 100–110 g at the beginning of the experiment were used as non-aggressive stimulus animals during conditioned defeat testing. All animals were housed in polycarbonate cages (20 × 40 × 20 cm) with wire mesh tops, corn cob bedding, and cotton nesting materials, and food and water were available ad libitum. Non-aggressive intruder animals were left intact and were group housed (five animals per cage) to minimize aggressiveness. It has been shown that there is no difference in the display of submissive or aggressive behavior in female hamsters that are paired with

intact versus ovariectomized female stimulus hamsters during conditioned defeat testing (Huhman et al., 2003). All procedures and protocols were approved by the Georgia State University Institutional Animal Care and Use Committee.

Surgical procedures

At the beginning of the experiment, animals were deeply anesthetized with sodium pentobarbital (90 mg/kg) and were ovariectomized and subcutaneously implanted with Silastic capsules at the back of the neck above the animals' shoulder blades. These capsules contained either estradiol, testosterone, progesterone, dihydrotestosterone, or no hormone (empty capsules) (n = 10 per capsule type). The estrogen (E_2) capsules were made of Silastic Brand medical-grade tubing (0.062 in. i.d. × 0.125 in. o.d.), 10 mm in length, sealed with Factor II 6382 RTV Silicone and Elastomer, and filled 5 mm with 17-β-estradiol (Sigma, cat. number E-8875, St. Louis, MO). The E_2 dosage was chosen because this size capsule has previously been shown to produce blood levels within the physiological range of estradiol measured in intact female hamsters during early proestrus (when E_2 levels are at their peak) (Albers and Prishkolnik, 1992). Testosterone (T), progesterone (P), and dihydrotestosterone (DHT) capsules were made of Silastic tubing (0.078 in. i.d. × 0.125 in. o.d.), 28 mm long, and filled 20 mm with either testosterone propionate (Sigma, cat. number T-1500), progesterone (Sigma, cat. number P-0130), or dihydrotestosterone (Sigma, cat. number A-8380), respectively. The dose of T was chosen because that dose has previously been shown to produce circulating serum T concentrations similar to that of intact male Syrian hamster circulating T concentrations (Mary Karom, personal communication). The dosage of DHT was chosen to mimic the dosage in the T capsules. Hamsters receiving P capsules received either two or three capsules. Two doses of P were used in an attempt to mimic circulating serum P concentrations in intact female hamsters during late proestrus (when P levels are at their peak). Blank capsules were made to the same specifications as were T, P, and DHT but were sealed empty. After surgery, all experimental hamsters were allowed a 3-week recovery period before defeat training.

Behavioral procedures

Defeat training

On the day of training, female hamsters were transported in their home cages from the colony room to the behavioral testing room where they were placed into the cage of a resident aggressor for four 5-min training trials. Training began at 09:00 h with 2 h intervals between each 5-min training session. The resident aggressors were larger animals that were known to be aggressive. Notes of each encounter were taken by trained observers to ensure that there were no systematic differences in the treatment of the experimental hamsters by the resident aggressors.

Behavioral testing

Behavioral testing began 1 day following defeat training, and all testing was completed during the first 2 h of the dark phase of the LD cycle. A resident/intruder pairing was used in which a group-housed, non-aggressive intruder was placed into the home cage of each experimental animal for 5 min. The non-aggressive intruders were randomly paired with the experimental animals unless they were showing signs of sexual receptivity or aggressive behavior. If an intruder exhibited aggressive behavior toward an experimental animal, that experimental animal was excluded from final statistical analysis. All sessions were recorded on VHS tape and behavior was analyzed after serum hormone assays were performed.

The behavioral tapes were scored using the Observer for Windows, version 3.0 (Noldus Information Technology B.V., Wageningen, The Netherlands). The following behaviors were observed and recorded as total duration in seconds over the 5-min testing period: non-social (locomotor/exploratory, self-groom, nesting, feeding, sleeping); social (attend, approach, investigate, sniff, touching nose); submissive (upright/side defense, tail lift, tooth chatter, flee, full submissive posture); aggressive (upright/side offense, chase, bite, attack) (Jasnow et al., 1999). Aggressive behavior refers only to offensive aggression; little to no defensive aggression has been observed in any conditioned defeat test that we have performed. The videotapes were scored by two observers that were experienced in scoring agonistic behavior and were blind to the experimental condition of each hamster. Inter-rater reliability was 92.6%.

Following the experiment, hamsters were given an overdose of sodium pentobarbital, Silastic capsules were removed, and 3 ml of blood was drawn from the posterior vena cava of each animal for hormone assay.

