
34 DHEA and Aggression

Gregory E. Demas, Kiran K. Soma, and H. Elliott Albers

CONTENTS

Introduction.....	415
DHEA and Rodent Aggression	416
DHEA and Avian Aggression	423
DHEA and Human Aggression.....	424
Conclusions.....	426
Acknowledgments.....	427
References.....	427

INTRODUCTION

Aggression is one of the most important social behaviors, is displayed by virtually all animals, and serves a wide range of adaptive functions. Nonetheless, the precise mechanisms that regulate aggression remain largely unknown. Aggressive behavior occurs whenever the interests of two or more individuals are in conflict, typically over limited resources (e.g., food, territories, and mates). Aggression is difficult to define and has been defined in a variety of ways. Aggression has traditionally been defined as overt behavior with the intention of inflicting physical damage on another individual (Moyer 1971). Moyer (1971) divided aggression into specific subtypes, including predatory aggression, intermale aggression, fear-induced aggression, irritable aggression, maternal aggression, territorial defense, and instrumental aggression, based on differences in the social conditions in which the behavior was elicited. A simplified classification of aggressive behavior has been suggested in which aggression is divided into offensive and defensive aggression (Blanchard and Blanchard 1988). Offensive aggression involves behaviors used in an attack, whereas defensive behaviors do not involve an active approach to the opponent but, rather, they serve as a defense against an attack. This latter classification system provides a more functional framework with which to identify and characterize aggressive behavior across a range of vertebrate taxa. A key aspect of both classifications is that, although different forms of aggression share specific behavioral features, the environmental factors eliciting these responses, as well as the biological substrates underlying their manifestation, may differ markedly.

Aggressive behavior has received extensive study under a wide range of environmental settings and experimental conditions. The experimental models used, the types of aggression measured, and the species tested, however, can vary considerably from study to study. Thus, it is often difficult to compare results across a range of studies. Although a relatively large number of experimental paradigms have been developed to evaluate aggression in animal models, one of the most prevalent models of assessing offensive aggression has been the resident-intruder model. This model simulates rodent territorial aggression and involves introducing a group-housed, nonexperimental “intruder” into the home cage of an experimental animal, and the amount and duration of aggressive behavior (e.g., chases, attacks, bites) are subsequently recorded in a timed test. Another less-commonly employed but useful model is the neutral arena model, which involves placing two animals in a novel “neutral” cage and recording the amount of aggression directed toward each animal. In addition, this latter model has the added benefit of assessing the formation of dominance relationships among animals because “territories” have not been established at the time of testing.

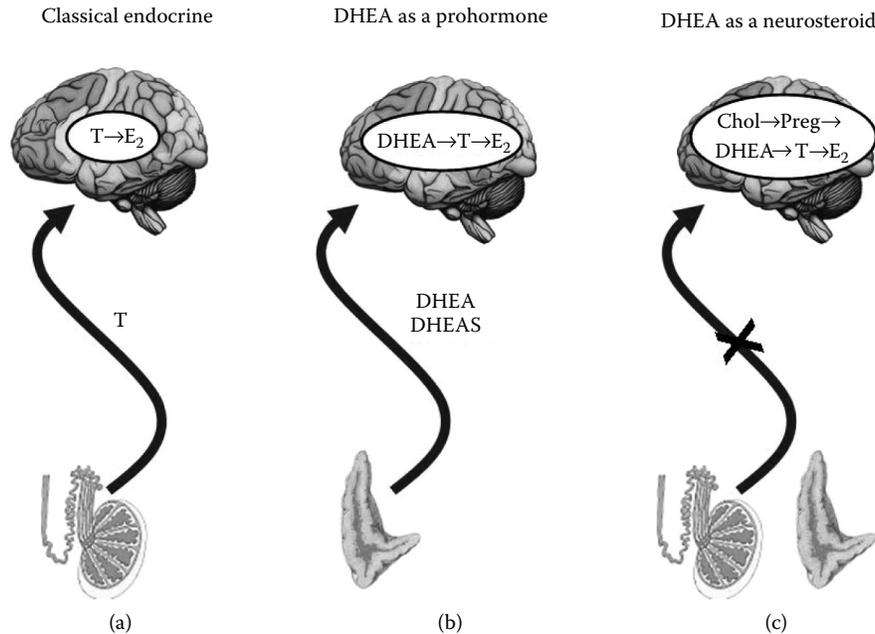


FIGURE 34.1 Steroid hormones can reach the brain to affect aggression via several possible mechanisms. (a) The classical endocrine pathway involves gonadal testosterone acting directly, or indirectly via local conversion to estradiol, on the brain. (b) Adrenal DHEA can act as a prohormone by being converted locally to T or E₂. (c) DHEA can act as a neurosteroid by being produced locally in the brain in the absence of gonadal and adrenal steroid production.

Much of the early research on the neuroendocrine mechanisms of aggression focused on the role of gonadal steroid hormones, and predominantly testosterone (T), as the primary factor regulating aggression. In fact, most behaviorally oriented textbooks discuss the role of T in aggression almost exclusively, with much less emphasis on the role of other factors (e.g., dehydroepiandrosterone [DHEA]) in regulating this behavior. One of the goals of this chapter is to suggest that the idea that a single hormone mediates aggression is overly simplistic. For example, recent evidence indicates that T can be converted to 17 β -estradiol (E₂) within the brain and that E₂ may mediate aggressive behavior, at least in some species and contexts (Soma et al. 2000). Alternatively, androgen precursors such as DHEA may be produced in extragonadal peripheral tissues (e.g., adrenals) or de novo within the brain. In fact, it is suggested that both adrenal and neurally derived androgens, called neurosteroids (Baulieu 1991), may play an important role in regulating aggressive responses (Simon 2003). Collectively, these important findings have helped elucidate several possible pathways by which androgens can act on the brain, either directly or indirectly, to affect aggression (Figure 34.1). While numerous endocrine and neural factors are now known to affect aggressive behaviors, this chapter will focus on emerging evidence suggesting a role of DHEA in the regulation of aggression across vertebrate taxa.

DHEA AND RODENT AGGRESSION

Despite the traditional research focus on the role of T in the regulation of aggression in vertebrates, it is becoming increasingly clear that steroid hormones other than T (e.g., DHEA) play important roles in the regulation of aggressive behavior, either by acting independent of or in conjunction with T (Demas et al. 2007; Soma et al. 2008). For example, DHEA is shown to be a potent inhibitor of

AU: Please note that the reference "Simon 2002" has been changed as "Simon 2003" so as to match the list. Please changed as correct.

AU: There are two Soma et al. 2000 in the reference list. Please indicate whether this should be Soma, Sullivan et al. 2000 or Soma, Tramontin, and Wingfield 2000. Also check other citations of Soma et al. 2000.

female typical aggression in mice (Bayart et al. 1989; Haug et al. 1989, 1992; Perché et al. 2000; Young et al. 1996). Attack behavior in ovariectomized female mice, intact female mice, or castrated male mice toward lactating female mice can be significantly reduced following treatment with exogenous DHEA (Bayart et al. 1989; Brain and Haug 1992). Because this effect requires prolonged (~15 days) DHEA treatment, the results are consistent with a genomic mechanism of action (Lu et al. 2003).

