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Aggressive encounters differentially affect serum dehydroepiandrosterone and testosterone concentrations in male Siberian hamsters (*Phodopus sungorus*)

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ABSTRACT

The gonadal hormone testosterone (T) regulates aggression across a wide range of vertebrate species. Recent evidence suggests that the adrenal prohormone dehydroepiandrosterone (DHEA) may also play an important role in regulating aggression. DHEA can be converted into active sex steroids, such as T and estradiol (E_2), within the brain. Previous studies show that circulating DHEA levels display diurnal rhythms and that melatonin increases adrenal DHEA secretion *in vitro*. Here we examined serum DHEA and T levels in long-day housed Siberian hamsters (*Phodopus sungorus*), a nocturnal species in which melatonin treatment increases aggression. In Experiment 1, serum DHEA and T levels were measured in adult male hamsters during the day (1200 h, noon) and night (2400 h, midnight). In Experiment 2, aggression was elicited using 5-min resident–intruder trials during the day (1800 h) and night (2000 h) (lights-off at 2000 h). Serum DHEA and T levels were measured 24 h before and immediately after aggressive encounters. In Experiment 1, there was no significant difference in serum DHEA or T levels between noon and midnight, although DHEA levels showed a trend to be lower at midnight. In Experiment 2, territorial aggression was greater during the night than the day. Moreover, at night, aggressive interactions rapidly decreased serum DHEA levels but increased serum T levels. In contrast, aggressive interactions during the day did not affect serum DHEA or T levels. These data suggest that nocturnal aggressive encounters rapidly increase conversion of DHEA to T and that melatonin may play a permissive role in this process.

Introduction

Aggression is a complex behavior displayed by virtually all organisms and serves a wide range of adaptive functions. Many studies of male aggressive behavior have demonstrated the effects of the gonadal androgen testosterone (T) on territorial aggression. For example, studies of rats (*Rattus norvegicus*), house mice (*Mus musculus*), Mongolian gerbils (*Meriones unguiculatus*) and Syrian hamsters (*Mesocricetus auratus*) have demonstrated that male–male aggression is reduced by castration and restored by T replacement (Beeman, 1947; Payne, 1972, 1974; Sayler, 1970; Uhrich, 1938). Further, individuals with higher circulating T levels can be more aggressive than conspecifics with lower circulating T levels (Beehner et al., 2006; Cavigelli and Pereira, 2000). This relationship between T and aggression is observed across many vertebrate species (Francis et al., 1992; Moore, 1988; Quiring, 1944). Interestingly, aggressive encounters can trigger a rapid and marked increase in circulating androgens, a phenomenon first predicted by the challenge hypothesis (Wingfield et al., 1990). In some species (e.g., cichlids, toadfish, ring-tailed lemurs, white-crowned sparrows), circulating androgen levels in males, although higher in the breeding than the non-breeding season, are further elevated over breeding baseline in response to an aggressive interaction (Cavigelli and Pereira, 2000; Hirschenhauser et al., 2004; Remage-Healey and Bass, 2005; Wingfield et al., 1990). Elevated T might facilitate aggressive behavior necessary to defend an individual's territory. Support for the challenge hypothesis has been reported for many but not all species.

In some species or environmental contexts, however, a positive relationship between T and aggression is lacking (For Review: Demas et al., 2007; Soma et al., 2008). For example, dusky footed wood rats (*Neotoma fuscipes*), song sparrows (*Melospiza melodia*), and European stonechats (*Saxicola rubicola*) maintain high levels of aggressive behavior outside of the breeding season, when circulating T levels are relatively low, and castration has no effect on aggression (Caldwell et al., 1984; Canoine and Gwinner, 2002; Wingfield and Soma, 2002). In Syrian (*M. auratus*) and Siberian hamsters (*Phodopus sungorus*), aggression is actually higher during the non-breeding season than the breeding season. In fact, aggression can be independent of or even

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inversely related to gonadal T (Jasnow et al., 2000; Scotti et al., 2008). Specifically, castration has no effect on the aggressive behavior of male Siberian hamsters and exogenous T decreases aggression (Scotti et al., 2008).