Radioimmunoassay

Nonextracted hamster serum samples were assayed in duplicate for estradiol, progesterone, and testosterone using commercial radioimmunoassay kits (Coat-a-count™ Estradiol and Coat-a-count™ Progesterone, Diagnostic Products Corporation, Los Angeles, CA, and Active® Testosterone RIA DSL-4000, Diagnostic Systems Laboratories, Inc., Webster, TX, respectively). All kits were validated with Syrian hamster serum. Estradiol, progesterone, and testosterone intra-assay reliability statistics were 3.3% (0.36–11.21 pg/ml detection range), 6.3% (0.25–11.1 ng/ml detection range), and 2.2% (0.1–25 ng/ml detection range), respectively. The DHT assay was performed by the Endocrine Core Laboratory, Yerkes Primate Research Center of Emory University (Atlanta, GA), using a commercially prepared radioimmunoassay kit (antibody-coated tubes) distributed by Diagnostic Systems Laboratories (Webster, TX). Due to antibody cross-reactivity to testosterone, samples were subjected to oxidation/extraction to remove most of the testosterone interference (leaving 0.02% cross-

reactivity) prior to assay. Intra-assay reliability was 8%. All samples for each hormone treatment group were run in the same hormone assays, thereby eliminating inter-assay variability. Pooled female hamster serum obtained from a stock of serum collected from female Syrian hamsters across the estrous cycle was used for intact controls in all assays.

Statistical analysis

A number of animals in each group did not display any aggressive and/or submissive behaviors, thus the data were not normally distributed. In addition, the data violated the assumption of homogeneity of variance (Levene's Test for Equality of Variances), therefore nonparametric statistical tests were used to analyze all behavioral data. Categorically-scored data were compared using Chi-square goodness of fit tests. A Kruskal–Wallis test was used to compare total duration of each behavior by hormone treatment. Individual significant differences were then determined using a series of Mann–Whitney *U* (two-tailed) tests with results reported as *Z* scores. For all analyses, significance was ascribed at $P < 0.05$. There were no statistical differences in behavior between the two- and three-capsule progesterone groups, and, therefore, the groups were collapsed for all statistical analyses.

Results

Radioimmunoassay

Mean (±SEM) estradiol and progesterone concentrations in intact control females (pooled female hamster serum; see Materials and methods) were 319.03 ± 52.46 pg/ml and 32.24 ± 2.16 ng/ml, respectively. Mean (±SEM) serum concentrations for E_2, T, P, and DHT in our experimental groups were as follows: E_2 = 249.76 ± 14.17 pg/ml; T = 4.33 ± 0.55 ng/ml; P = 45.36 ± 6.42 ng/ml; DHT = 943.07 ± 84.06 pg/ml. Blank capsule animal serum had significantly lower concentrations of each hormone tested than the mean for each respective hormone-treated group. Two animals had serum hormone concentrations that were inconsistent with their respective group means and were therefore excluded from any statistical analysis. These were a female in the *P* group whose serum concentration was 11.73 ng/ml versus a group mean of 45.36 ± 6.42 ng/ml and a female in the T group whose serum concentration was 0.69 ng/ml versus a group mean of 4.33 ± 0.55 ng/ml. Additionally, one animal (blank capsule group) was excluded from statistical analysis because its hormone levels indicated that it did not receive a complete ovariectomy.

Behavioral testing

Any experimental hamster that was attacked by a stimulus hamster was excluded from the analysis. Seven hamsters were attacked during CD testing and were therefore removed from final statistical analysis (E = 2, P = 1, DHT = 3, B = 1). It is possible that these animals were attacked because of behavior that they were displaying and that removing them from further statistical analysis may have actually changed the statistical outcome of the study. Therefore, to determine whether the pattern of the behavioral results would be different if these animals were included, a statistical analysis of the animals' initial agonistic behavior during testing was performed. All experimental hamsters (except for the three exclusions based on hormone assay results, see above) were categorized as submissive, aggressive, or neutral based on their behavior during the first 30 s of the test (i.e., before any animal was attacked by the non-aggressive intruder). To be scored as submissive, an animal had to display 10 or more seconds of submissive behavior and no aggressive behavior. To be scored as aggressive, an animal had to display 10 or more seconds of aggressive behavior. Animals that showed less than 10 s of submissive or aggressive behavior were categorized as neutral (these animals exhibited primarily social and nonsocial behavior). Total numbers of submissive, aggressive, or neutral animals in each hormone group are shown in Fig. 1. Individual Chi-square goodness of fit tests revealed significant differences in submissive and neutral behavior between hormone groups. These differences are illustrated in Fig. 1.