It has been shown that prenatal T treatment enhances DHEA-induced inhibition of aggression in female offspring (Perché et al. 2001). It is important to note, however, that this testing paradigm (i.e., aggression toward a lactating intruder) is employed far less than more traditional models of aggression (e.g., intermale aggression); thus, the role of DHEA in mediating other forms of aggression has received very little experimental attention. One finding, however, suggests that increases in aggressive behavior can be induced by a single injection of the sulfated form of DHEA (i.e., dehydroepiandrosterone sulfate [DHEAS]) immediately prior to behavioral testing in mice tested in a neutral arena (Nicolas et al. 2001). Furthermore, treatment with COUMATE, a drug that inhibits the steroid sulfatase enzyme that converts DHEAS to DHEA, also increased aggression in male mice (Nicolas et al. 2001). Despite these intriguing results, more studies are needed to fully elucidate the role of DHEA and DHEAS in intermale aggression.

The effects of DHEA on aggression have led to an attempt at determining the physiological mechanisms underlying this behavioral response, with much of the work focused on interaction of this steroid with GABA neurotransmission (reviewed in a study by Simon 2003). It has been demonstrated that DHEA alters brain levels of pregnenolone sulfate (PREG-S), a neurosteroid that inhibits GABAergic actions via the GABA_A receptor. Specifically, DHEA-induced changes in GABA activity appear to be responsible for the effects of DHEA on aggression. These results are consistent with previous findings demonstrating an inhibitory effect of GABA on aggression (Miczek et al. 1994, 1997). Although the precise mechanisms of action are still unknown, DHEA can modulate the actions of both GABA and glutamatergic NMDA receptors (Labrie 1998; Mellon and Vaudry 2001). Alternatively, DHEA may act by further conversion in the brain to T and E₂ via the enzymes 3 β -HSD and aromatase (Soma et al. 2004).

More recent findings suggest that an additional mechanism for the effects of DHEA on aggression may exist (Simon 2003). Although it has long been assumed that DHEA is incapable of directly interacting with the androgen receptor (AR), recent data suggest that DHEA upregulates AR in the mouse brain (Lu et al. 2003; Mo et al. 2005). Intact and gonadectomized, T-treated male mice do not display aggression toward female mice, and prolonged treatment with DHEA is necessary to elicit antiaggressive effects. Thus, it has been speculated that androgens such as DHEA play an inhibitory role, presumably through a genomic action by binding directly to AR and altering AR transcription and translation (Simon 2003). For example, DHEA can compete for recombinant AR binding, upregulate neural AR protein levels in mouse brains and immortalized GT1-7 hypothalamic cells, and induce transcription through AR in CV-1 cells, suggesting direct actions of DHEA on AR (Simon 2003). Although this idea is intriguing, the affinity of DHEA for AR is low relative to T, so high local levels of DHEA would be necessary for this mechanism to be plausible.

Several studies have examined the role of androgens including T and DHEA in aggression in a seasonal context. Many nontropical rodent species are seasonal breeders, maintaining reproductive function during the summer and curtailing breeding during the winter. Ambient day length (photoperiod) is the proximal environmental cue used by individuals within these species to coordinate their reproduction to the appropriate season (Goldman 2001). For example, reproductive activity (with high levels of circulating androgens) is maintained during long “summer-like” days (e.g., >12.5 hours of light/day), whereas reproductive regression, including virtual collapse of the gonads and marked decreases in T, occur during the short “winter-like” days (e.g. <12.5 hours of light/day; Goldman 2001). Interestingly, although short-day exposure produces a substantial reduction in circulating T levels in males, it also significantly increases circulating levels of DHEA (Caldwell, Smith, and Albers 2008). Surprisingly, male Syrian hamsters (*Mesocricetus auratus*)

AU: Please note that the reference “Mo 2004” has been changed as “Mo 2005” so as to match the list. Please changed as correct.

maintained in short days actually display *increased* resident-intruder aggression compared with long-day animals despite gonadal regression and relatively low T levels (Garrett and Campbell 1980). Specifically, adult male Syrian hamsters housed in short days for 9 weeks display approximately twice the amount of aggression in a resident-intruder test compared with long-day controls when tested 4 hours before dark, despite gonadal regression (Garrett and Campbell 1980). After prolonged maintenance in short days (>15 weeks), hamsters typically undergo spontaneous gonadal recrudescence (i.e., increased testicular mass and circulating T), despite continued maintenance in short days. The short-day increases in aggressive behavior largely disappear in animals undergoing spontaneous recrudescence, returning to long-day levels of aggression by 21 weeks (Garrett and Campbell 1980). Short-day increases in aggression in male Syrian hamsters have been confirmed (Jasnow et al. 2002; Caldwell and Albers 2004). For example, Syrian hamsters housed in short days (light:dark [LD] 10:14) for 10 weeks displayed a significantly greater number of attacks and a longer duration of attacks than did long-day hamsters when tested using a resident-intruder test (Jasnow et al. 2002). It has been shown that short-day gonadal regression does not affect the frequency of a form of social communication in Syrian hamsters called “flank marking” (Caldwell and Albers 2003). Flank marking, which is an androgen-dependent behavior in hamsters housed in long days, continues to be displayed at high levels during social encounters and in response to conspecific odors in male hamsters exposed to short days despite low circulating levels of gonadal steroids (Caldwell and Albers 2003; Gutzler et al. in press). These findings suggest that neuroendocrine factors other than T may mediate flank marking as well as overt aggression in this species.

In Syrian hamsters, unlike most rodent species, females are more aggressive than males (Ciacco, Lisk, and Rueter 1979; Marques and Valenstein 1977). Not surprisingly, photoperiodic changes in aggression have been demonstrated in female Syrian hamsters (Badura and Nunez 1989; Fleming et al. 1988). Female hamsters were housed in long (LD 14:10) or short days (LD 6:18) for 12 weeks, and then both offensive and defensive aggression were tested (Fleming et al. 1988). Female hamsters maintained in short days displayed significantly less defensive aggression compared with long-day animals and thus had a higher ratio of offensive to defensive aggression than long-day animals (Fleming et al. 1988). To further examine the physiological mechanisms mediating short-day aggression in females of this species, the effects of short-day exposure on circulating levels of adrenal steroids were assessed (Gutzler et al. 2009). Specifically, animals were housed in either long or short days, and circulating concentrations of cortisol, DHEA, and DHEAS were determined (Figure 34.2). While exposure to short days decreased cortisol and DHEA levels (Gutzler et al. 2009), DHEAS concentrations were significantly higher in short-day exposed hamsters (Figure 34.3). Furthermore, short days increased aggression, regardless of the endocrine state of the animals. Exogenous E_2 , however, reduced aggression in long-day hamsters but not in short-day hamsters, suggesting that exposure to short photoperiod renders females less sensitive to E_2 -induced decreases in aggressive behavior, at least in females of this species (Gutzler et al. 2009). The precise role of the decrease in DHEA and the increase in DHEAS in short-day hamsters and its relationship with increased aggression, however, remain unknown.