Melatonin appears to play an important role in regulating aggression in hamsters. Melatonin is secreted from the pineal gland predominantly during the dark of night and is suppressed by light. Thus, the pattern of melatonin secretion serves as the biochemical code for photoperiodic (day–night) information in mammals. Pinealectomy blocks short-day increases in aggression in Syrian hamsters (Badura and Nunez, 1989; Fleming et al., 1988) and exogenous melatonin increases aggression in Syrian (Jasnow et al., 2002) and Siberian hamsters (Demas et al., 2004) and house mice (Paterson and Vickers, 1981). Melatonin-induced increases in aggression are blocked by bilateral removal of the adrenal glands, but not by adrenal demedullation, in Siberian hamsters (Demas et al., 2004). These results suggest that in addition to T, melatonin and adrenocortical hormones regulate aggression in this system. An adrenocortical steroid that is particularly intriguing in this regard is dehydroepiandrosterone (DHEA). DHEA serves largely as an androgen precursor. Unlike T, DHEA is generally thought to be biologically inactive and does not bind with high affinity to classical intracellular steroid receptors (Mo et al., 2004; Widstrom and Dillon, 2004). Although there is some evidence for a DHEA-specific receptor (Arnold and Blackman, 2005; Widstrom and Dillon, 2004), DHEA appears to serve primarily as a prohormone and can be rapidly metabolized within target tissues into biologically active steroids, including androstenedione (AE), T, estrone (E_1), and estradiol (E_2). The metabolism of DHEA occurs within tissues (e.g., brain, gonads) that contain the appropriate steroidogenic enzymes (Beck and Handa, 2004; Hajszan et al., 2004; Labrie et al., 2005). Interestingly, melatonin can facilitate ACTH-induced DHEA production in cultured mouse adrenal glands (Haus et al., 1996), a finding supported by our preliminary studies in Siberian hamsters (M.-A.L. Scotti, A.E.M. Newman, K.K. Soma and G.E. Demas, unpublished). Furthermore, melatonin treatment increases circulating DHEA-sulfate (DHEA-S) concentrations in elderly humans without affecting serum cortisol levels (Pawlikowski et al., 2002).

Several recent studies have suggested a role for DHEA in non-breeding aggression (Hau et al., 2004; Soma et al., 2004, 2000; Soma and Wingfield, 2001; Soma et al., 2002) For example, non-breeding aggression is positively correlated with circulating DHEA levels in birds (Hau et al., 2004). Further, DHEA treatment increases aggressive vocalizations (Soma et al., 2002). Evidence for a role of DHEA in mediating mammalian aggression is more limited. Castrated male Syrian hamsters display an increase in plasma levels of DHEA-S (Pieper and Lobocki, 2000), suggesting an inverse relationship between gonadal T and adrenal DHEA. Preliminary studies in male Siberian hamsters indicate that endogenous serum DHEA levels are elevated under short days, when aggression is relatively high (Demas and Jasnow, 2004). Exogenous DHEA does not increase aggression in either long or short-day housed animals this system (Scotti et al., 2008). Treatment with exogenous DHEA, however, may not affect the rate of conversion of this prohormone to biologically active steroids (e.g., T, E_2). Thus, elevated DHEA may be necessary but not sufficient to elicit increased aggression in this and other species.

The goal of the current study was to test the hypothesis that daily changes in circulating DHEA levels or DHEA metabolism mediate aggression in Siberian hamsters. To this end we explored the possibilities that DHEA levels might change both during the course of a 24 hour day as well as in response to aggressive social interactions. Further, we examined whether T, which is a DHEA metabolite, might also show a change in circulating levels in response to an aggressive interaction. In Experiment 1, we examined circulating levels of DHEA and T during the day (1200 h, noon) and night (2400 h, midnight), when secretion of melatonin is relatively low and high, respectively. We investigated this possibility because daily changes in circulating DHEA levels could have important behavioral significance. In Experiment 2, we investigated the rapid effects of aggressive interactions during the day or night on circulating levels of DHEA and T, to determine whether social regulation of steroid levels varies with time of day.