Forty-eight hamsters were included in the final behavioral analysis (E_2: $n = 10$; T: $n = 11$; P: $n = 9$; DHT: $n = 9$; blank: $n = 9$). A Kruskal–Wallis test revealed significant differences in submissive ($\chi^2(4, n = 47) = 13.25$), social ($\chi^2(4, n = 47) = 11.64$), and nonsocial ($\chi^2(4, n = 47) = 10.72$) behavior. No significant differences in aggressive behavior were found.

Hamsters receiving estradiol or testosterone showed significantly less submissive behavior than did hamsters that received progesterone, dihydrotestosterone, or no hormone replacement (blank capsule). Animals that received testosterone showed significantly more social behavior than did animals that received progesterone or blank capsules. Finally, hamsters receiving testosterone or DHT showed significantly less non-social behavior than did hamsters receiving estradiol. These data are illustrated in Fig. 2. The results of these analyses are consistent with the results of the Chi-square goodness of fit tests (see above).

Discussion

The present data indicate that previously defeated, ovariectomized female hamsters given estradiol or testosterone display significantly less submissive behavior when subsequently tested against a non-aggressive intruder than do ovariectomized females given dihydrotestosterone, progesterone, or no hormone replacement. Consistent with

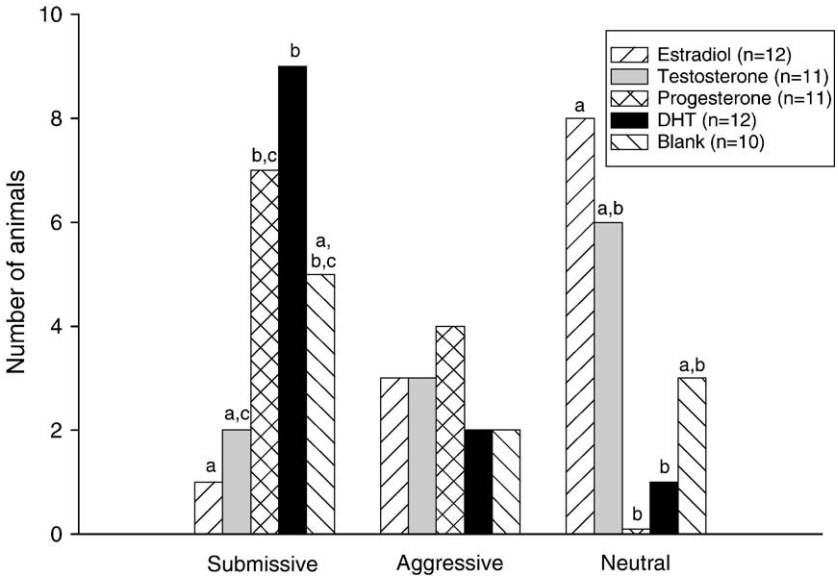

Fig. 1. Number of animals showing submissive, aggressive, or neutral behavior for each hormone group. Non-shared letters depict significant differences ($P < 0.05$) determined by a series of Chi-square goodness of fit tests. Total number of animals in each group is listed in the legend.

previous data examining chronic E_2 treatment in ovariectomized, female hamsters (for a review, see: (Albers et al., 2002)) or T (Floody and Pfaff, 1977; Grelk et al., 1974; Vandenbergh, 1971), E_2 or T treatment did not increase aggressive behavior in hamsters in the current experiment. Previous research on agonistic behavior in female hamsters has primarily focused on aggressive behavior and not on submissive behavior, thereby providing no results with which to compare the current findings. It is clear that sex differences exist in hamsters for both aggressive (Beatty, 1979; Brain, 1972; Payne and Swanson, 1970) and submissive (Huhman et al., 2003) behavior. The current data suggest that there are hormonal influences on agonistic behavior in female hamsters that are specifically related to submissive behavior.

Given that E_2 and T, but not DHT, affected submissive behavior, it is possible that the effects of E_2 and T observed in the current study may have been mediated through estrogen receptors. It has been reported that testosterone may positively affect aggressive behavior in male mice via aromatization to estradiol (Beatty, 1979; Brain, 1983). Combined treatment of female hamsters with both exogenous testosterone and an aromatase inhibitor would test whether the effect of testosterone on submissive behavior was mediated via estrogen receptors. The present results suggest that female hamsters might display much lower