Unlike Syrian hamsters, male Siberian hamsters (*Phodopus sungorus*) display significantly more aggression than females. It has previously been demonstrated that short-day male Siberian hamsters are significantly more aggressive than long-day animals (Jasnow et al. 2000; Jasnow et al. 2002), consistent with previous studies in Syrian hamsters. Specifically, male Siberian hamsters housed in short days (LD 8:16) for 10 weeks display a greater number of attacks during a resident-intruder test and have a lower latency to initial attacks, relative to long-day (LD 16:8) animals. As previously reported for many rodent species, prolonged maintenance on short days (i.e., 20 weeks) resulted in spontaneous reproductive recrudescence in which the gonads, and thus T, returned to normal long-day levels (Jasnow et al. 2000). Interestingly, gonadally recrudescenced hamsters displayed less aggression than gonadally regressed animals even though both groups experienced the same photoperiod and melatonin signal; levels of aggression in recrudescenced hamsters were generally indistinguishable from long-day hamsters (Jasnow et al. 2000). These results support previous findings in male

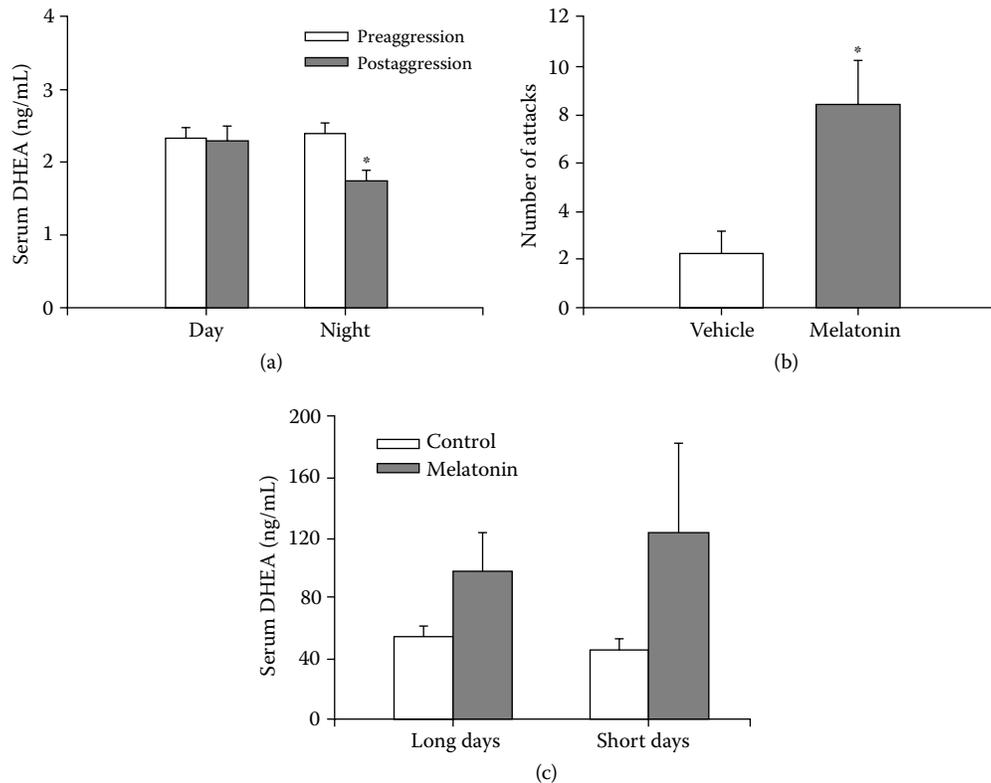


FIGURE 34.2 Effects of photoperiod on circulating DHEA, DHEAS, and cortisol concentrations across time in female Syrian hamsters. (a) Photoperiod altered DHEA concentrations, but time did not affect circulating hormone levels. (b) Photoperiod altered DHEAS concentrations, but as with DHEA, there was no effect of time on DHEAS. (c) Cortisol concentrations were not significantly different as a result of photoperiod, but a significant effect of time on hormone levels was found, with significantly higher cortisol concentrations in long photoperiod (LP) females than in short photoperiod (SP) females 2 and 3 hours after the onset of the dark phase. (Adapted from Gutzler, S. J., M. Karom, D. W. Erwin, and H. E. Albers. In press. *Behav Brain Res.*)

Syrian hamsters (Garrett and Campbell 1980). When short-day Siberian hamsters were implanted with Silastic capsules containing T (to achieve long day-like levels), aggression actually *decreased* compared with short-day control animals (Jasnow et al. 2000), suggesting that short-day increases in aggression may be *inversely* related to serum T concentrations.

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 Siberian hamsters (Scotti et al. 2008). Specifically, long- and short-day housed hamsters were implanted with Silastic capsules containing DHEA or no hormone (control). If short-day increases in DHEA occur in hamsters and regulate photoperiodic changes in aggression in this species, then it is predicted that exogenous DHEA mimicking long-day levels will increase aggression in long-day hamsters to levels comparable to those in short-day control animals. Further, short-day hamsters receiving DHEA would show levels of aggression significantly higher than all other experimental groups. While short days did increase aggression as predicted, exogenous DHEA had no effect on aggression in either long- or short-day hamsters (Scotti et al. 2009). Giving exogenous DHEA, however, may not affect the rate of conversion of this prohormone to biologically active steroids (e.g., T, E₂). Thus, elevated DHEA may be necessary but not sufficient to elicit increased aggression in this and other species.

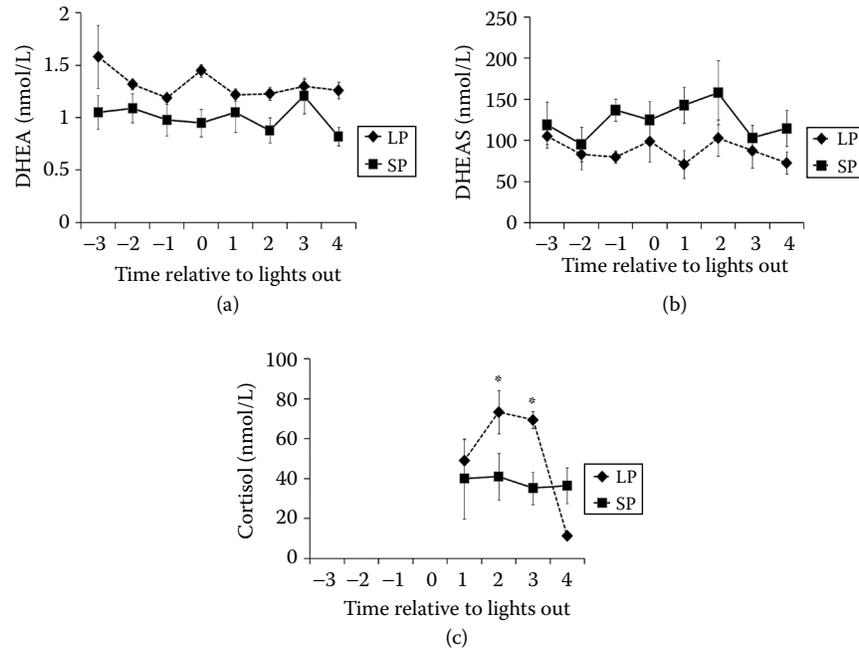


FIGURE 34.3 (a) Mean (\pm SEM) pre- and postaggression serum DHEA in Siberian hamsters. Hamsters were tested during the day and night, when circulating melatonin levels were relatively low and high, respectively. (Adapted from Scotti, M. L., A. E. M. Newman, K. L. Schmidt, T. N. Bonu, K. K. Soma, and G. E. Demas. 2009. *Horm Behav* 56:376–81.) (b) Resident-intruder aggression, as measured by the number of attacks during a 5-minute test in hamsters treated with exogenous melatonin or no melatonin (control). (Adapted from Jasnow et al. 2004.) (c) In vitro adrenal DHEA in cultured adrenal glands from hamsters housed in either long or short days. Hamsters were housed in their respective photoperiods for 10 weeks prior to testing. Adrenal DHEA release was stimulated by application of adrenocorticotropic hormone alone or in combination with melatonin. (Demas, Scotti and Soma, unpublished data.)