Materials and methods

Animals and housing conditions

Adult (>60 days of age) male Siberian hamsters (*P. sungorus*) ($n=47$) were obtained from our breeding colony and were housed individually in polypropylene cages (27.5×17.5×13.0 cm) in colony rooms with a long-day light cycle of 16 h light and 8 h dark (L16:D8; lights-on at 0400 h EST). Temperature was kept constant at 20±2 °C and relative humidity was maintained at 50±5%. Food (Purina Rat Chow) and tap water were available *ad libitum* throughout the experiment. Additional animals were used as non-aggressive intruders during behavioral testing and were group-housed (3–4 animals per cage) in long days (16L:8D) (Brain, 1972; Svare and Leshner, 1973). These animals were approximately two months younger than experimental animals (and thus weighed less) and were chosen to facilitate aggression from the resident (Jasnow et al., 2000). Non-aggressive intruders were used no more than twice per test day. All animals were treated in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Bloomington Institutional Animal Care and Use Committee.

Experiment 1: diurnal changes in serum DHEA and T concentrations

Long-day housed Siberian hamsters ($n=47$ adult males total) were randomly assigned to have blood collected at either midnight (2400 h EST, $n=23$) or noon (1200 h EST, $n=24$). Hamsters were lightly anesthetized with diethyl ether (VWR, Indianapolis, IN) and blood samples were drawn (<5 min of initial disturbance) from the retro-orbital sinus. Serum was collected after centrifugation and stored at −20 °C until assayed.

Experiment 2: effects of aggression on DHEA and T concentrations

Two weeks after Experiment 1 was completed, blood samples were again drawn from the same 47 animals and serum was collected and stored as in Experiment 1. Approximately 24 h after baseline blood collection, all animals were tested using a resident–intruder model of aggression (Demas et al., 2004) by introducing a non-aggressive intruder into the home cage of an experimental animal for 5 min to assess territorial aggression (Jasnow et al., 2000). Animals were assigned randomly to be tested during either lights-on or lights-off. Behavior was tested either during the day (1800 h; 2 h before lights-off $n=23$) or during the night (2000 h; immediately after lights-off $n=24$) to determine the effects of lighting conditions on aggression. Trials occurring during the day were performed under standard laboratory fluorescent lighting (~500 lx) whereas trials occurring during the night were performed under dim red lighting (~200 lx), which allowed video recording and observation without disrupting the natural nocturnal behavior of the hamsters. Intruders were identified by small patches of shaved fur on their dorsal flanks. To increase territorial aggression of subjects, their bedding remained unchanged for at least one week prior to behavioral testing (Jasnow et al., 2000). Immediately following aggressive encounters (~24 h after the baseline blood sampling), subjects were anesthetized with ether and blood samples were again drawn from the retro-orbital sinus (<5 min of initial disturbance). Serum was collected after centrifugation and stored at −20 °C.

Behavioral assessment

Videotapes of behavioral interactions were scored using ODlog™ (Macropod Software) by an observer who was naïve to the experimental aims. Both the number of attacks and the latency to initial attack were quantified. We defined an attack as physical contact between the resident and intruder that was initiated by the resident and resulted in biting and/or pinning.

Hormone assays

DHEA was measured using a double-antibody ^{125}I radioimmunoassay (DSL-8900, Diagnostic Systems Laboratories, Webster, TX) that was modified to increase sensitivity, as described previously (Boonstra et al., 2008; Granger et al., 1999; Newman et al., 2008a,b). Steroids from 11 µl of serum were extracted with 3 ml HPLC-grade dichloromethane (×2). Extracts were dried under nitrogen at 37 °C and reconstituted in 220 µl assay buffer. Samples were measured in duplicate (100 µl×2). The DHEA antibody has a low cross-reactivity with DHEA-S (0.02%), cortisol (<0.001%), 16β-OH DHEA (0.041%), androstenedione (0.46%), testosterone (0.028%), and 17β-estradiol (<0.004%; E. Chin and K. Soma, unpublished data). Minimum detection limit for the assay was 2 pg/tube. Water blanks ($n=4$) were non-detectable (<2 pg DHEA) or just above the detection limit (2.20 pg DHEA). Inter-assay variation was 2.69% (low control) and 7.91% (high control).