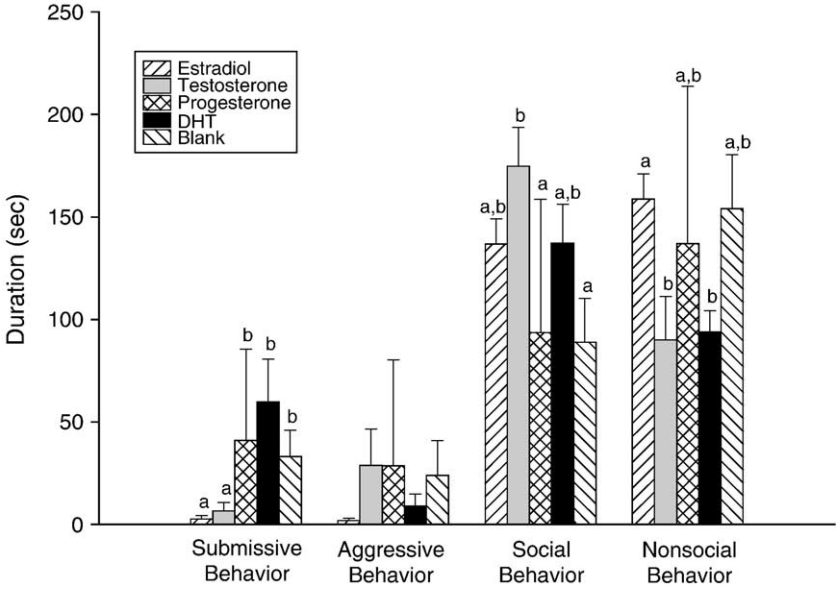

Fig. 2. Mean duration (s) ±SEM of submissive, aggressive, social, and nonsocial behavior for each hormone group. Non-shared letters depict significant differences ($P < 0.05$) determined by a series of Mann–Whitney U tests.

levels of submissive behavior than do males following defeat because of circulating estrogen. Relatedly, recent data from our laboratory indicate that there is a striking variation in submissive behavior across the estrous cycle in intact female hamsters (Matia B. Solomon and Kim L. Huhman, in preparation).

It is important to comment on the seven animals that were excluded from the behavioral analysis because they were attacked by the intruder during testing. One could argue that these animals were systematically attacked by the intruders (because of their behavior), and, therefore, exclusion of these animals from statistical analysis altered the outcome of the results. This argument is unlikely, however, for several reasons. First, the animals that were attacked were distributed in each of the treatment groups except for testosterone (see Results). Second, it is not surprising that there were more frequent instances of aggression in group-housed females than is normally observed in group-housed males because female hamsters are often more aggressive than are male hamsters (Beatty, 1979; Brain, 1972; Payne and Swanson, 1970). Furthermore, group-housing does not seem to reduce aggressiveness as effectively in females. In the current study, the attacks that occurred were not preceded by any particular display by the experimental animals. Finally, we categorized the behavior of all animals (except the three excluded based on hormone assay results) as submissive, aggressive, or neutral during the first 30 s of the encounter (before they were attacked by the intruder). Analysis of these data revealed that the overall effect (less submission in estrogen and testosterone groups) was maintained even when the attacked animals were included in the analysis.

The current data also revealed that animals receiving E_2 exhibited significantly more nonsocial behavior than did animals receiving T or DHT and that animals receiving T displayed significantly more social behavior than did animals receiving P or no hormone replacement. A more detailed behavioral analysis of the social and nonsocial behavior displayed by each group, however, revealed no qualitative differences in the types or in the proportions of particular social and nonsocial behaviors displayed by animals in each group. Thus, it does not appear that any of the hormone treatments stimulated abnormal or pathological behaviors. It is also important to remember that we scored the duration of all behaviors emitted during a 300-s test; thus, if one behavior decreases significantly, another behavior (or behaviors) will necessarily increase to fill the time.

In summary, chronic estradiol or testosterone treatment appears to reduce submissive behavior following a prior defeat in female Syrian hamsters, possibly by acting on estrogen receptors. Collectively, the results of the present study demonstrate the ability of gonadal hormones to modulate submissive behavior in female Syrian hamsters. It is important to note, however, that the level of submissiveness observed in the group that received no hormone replacement (though significantly higher than levels seen in the estradiol and testosterone groups) was low compared to the levels of submissiveness observed in male Syrian hamsters (Jasnow and Huhman, 2001). Although these experiments do not fully assess all possible influences of gonadal hormones on conditioned defeat, the comparatively lower levels of submissiveness observed in the current study suggest that sex differences in submissiveness are likely due to more than just hormonal influences. A final point, which we believe is strongly supported by the present findings, is that in studies of social conflict, it is critical that *all* aspects of agonistic behavior (aggression, defense, and submission) be measured. Limiting the behavioral dependent measure to only aggression (i.e., attack frequency and/or latency) may cause an important treatment effect to be missed. This limitation may explain in part why there has been such a lack of consensus in studies of hormonal influences on agonistic behavior.

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