AU: Please include Jasnow et al. (2004) in the reference list with complete information such as article/book title, journal/publisher name.

AU: Please update the source information.

To further test the hypothesis that changes in circulating DHEA levels or DHEA metabolism mediate aggression in Siberian hamsters, daily fluctuations in DHEA levels were assessed prior to and in response to aggressive interactions (Scotti et al. 2009). Specifically, circulating DHEA and T concentrations were measured during the day (noon) and night (midnight). Although there were no significant differences in serum DHEA concentrations at these times, there was a trend towards reduced circulating levels of DHEA at midnight (Scotti et al. 2009). In contrast, in male Syrian hamsters, there were robust diurnal changes in circulating DHEA levels, and DHEA levels peaked 30 minutes prior to lights off and remained elevated during the night (Pieper and Loboeki 2000). Next, the effects of a brief (5 minutes), aggressive encounter on serum androgens were examined. Postaggression DHEA levels were significantly lower than preaggression DHEA levels in animals tested during the night but not during the day (Figure 34.3a). An opposite pattern of results was found for serum T levels; postaggression T levels were significantly higher than preaggression T levels during the night but not during the day. Consistent with these results, resident-intruder aggression was significantly greater during the night, when circulating levels of melatonin were at their relative peak. These data suggest that circulating DHEA may 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 to T by 17β -HSD. Aggressive encounters at night may cause rapid increases in 3β -HSD activity in the brain or periphery. 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).

A recent study has examined circulating DHEA levels in territorial red squirrels (Boonstra et al. 2008). Both males and females of this species are highly aggressive during both the breeding and nonbreeding seasons due to the defense of food stores in their territories. Plasma DHEA concentrations in both males and females were considerably higher than levels typically seen in laboratory rodents (e.g., rats and mice; Boonstra et al. 2008). Furthermore, circulating DHEA levels displayed both seasonal and yearly variation that was negatively correlated with testis mass and positively correlated with population density (Boonstra et al. 2008). Plasma DHEA increased following ACTH challenges, suggesting that DHEA was predominantly of adrenal origin. Although aggression is not specifically addressed, these findings are consistent with the idea that DHEA is elevated at times of high territorial aggression in the field.

In virtually all mammals, photoperiodic responses are mediated by changes in the pineal indolamine melatonin. Melatonin is secreted predominantly during darkness, whereas daylight inhibits pineal melatonin secretion (Goldman 2001). Thus, changes in ambient day length result in changes in the pattern of secretion of melatonin. In this manner, it is the precise pattern of melatonin secretion, and not the amount of hormone per se, that provides the biochemical “code” for day length (Goldman 2001). Pinealectomy, which eliminates melatonin secretion and renders animals physiologically “blind” to day length, prevents the short-day increase in aggression in female Syrian hamsters, whereas treatment of long-day hamsters with exogenous short day-like melatonin increases aggression in female Syrian hamsters (Fleming et al. 1988). Ovariectomy, in contrast, has no effect on aggression. This finding suggests that photoperiodic changes in aggression are independent of changes in gonadal steroids in female Syrian hamsters (Fleming et al. 1988). A subsequent study in female Syrian hamsters confirmed these findings and provided further support for a role of pineal melatonin in mediating photoperiod changes in aggression. Specifically, a higher percentage of female hamsters housed in short days (LD 6:18) showed aggressive behavior compared with long-day housed (LD 16:8) hamsters (Badura and Nunez 1989). Consistent with previous findings, short-day aggression was attenuated by pinealectomy, but treatment with exogenous E_2 (alone or in combination with progesterone) had no effect on aggression. These results support the hypothesis that photoperiodic changes in aggression are mediated by pineal melatonin, but independent of gonadal steroids, at least in female Syrian hamsters. Furthermore, timed daily melatonin injections mimicking short-day patterns of the hormone in long-day, pineal-intact animals will produce short day-like increases in aggression. Because these injections occurred for only 10 days, gonadal mass and circulating levels of T are unaffected, supporting the hypothesis that photoperiodic changes in aggression are not mediated by changes in gonadal steroids in this species (Jasnow et al. 2002).

More recent research in male Siberian hamsters (Demas et al. 2004) confirms previous findings that treatment of long-day animals with short-day like levels of melatonin mimics photoperiodic changes in aggression; long-day hamsters given daily timed injections of melatonin 2 hours before lights out to mimic short-day levels of the hormone displayed elevated aggression in a resident-intruder test compared with control animals (Figure 34.3b). As with previous studies, these results were not likely due to changes in gonadal steroids, as serum T was unaffected by this injection protocol.

The effects of melatonin on aggression in rodents may be due to direct actions of this hormone on neural substrates mediating aggression (e.g., hypothalamus, limbic system). Alternatively, melatonin-induced aggression may be indirectly due to changes in hypothalamic-pituitary-adrenal (HPA) activity, as adrenal hormones (e.g., glucocorticoids, DHEA) have been implicated in aggressive behavior (Haller and Kruk 2003). In support of the latter hypothesis, changes in both the size and function of the adrenal gland are associated with changes in aggression (Paterson and Vickers 1981). In addition, male house mice housed in a LD 12:12 photoperiod and treated with melatonin display increased territorial aggression but decreased adrenal masses compared to saline-treated animals (Paterson and Vickers 1981). The increases in aggression displayed by melatonin-treated animals, however, can be blocked by adrenalectomy (Paterson and Vickers 1981). Experimental reductions in both adrenomedullary catecholamines and adrenocortical glucocorticoids are associated with

decreased aggression in rodents (Haller and Kruk 2003; Paterson and Vickers 1981), and reductions of glucocorticoids via pharmacological blockade of adrenocorticotrophic hormone (ACTH) release can attenuate melatonin-induced increases in aggression in mice (Paterson and Vickers 1981). Thus, exogenous melatonin, despite reducing adrenal mass, appears to increase aggression by stimulating adrenocortical steroid release. These results are particularly intriguing given that house mice are generally reproductively nonresponsive to photoperiod (Nelson 1990).

More recently, research has implicated changes in adrenocortical hormones in mediating melatonin-induced aggression in Siberian hamsters. Long-day hamsters treated with short-day like levels of melatonin displayed increased aggression, comparable to levels seen in short-day animals (Demas et al. 2004). Interestingly, melatonin-induced aggression could be blocked by bilateral adrenalectomy, consistent with previous results in house mice (Paterson and Vickers 1981). Adrenal demedullation, which eliminates adrenal catecholamines (i.e., epinephrine), but leaves adrenocortical steroid release (i.e., cortisol, DHEA) intact, had no effect on melatonin-induced aggression (Demas et al. 2004). Collectively, these results support the hypothesis that the effects of exogenous melatonin on aggression are mediated by the effects of this hormone on adrenocortical steroids. However, it is currently unknown which class of steroid hormones may mediate this effect, as both adrenal androgens (e.g., DHEA) and glucocorticoids (e.g., cortisol) have been implicated in aggression in rodents (Haller and Kruk 2003; Schlegel et al. 1985). In laboratory rats and mice, corticosterone is the predominant adrenal glucocorticoid, and these species secrete little to no adrenal DHEA. In contrast, in hamsters, as in humans, cortisol is the primary adrenal glucocorticoid (Albers et al. 1985), and both hamsters and humans secrete measurable amounts of DHEA and its sulfated form, DHEAS (Mellon and Vaudry 2001; Pieper et al. 2000).