Testosterone was measured via a commercial EIA kit using unextracted serum (Correlate-EIA Kit #900-065; Assay Designs, Ann Arbor, MI). The antibody used in this kit is highly specific; cross-reactivity is 7.20% for androstenedione, 0.72% for DHEA, 0.4% for 17β-estradiol and <0.01% for other steroids. This assay has been previously validated for use in Siberian hamsters (Scotti et al., 2008). T was measured in a subset of animals ($n=36$); these were the only samples for which we had sufficient serum remaining to perform the assay. Samples were diluted 1:20 with assay buffer and run in duplicate for each sample. Samples from experiments 1 and 2 were run on separate assay plates. The sensitivity of this assay is 3.82 pg/ml and the intra-assay coefficient of variation was 0.40% for Experiment 1 and 2.27% for Experiment 2. The inter-assay variation was 7.44%. All procedures were followed as per the guidelines provided by the manufacturer. For both hormones, samples that did not fall on the standard curve were not included in analysis.

Statistical analyses

All statistical analyses were performed using SPSS version 14 (SPSS Inc., Chicago). Data were log transformed when they violated the assumptions of normality and homoscedasticity. In Experiment 1, independent-sample *t*-tests were used to compare DHEA and T levels at noon vs. midnight. In Experiment 2, a two-way mixed-design analysis of variance (ANOVA) test was run on both DHEA and T levels, with Time (day vs. night) as a between-subjects variable and Aggression (pre-aggression test vs. post-aggression test) as a within-subjects variable. Hormone data were compared between animals examined during the day vs. night using Fisher's Least Significant Difference (LSD) tests. All statistical comparisons were considered significant if $p \leq 0.05$.

Results

Experiment 1

There was a small, non-significant trend towards higher DHEA concentrations at noon (the middle of the day) than midnight (the middle of the night) ($t_{44}=1.82$; $p=0.068$) (Fig. 1A). Serum T concentrations did not differ between animals bled at noon or midnight ($t_{45}=0.375$; $p=0.710$) (Fig. 1B).

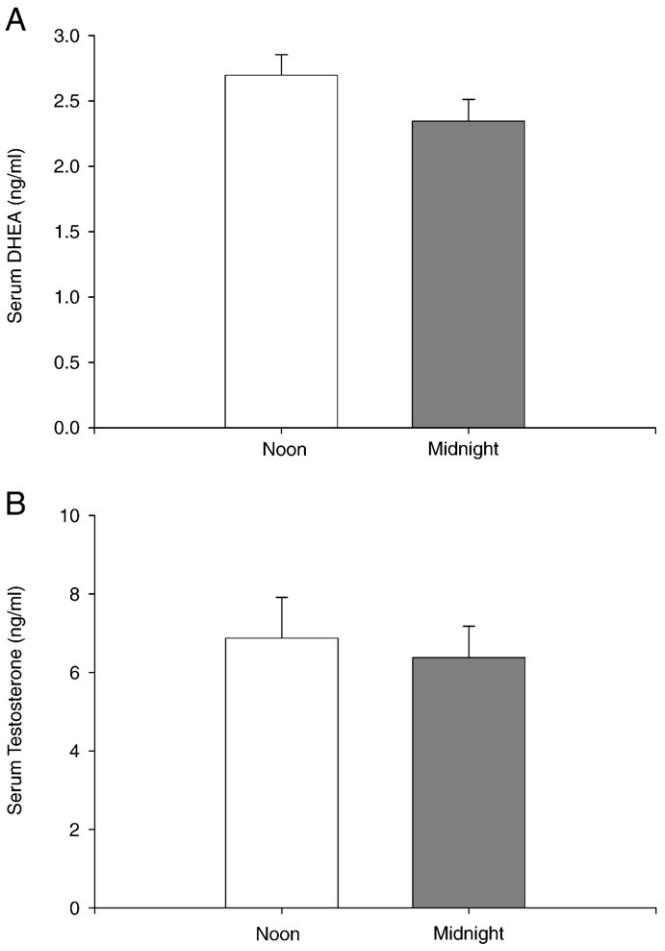

Fig. 1. Mean (±SEM) serum (A) dehydroepiandrosterone (DHEA) (Day $n=24$; Night $n=23$) and (B) testosterone (Day $n=23$; Night $n=23$) concentrations in male Siberian hamsters sampled either during the day (noon) or night (midnight).