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; Figure 34.3c). Specifically, incubation of cultured adrenal glands for 2 hours 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. As discussed above, the enzyme 3β -HSD catalyzes the conversion of DHEA to AE, which can then be subsequently converted to T. It is possible that increased aggression when melatonin levels are elevated (e.g., short days or nighttime) may be driven by increased adrenal DHEA and subsequent rapid increases in 3β -HSD activity in the brain or periphery, thus leading to increased T. 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) previously reported (Scotti et al. 2008).

In addition to peripheral secretion of androgens, it is now commonly accepted that the brain is a significant source of steroid production. The idea of “neurosteroids” (i.e., brain-derived steroid hormones) was first introduced to describe the high levels of the androgen DHEA, and its sulfated form DHEAS, seen in rat brain even after castration and adrenalectomy (Baulieu 1981; Corpechot et al. 1981). It is now established that DHEA, among other steroid hormones (e.g., allopregnanolone [ALLO]), can be synthesized *de novo* within the central nervous system and can act locally on specific neural substrates to regulate behavior (Simon 2003). For example, a recent study has demonstrated that intermale aggression is associated with changes in brain neurosteroid synthesis (Pinna, Costa, and Guidotti 2005). Specifically, administration of T propionate (TP) to male mice decreased brain ALLO content by about 40% and was correlated with increased aggression. Increasing brain ALLO levels pharmacologically attenuated aggressive behavior in these mice. Similar changes in brain DHEA may also occur, but this remains to be examined in rodents. It remains unclear, however, how neurosteroids might be synthesized in adult rodent brains, given that a key synthetic enzyme (P450c17) is nondetectable in the rodent brains in several studies (Mellon and Vaudry 2001; but see Hojo et al. 2004).

AU: Please note that the references Albers et al. 1985; Bayart et al. 1989; Berenbaum and Resnick 1997; Caldwell and Albers 2003; Demas and Jasnow 2004; Gutzler et al. 2009; Haug et al. 1992; Jasnow et al. 2004; Labrie 1998; Mazur and Booth 1998; Newman et al. 2009; Owen-Ashley et al. 2004; Perché et al. 2001; Pieper et al. 2000; Pradhan et al. 2008; Soma et al. 2001 and Wingfield et al. 1987 are cited in text but not listed. Please add it to list or delete it from the text.

AU: Please update this citation with details such as article.

DHEA AND AVIAN AGGRESSION

AU: Please note that the reference "Wingfield and Soma 2001" has been changed as "Wingfield and Soma 2002" so as to match the list. Please changed as correct.

AU: Please check/confirm the spelling.

As with the rodent studies discussed above, most avian species show seasonal breeding, with distinct breeding and nonbreeding seasons. Recent investigations of avian species that exhibit year-round territorial aggression have found that nonbreeding aggression can be independent of circulating T levels. The males and females of many bird species exhibit high levels of territorial aggression throughout the year (Soma and Wingfield 1999). Often the territoriality expressed during the reproductive and nonreproductive seasons is quantitatively and qualitatively similar (Wingfield and Hahn 1994; Soma and Wingfield 2001). While aggression during the breeding season is generally regulated by gonadal steroids, aggression outside of the breeding season may be regulated by non-gonadal steroids (Wingfield and Soma 2002; Soma et al. 2000; Soma 2004).

Several studies have focused on nonbreeding aggression in song sparrows (*Melospiza melodia morphna*), a common North American songbird (Soma et al. 1999, Soma et al. 2000; Soma et al. 2001; Soma and Wingfield 2001). Male song sparrows are highly territorial during the spring (breeding season) and autumn/winter (nonbreeding season; Wingfield and Hahn 1994). Note that the testes are completely regressed (≤ 1 mm in length) and plasma T levels are basal or nondetectable during the nonbreeding season (Soma et al. 2003). Furthermore, castration of nonbreeding male song sparrows has no effect on territorial aggression in autumn (Wingfield 1994). These data led to the hypothesis that aggression during the nonbreeding season is not regulated by sex steroids.

To test this hypothesis, male song sparrows were treated with the aromatase inhibitor fadrozole in the nonbreeding season (Soma et al. 2000). Fadrozole strongly decreases aggressive behavior in nonbreeding song sparrows (Soma et al. 2000). Moreover, the effects of fadrozole are rescued by E_2 replacement (Soma et al. 2000). These data suggest that sex steroids, in particular estrogens, are necessary for the expression of aggressive behavior in the nonbreeding season, even though plasma sex steroid levels are nondetectable (Soma et al. 2000). Similar results were obtained in two other field experiments (Soma et al. 1999; Soma et al. 2000).

The source of androgen substrate for brain aromatase in the nonbreeding season could be circulating DHEA (Soma and Wingfield 2001). Although DHEA cannot be directly aromatized, DHEA can be metabolized to AE by 3β -HSD, an aromatizable androgen. In contrast to T and E_2 , DHEA is detectable and elevated in the circulation of nonbreeding birds (Soma and Wingfield 2001; Newman, Pradhan, and Soma 2008; Newman and Soma 2009; Newman et al. 2010; Pradhan et al. 2010). DHEA concentrations in the adrenals and regressed testes of nonbreeding birds are even higher than plasma levels, suggesting that both organs could secrete DHEA into the general circulation (Soma and Wingfield 2001; Newman et al. 2009). Interestingly, DHEA concentrations in the brain are also very high (Newman and Soma 2009).

Treatment of nonbreeding male song sparrows with a physiological dose of DHEA increases territorial singing and the size of HVC, a brain region involved in the production of songs (Soma et al. 2002). DHEA treatment also regulates cell proliferation and new cell incorporation into HVC in adult song sparrows (Newman et al. 2010). These are some of the largest reported effects of DHEA on adult neuroplasticity and similar to the effects of T and E_2 on song behavior and neuroanatomy (Soma et al. 2004). However, DHEA treatment does not affect other territorial behaviors or, importantly, T-dependent secondary sexual characteristics (Soma et al. 2002). Other studies demonstrate that DHEA, unlike T, does not suppress immune function in song sparrows (Owen-Ashley et al. 2004).

Further investigations examined the metabolism of DHEA to active sex steroids within the songbird brain (Soma et al. 2004; Pradhan et al. 2008; Schlinger, Pradhan, and Soma 2008). To do so, brain tissue was incubated with 3H -DHEA in vitro. The biochemical assay measures the conversion of 3H -DHEA to 3H -AE by the enzyme 3β -HSD. 3H -AE can be metabolized subsequently to 3H -T or 3H -estrogens. In captive adult zebra finches (*Taeniopygia guttata*), brain tissue clearly metabolizes 3H -DHEA to 3H -AE, which is in turn aromatized to 3H - E_1 . Importantly, trilostane, a specific 3β -HSD inhibitor, blocks the production of 3H -AE, and fadrozole, a specific aromatase inhibitor, reduces the production of 3H - E_1 . The song sparrow brain can also convert DHEA to androgens and

AU: Please note that the reference "Soma 2006" has been changed as "Soma 2004" so as to match the list. Please changed as correct.

AU: There are three Soma et al. 1999 in the reference list. Please indicate whether this should be Soma, Bindra et al. 1999 or Soma, Hartman et al. 1999 or Soma, Sullivan, and Wingfield 1999. Also check other citations of Soma et al. 1999.

AU: There are two Soma et al. 2002 in the reference list. Please indicate whether this should be Soma, Alday, and Schlinger 2002 or Soma, Wissman et al. 2002. Also check other citations of Soma et al. 2002.

AU: Please expand HVC at its first instance.

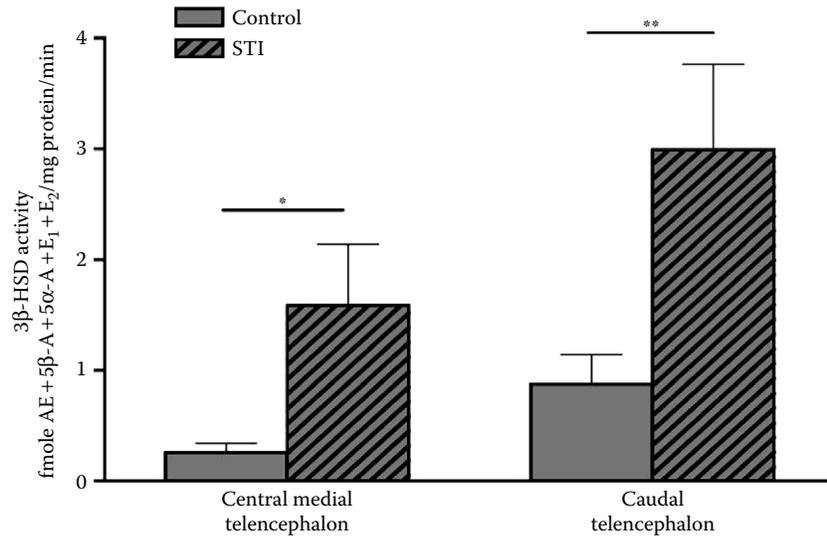


FIGURE 34.4 Effect of a simulated territorial intrusion (STI) for 30 minutes on DHEA metabolism by brain 3β -HSD in wild male song sparrows during the nonbreeding season. Exogenous NAD⁺ was not added. The STI rapidly increased DHEA metabolism by 3β -HSD in the central medial telencephalon ($n = 9$ control and 8 STI) and caudal telencephalon ($n = 7$ control and 8 STI). * $p < .05$, ** $p < .01$. (Adapted from Pradhan, D. S., A. E. Newman, D. W. Wacker, J. C. Wingfield, B. A. Schlinger, and K. K. Soma. 2010. *Horm Behav* 57:381–9.)

estrogens (Pradhan et al. 2010). Brain 3β -HSD activity is higher during the nonbreeding season than during the breeding season, consistent with a greater role of neurosteroids in the nonbreeding season. Moreover, aggressive interactions rapidly (within 30 minutes) upregulate brain 3β -HSD activity in the nonbreeding season (Pradhan et al. 2010; Figure 34.4). Taken together, these data support the hypothesis that nonbreeding song sparrows combine peripheral DHEA synthesis with neural DHEA metabolism to maintain territorial behavior when gonadal T secretion is low. Moreover, it remains possible that the brain itself is a significant site of DHEA synthesis in nonbreeding song sparrows (Newman and Soma 2009).

Other studies have examined the spotted antbird (*Hylophylax n. naevioides*; Hau et al. 2000; Hau, Stoddard, and Soma 2004). The spotted antbird is a tropical species that exhibits year-round territorial aggression (Hau, Stoddard, and Soma 2004). Despite the presence of year-round territorial aggression, these birds generally have low or nondetectable levels of plasma T, even during the breeding season (Hau et al. 2000). Nonetheless, experiments have shown that T or its estrogenic metabolites do play a role in male territoriality (Hau et al. 2000). Results of a recent study that examined male and female antbirds during the nonbreeding season indicate that both sexes exhibit robust aggressive behavior during the nonbreeding season, and in both sexes, plasma DHEA levels are detectable and higher than plasma T and E₂ levels (Hau, Stoddard, and Soma 2004). In addition, plasma DHEA levels in males are positively correlated with aggressive vocalizations. Plasma DHEA, therefore, might serve as a precursor for synthesis of sex steroids in the brain throughout the year in these birds, in both males and females (Hau, Stoddard, and Soma 2004).

DHEA AND HUMAN AGGRESSION

Although the study of DHEA as a regulator of aggression in primates, including humans, has received some limited experimental attention, much less is known compared with nonprimates. Alterations in DHEA and DHEAS, however, have been implicated in a range of psychiatric disorders in humans (Maninger et al. 2009). Circulating levels of DHEAS are generally 1000-fold higher

than DHEA in humans. Studies from rodents and birds suggest that androgens such as DHEA may regulate aggression in situations where aggression seems otherwise T-independent. Some studies in nonhuman primates also suggest that aggressive behavior can be unrelated to fecal T levels (Lynch, Ziegler, and Strier 2002; Ostner, Kappeler, and Heistermann 2002). Although the zona reticularis of the primate adrenal glands can secrete high levels of DHEA and DHEAS (Rehman and Carr 2004), the role of adrenal DHEA and DHEAS in primate aggression is largely unknown. In some primate studies, measures of T may be confounded by adrenal DHEA and DHEAS, causing difficulty in interpretation. For example, metabolites of T and DHEA may cross-react with T antibodies in urine and fecal assays in macaques (Mohle et al. 2002). Thus, potential correlations between aggression and fecal or urinary androgens are confounded, making it difficult to determine with certainty the identity and origin of the relevant steroid. In addition, a lack of correlation between aggression and excreted T does not necessarily mean that aggression is androgen independent, as other androgens such as DHEA may regulate behavior. One study has assessed circulating DHEAS levels in a population of wild baboons (Sapolsky et al. 1993). DHEAS concentrations were high in both male and female baboons and showed marked age-related decreases in both sexes; however, circulating levels of DHEAS were not compared with aggression (Sapolsky et al. 1993).

Adrenal DHEA appears to play a role in human aggression, as indicated by studies on “conduct disorder,” which is typically defined as a collection of symptoms including aggression directed toward humans or animals, destruction of property, theft, and serious violations of rules. Prepubertal boys with conduct disorder were found to have higher levels of plasma DHEAS, but not T, than normal control boys (van Goozen et al. 1998). Also, DHEAS concentrations were correlated with the intensity of aggression as rated by parents and teachers. In another study, plasma DHEAS concentrations were found to be higher in boys with conduct disorder than in boys with attention-deficit hyperactivity disorder (ADHD) or normal controls (van Goozen et al. 2000). Finally, a recent study examined plasma levels of cortisol, DHEA, and DHEAS in delinquent adolescent boys diagnosed with conduct disorder compared with healthy controls. Hormone levels were correlated with aggression as determined by the Child Behavior Checklist and the Overt Aggression Scale (Golubchik et al. 2009). Delinquent boys tended to have higher DHEAS levels than control boys, but did not show any differences in either DHEA or cortisol (Golubchik et al. 2009). Collectively, these data suggest an important relationship between changes in DHEAS and aggression, at least in male adolescents diagnosed with clinically relevant psychiatric conditions.