Experiment 2

Aggression

Animals tested during the night displayed significantly more attacks than animals tested during the day ($t_{45}=2.109$; $p=0.041$) (Fig. 2A). Hamsters tested during the night also had a shorter latency to initial attack than those tested during the day ($t_{45}=2.033$; $p=0.048$) (Fig. 2B).

Dehydroepiandrosterone (DHEA)

There was a significant main effect of Aggression ($F_{1,43}=5.35$; $p=0.026$) but not of Time ($F_{1,43}=2.15$; $p=0.150$) on circulating DHEA concentrations. However, there was a marginally significant interaction between Aggression and Time ($F_{1,43}=3.99$; $p=0.052$); aggressive interactions decreased DHEA levels during the night, but not during the day (Fig. 3A).

Testosterone (T)

There were no main effects of Aggression ($F_{1,35}=0.19$; $p=0.66$) or Time ($F_{1,35}=2.24$; $p=0.14$) on circulating T concentrations. The interaction between Aggression and Time was significant ($F_{1,35}=4.239$; $p=0.047$); aggressive interactions increased T levels during the night, but not during the day (Fig. 3B). There was no significant correlation between serum DHEA and T either pre- or post-aggressive encounters ($p>0.05$ in both cases).

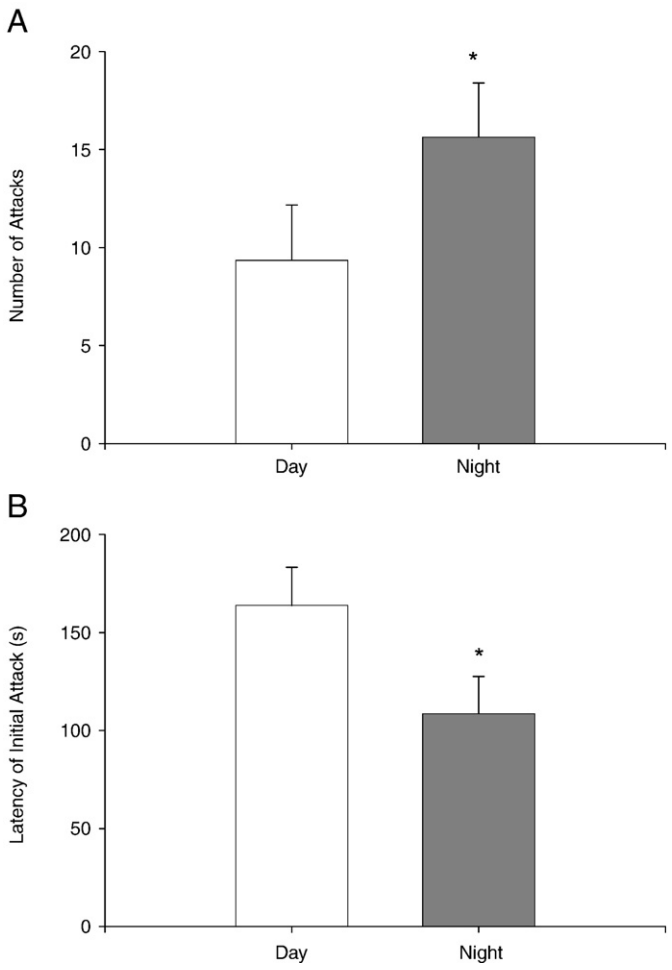

Fig. 2. Mean (±SEM) (A) number of attacks and (B) latency to initial attack (s) in male Siberian hamsters tested either during the day (1800 h; $n=23$) or night (2000 h; $n=24$). *$p \leq 0.05$.