These studies suggest that adrenal androgen precursors play an important role in the onset of aggression in adolescent boys. Adrenal androgen precursors may also contribute to the regulation of aggression in women. Adolescent and adult women with congenital adrenal hyperplasia, who were exposed to high levels of adrenal androgen precursors in the prenatal and early postnatal periods, were found to have greater self-reported aggression ratings than were control women (Berenbaum and Resnick 1997). Adrenal androgen precursor levels have been determined in adolescent girls diagnosed with conduct disorder (Pajer et al. 2006). Specifically, blood samples were drawn from adolescent girls with either conduct disorder or no psychiatric disorder, and samples were assessed for DHEA, DHEAS, cortisol, as well as for gonadal androgens and estrogens. Girls with conduct disorder scored higher on a clinical aggression scale and demonstrated significantly lower cortisol to DHEA ratio but did not differ from control girls on any other hormone measurement (Pajer et al. 2006). Furthermore, girls diagnosed with aggressive conduct disorder had lower cortisol to DHEA ratios than those with nonaggressive conduct disorder.

DHEA can play a role in adult aggression as well. In a study of alcohol withdrawal, serum levels of DHEAS and cortisol, as well as DHEAS response to treatment with exogenous dexamethasone (i.e., dexamethasone suppression test), were determined in adult alcohol-dependent or healthy control men (Ozsoy and Esel 2008). Alcohol-dependent subjects displayed reduced basal as well as dexamethasone-induced levels of DHEAS compared to control subjects in late alcohol withdrawal. When alcohol-dependent subjects were separated into high and low aggression groups, lower basal DHEAS levels were seen only during early alcohol withdrawal in high aggression individuals,

AU: Please note that the reference “Ozsoy and Esel 2007” has been changed as “Ozsoy and Esel 2008” so as to match the list. Please changed as correct.

whereas DHEA was lower only during late withdrawal in low aggression individuals relative to control subjects. In contrast, dexamethasone-induced decreases in DHEAS were observed during both early and late alcohol withdrawals whereas lower DHEA levels were only seen during early withdrawal (Ozsoy and Esel 2008). Although it is not entirely clear what these results mean, they do indicate that there are significant changes in HPA axis activity, suggesting an important link between DHEA and aggressive behavior, at least under conditions of drug withdrawal. Whether a link between DHEA, DHEAS, and aggressive behavior exists in healthy adult and adolescent men and women remains to be determined. Regardless, it is clear that considerably more research on DHEA and human aggression is needed.

CONCLUSIONS

In many vertebrate species, including humans, rates of aggression in males are often associated with circulating levels of T. This relationship has been extensively demonstrated in rodents, predominantly rats and mice, where castration has been shown to reduce aggression and exogenous T treatment restores aggressive behavior (Edwards 1969, 1970; Barfield 1971). In birds, a positive correlation between plasma T and rates of aggression has been repeatedly documented during periods of social challenge, and particularly during mate competition (Wingfield et al. 1987). It is important to remember, however, that in many cases, aggression is independent of or even inversely related to circulating levels of T. Seasonal aggression provides a valuable paradigm in which to study the neuroendocrine mechanisms of aggression. In many species (e.g., song sparrows, Siberian and Syrian hamsters), high rates of aggression in males occur outside the period of high circulating T levels (Soma et al. 2000; Garrett and Campbell 1980; Lynch, Ziegler, and Strier 2002, respectively). The neuroendocrine mechanisms regulating aggression under these conditions are poorly understood, but recent data provide some interesting possibilities. In birds, the metabolism of T to E₂ may mediate aggression during the mating season. During the nonmating season when circulating T is basal, steroid metabolism may still mediate aggression, albeit via a different endocrine mechanism (Soma et al. 2000). Despite low levels of circulating T, the androgen precursor DHEA remains elevated in blood, and conversion of DHEA to E₂ within the brain appears to play an important role in nonbreeding season aggression in some species (Soma et al. 2000; Soma and Wingfield 2001). In rodents, the aromatization of androgens such as DHEA also appears to regulate, at least in part, intermale aggression. Furthermore, it seems likely that melatonin might regulate aggression under these conditions by affecting DHEA secretion or metabolism (Haus et al. 1996).

Human and nonhuman primates secrete relatively high levels of DHEA and DHEAS from the adrenal glands, but the role of DHEA in mediating primate aggression has received little attention. Recent evidence, however, suggests that plasma DHEAS levels are associated with conduct disorder, and, in particular, with the aggressive symptoms of conduct disorder in prepubertal boys and adolescent girls (van Goozen et al. 1998; Pajer et al. 2006), as well as in alcohol withdrawal-induced aggression in adults (Ozsoy and Esel 2008).

Traditionally, a nearly exclusive focus on T in the regulation of aggressive behavior has limited our understanding of additional neuroendocrine mechanism regulating aggression and strengthens the misperception that aggression is simply a function of changes in this one steroid. More recently, however, the idea that circulating T is not always associated with physical aggression and instead is more often associated with competition in specific situations has been suggested in humans (Mazur and Booth 1998) and nonhumans (Demas et al. 2007; Soma et al. 2008). Among several factors recently identified as potential regulators or modulators of aggression, DHEA has received considerable attention. While much of this initial work has been correlational and thus a causal role for this hormone has not been identified, continued research on the role of DHEA and its metabolites in the regulation of aggression in human and nonhumans animals, via its actions as both an adrenal hormone and as a neurosteroid, will improve our understanding of normal and abnormal aggression and violence.

ACKNOWLEDGMENTS

This work was supported in part by Eli Lilly Endowment METACyt grant, Indiana University Faculty Research Support Program and NSF IOB 0543798 to G.E.D, NSERC, Canadian Institutes of Health Research, Michael Smith Foundation for Health Research, and Canada Foundation for Innovation to K.K.S. and NSF IBN 9876754 and NSF IOS 0923301 to H.E.A.