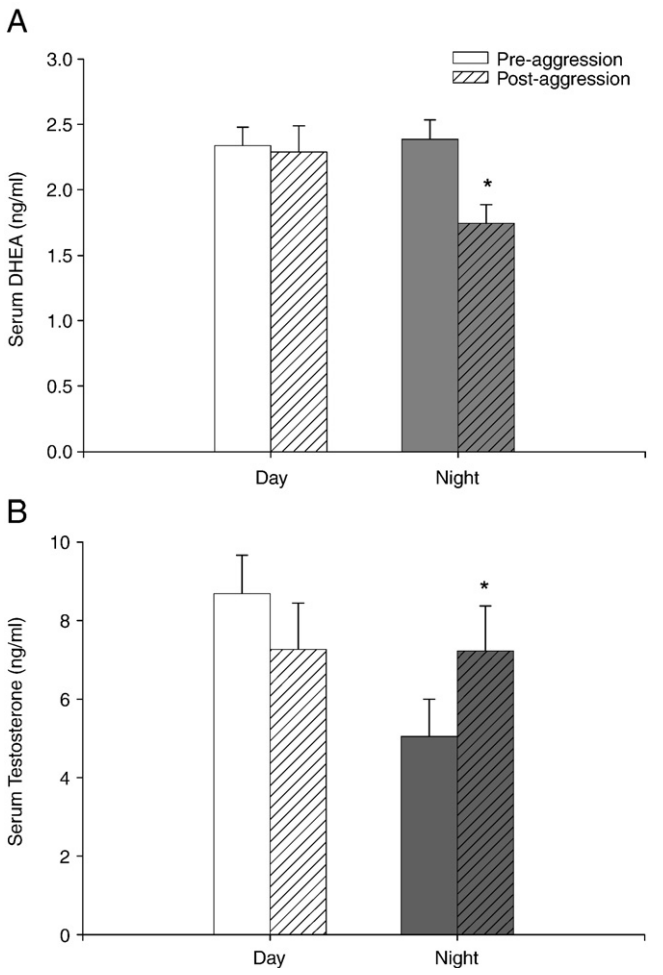

Fig. 3. Mean (±SEM) pre- and post-aggression serum (A) DHEA (Day $n=22$; Night $n=23$) and (B) testosterone (Day $n=19$; Night $n=18$) concentrations in male Siberian hamsters tested during either during the day (1800 h) or night (2000 h). Pre-aggression samples were collected approximately 24 h prior to aggression trial and post-aggression samples were collected immediately after aggression trials. *$p \leq 0.05$.

Discussion

The primary goals of the present study were to characterize diurnal changes in baseline circulating DHEA and T levels and to determine the effects of aggressive interactions on circulating DHEA and T levels in Siberian hamsters. In Experiment 1, we measured circulating DHEA and T concentrations during the day (noon) and night (midnight). We did not find significant differences in serum DHEA concentrations at these times. However, there was a trend towards reduced circulating levels of DHEA at midnight ($p=0.068$). In contrast, in Syrian hamsters, DHEA levels begin to increase ~120 prior to lights-off and remain elevated during the night (Pieper and Lobocki, 2000).

In Experiment 2, we tested the hypothesis that serum androgens would be altered in response to a brief (5 min) aggressive encounter. Post-aggression DHEA levels were significantly lower than pre-aggression DHEA levels in animals tested during the night but not during the day. We found the opposite pattern of results for serum T levels; post-aggression T levels were significantly higher than pre-aggression T levels during the night but not during the day. Consistent with these results, resident–intruder aggression was significantly greater during the night. Taken together, these findings support the idea that aggressive interactions rapidly increase conversion of DHEA to T at night. Although we previously demonstrated that exogenous DHEA treatment does not increase aggressive behavior in Siberian hamsters, DHEA treatment did increase serum T levels, especially in short-day hamsters (Scotti et al., 2008).

One possibility is that increased T observed after nighttime aggression trials might originate from the testes, rather than from conversion of DHEA to T in the brain. Although this possibility cannot be ruled out based on the present findings, melatonin, unlike its effects on adrenal DHEA, typically inhibits gonadal T release in small rodents (Petterborg and Reiter, 1981; Yilmaz et al., 2000); thus this possibility seems unlikely. However, future studies that assess changes in steroid-converting enzymes, as described below, will be critical in addressing this question. Collectively, the results of these studies suggest that aggressive encounters trigger rapid and marked changes in steroid concentrations and are consistent with the idea that social challenges stimulate the conversion of DHEA to a biologically active steroid (i.e., T). In addition, this is the first report of the effects of aggressive encounters on circulating T and DHEA concentrations in this species.

Siberian hamsters, like most rodents, are nocturnal, which likely contributed to the increased aggression at night in Experiment 2. Pineal melatonin secretion is elevated during nighttime, suggesting that increases in circulating levels of melatonin may mediate, at least in part, increased aggression in hamsters. Previous research has implicated melatonin in the control of rodent aggression. For example, pinealectomy attenuates aggression in house mice and Syrian hamsters (Badura and Nunez, 1989; Fleming et al., 1988). Furthermore, in long-day housed hamsters, administration of melatonin (in a manner that mimics melatonin patterns under short days) causes an

increase in aggression (Demas et al., 2004; Jasnow et al., 2002). Conversely, aggressive interactions can also lead to elevated melatonin levels; a single 3-min aggressive encounter elevates circulating melatonin levels in gerbils (Heinzeller et al., 1988). Changes in melatonin may contribute to diurnal changes in aggression in hamsters, although this idea remains to be tested.

Increased aggression during nighttime may not be entirely dependent on elevated melatonin at the time of testing. Short-day housed hamsters that experience prolonged patterns of nighttime melatonin secretion are more aggressive than long-day housed animals; this difference is present even when both groups are tested during the day, when melatonin concentrations are presumably low (Demas et al., 2004; Scotti et al., 2007). Thus, elevated melatonin is not required at the time of behavioral testing to see short-day increases in aggression. Whether elevated short-day aggression is a result of prolonged durations of nocturnal melatonin secretion in short compared long-day housed hamsters for eight weeks prior to behavioral testing remains to be determined.

Melatonin also facilitates DHEA secretion from cultured adrenal glands in both hamsters and mice (Haus et al., 1996; M.-A.L. Scotti, A.E.M. Newman, K.K. Soma, G.E. Demas, unpublished). Specifically, incubation of cultured adrenal glands for 2 h with a combination of ACTH and melatonin results in higher concentrations of DHEA in the culture media compared with ACTH alone. These results suggest that melatonin plays a permissive role in the regulation of adrenal DHEA release.

Circulating DHEA may, in turn, be converted to active sex steroids within the brain to influence aggressive behavior. The enzyme 3β-hydroxysteroid dehydrogenase/isomerase (3β-HSD) catalyzes the conversion of DHEA to androstenedione (AE), which can then be converted by 17β-HSD to T. Although steroidogenic enzymes were not measured in the present study, it is possible that aggressive encounters at night cause rapid increases in 3β-HSD activity in the brain, testes or elsewhere. Increased 3β-HSD activity would be consistent with the pattern of results in animals tested at nighttime (rapid decrease in DHEA and increase in T levels in serum).

Although the effects of melatonin on 3β-HSD activity have not been examined, it is possible that high melatonin levels seen during nighttime or under short photoperiods regulate 3β-HSD activity. For example, in song sparrows, brain 3β-HSD activity is higher in winter than in spring (K.K. Soma, unpublished results). Future studies are needed in which steroidogenic enzymes are measured in response to social interactions. Regardless of the precise neuroendocrine mechanisms, the present findings suggest that aggressive social interactions lead to rapid and robust changes in both serum DHEA and T concentrations in Siberian hamsters. Future research, however, should explore if changes in DHEA occur with other social behaviors as well. The changes we observed occurred during the night but not the day, suggesting a role for melatonin. Siberian hamsters, unlike laboratory rats and mice, have relatively high circulating levels of DHEA, which may serve as an important precursor for biologically active steroids (e.g., T, E_2) that play important roles in the regulation of social behavior in this and other species (Adkins-Regan, 2005). The results of the present study support the idea that Siberian hamsters are an ideal small animal model with which to examine the neuroendocrine responses to social interactions.

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