REFERENCES

- Albers, H. E., and M. Bamshad. 1998. Role of vasopressin and oxytocin in the control of social behavior in Syrian hamsters (*Mesocricetus auratus*). *Prog Brain Res* 119:395–408.
- Albers, H. E., K. L. Huhman, and R. L. Meisel. 2002. Hormonal basis of social conflict and communication. In *Hormones, Brain and Behavior*, ed. D. W. Pfaff, A. P. Arnold, A. M. Etgen, S. E. Fahrback, and R. T. Rubin, 393–433. New York: Academic Press.
- Badura, L. L., and A. A. Nunez. 1989. Photoperiodic modulation of sexual and aggressive behavior in female golden hamsters (*Mesocricetus auratus*): Role of the pineal gland. *Horm Behav* 23:27–42.
- Barfield, R. J. 1971. Activation of sexual and aggressive behavior by androgen implanted into male ring dove brain. *Endocrinology* 89:1470–7.
- Baulieu, E. E. 1981. In *Steroid Hormone Regulation of the Brain*, ed. K. Fuxe, and J. A. Gustafsson, 3–14. Oxford: Pergamon Press.
- Baulieu, E. E. 1991. Neurosteroids: A new function in the brain. *Biol Cell* 71:3–10.
- Blanchard, D. C., and R. J. Blanchard. 1988. Ethoexperimental approaches to the biology of emotion. *Annu Rev Psychol* 39:43–68.
- Blanchard, D. C., R. L. Spencer, S. M. Weiss, R. J. Blanchard, B. McEwen, and R. R. Sakai. 1995. Visible burrow system as a model of chronic social stress: Behavioral and neuroendocrine correlates. *Psychoneuroendocrinology* 20:117–34.
- Boonstra, R., J. E. Lane, S. Boutin, A. Bradley, L. Desantis, A. E. Newman, and K. K. Soma. 2008. Plasma DHEA levels in wild, territorial red squirrels: Seasonal variation and effect of ACTH. *Gen Comp Endocrinol* 158:61–7.
- Brain, P. F., and M. Haug. 1992. Hormonal and neurochemical correlates of various forms of animal “aggression”. *Psychoneuroendocrinology* 17:537–51.
- Brain, P. F., and A. E. Poole. 1974. Some studies on the use of ‘standard opponents’ in intermale aggression testing in TT albino mice. *Behaviour* 50:100–10.
- Caldwell, H. K., and H. E. Albers. 2004. Effect of photoperiod on vasopressin-induced aggression in Syrian hamsters. *Horm Behav* 46:444–9.
- Caldwell, G. S., S. E. Glickman, and E. R. Smith. 1984. Seasonal aggression independent of seasonal testosterone in wood rats. *Proc Natl Acad Sci U S A* 81:5255–7.
- Caldwell, H. K., D. A. Smith, and H. E. Albers. 2008. Photoperiodic mechanisms controlling scent marking: Interactions of vasopressin and gonadal steroids. *Eur J Neurosci* 27:1189–96.
- Ciaccio, L. A., R. D. Lisk, and L. A. Rueter. 1979. Prelordotic behavior in the hamster: A hormonally modulated transition from aggression to sexual receptivity. *J Comp Physiol Psychol* 93:771–80.
- Corpechot, C., P. Robel, M. Axelson, J. Sjovall, and E. E. Baulieu. 1981. Characterization and measurement of dehydroepiandrosterone sulfate in rat brain. *Proc Natl Acad Sci* 78:4704–7.
- Demas, G. E., H. E. Albers, M. Cooper, and K. K. Soma. 2007. Novel mechanisms underlying neuroendocrine regulation of aggression: A synthesis of bird, rodent and primate studies. In *Behavioral Neurochemistry, Neuroendocrinology and Molecular Neurobiology*, ed. J. D. Blaustein, 337–72. Kluwer Press.
- Demas, G. E., K. M. Polacek, A. Durazzo, and A. M. Jasnow. 2004. Adrenal hormones mediate melatonin-induced increases in aggression in male Siberian hamsters (*Phodopus sungorus*). *Horm Behav* 46:582–91.
- Edwards, D. A. 1969. Early androgen stimulation and aggressive behavior in male and female mice. *Physiol Behav* 4:333–8.
- Edwards, D. A. 1970. Post-neonatal androgenization and adult aggressive behavior in female mice. *Physiol Behav* 5:465–46.
- Fleming, A. S., A. Phillips, A. Rydall, and L. Levesque. 1988. Effects of photoperiod, the pineal gland and the gonads on agonistic behavior in female golden hamsters (*Mesocricetus auratus*). *Physiol Behav* 44:227–34.
- Foidart, A., O. Tlemcani, N. Harada, S. Abe-Dohmae, and J. Balthazart. 1995. Pre- and post-transcriptional regulation of aromatase by steroidal and non-steroidal aromatase inhibitors. *Brain Res* 701:267–78.

AU: Please provide article title for reference Baulieu 1981.

AU: Please note that the references Albers and Bamshad 1998; Albers, Huhman, and Meisel 2002; Blanchard et al. 1995; Brain and Poole 1974; Caldwell, Glickman, and Smith 1984; Foidart et al. 1995; Haller, Makara, and Kruk 1998; Haug et al. 1991; Haug, Brain, and Kamis 1986; Labrie 2003; Labrie et al. 1995; Labrie et al. 2001; Pieper et al. 1999; Pinxten et al. 2000 and Simon et al. 2004 are listed but not cited. Please cite it in text or delete it from the list.

AU: Please provide location of the publisher for reference Demas et al. 2007.

AU: Please check page range for reference Edwards 1970.

AU: Please provide volume number and page range for references Gutzler et vval. In press and Soma, Alday, and Schlinger 2002.

- Garrett, J. W., and C. S. Campbell. 1980. Changes in social behavior of the male golden hamster accompanying photoperiodic changes in reproduction. *Horm Behav* 14:303–19.
- Goldman, B. D. 2001. Mammalian photoperiodic system: Formal properties and neuroendocrine mechanisms of photoperiodic time measurement. *J Biol Rhythms* 16:283–301.
- Golubchik, P., T. Mozes, R. Maayan, and A. Weizman. 2009. Neurosteroid blood levels in delinquent adolescent boys with conduct disorder. *Eur Neuropsychopharmacol* 19:49–52.
- Gutzler, S. J., M. Karom, D. W. Erwin, and H. E. Albers. In press. Seasonal regulation of social communication by photoperiod and testosterone: Effects of arginine-vasopressin, serotonin and galanin in the medial preoptic area—anterior hypothalamus. *Behav Brain Res*.
- Haller, J., and M. R. Kruk. 2003. Neuroendocrine stress responses and aggression. In *Neurobiology of Aggression*, ed. M. P. Mattson, 93–118. Totawa, NJ: Humana Press.
- Haller, J., G. B. Makara, and M. R. Kruk. 1998. Catecholaminergic involvement in the control of aggression: Hormones, the peripheral sympathetic, add central noradrenergic systems. *Neurosci Biobehav Rev* 22:85–97.
- Hau, M., S. T. Stoddard, and K. K. Soma. 2004. Territorial aggression and hormones during the non-breeding season in a tropical bird. *Horm Behav* 45:40–9.
- Hau, M., M. Wikelski, K. K. Soma, and J. C. Wingfield. 2000. Testosterone and year-round territorial aggression in a tropical bird. *Gen Comp Endocrinol* 117:20–33.
- Haug, M., P. F. Brain, and A. B. Kamis. 1986. A brief review comparing the effects of sex steroids on two forms of aggression in laboratory mice. *Neurosci Biobehav Rev* 10:463–8.
- Haug, M., M. L. Ouss-Schlegel, J. F. Spetz, P. F. Brain, V. Simon, E. E. Baulieu, and P. Robel. 1989. Suppressive effects of dehydroepiandrosterone and 3-beta-methylandro-5-en-17-one on attack towards lactating female intruders by castrated male mice. *Physiol Behav* 46:955–9.
- Haug, M., J. Young, P. Robel, and E. E. Baulieu. 1991. Inhibition by dehydroepiandrosterone of aggression responses of spayed female mice towards lactating intruders is potentiated by neonatal androgenization. *C R Acad Sci III* 312:511–6.
- Haus, E., G. Y. Nicolau, E. Ghinea, L. Dumitriu, E. Petrescu, and L. Sackett-Lundeen. 1996. Stimulation of the secretion of dehydroepiandrosterone by melatonin in mouse adrenals in vitro. *Life Sci* 58:PL263–7.
- Hojo, Y., T. A. Hattori, T. Enami, A. Furukawa, K. Suzuki, H. T. Ishii et al. 2004. Adult male rat hippocampus synthesizes estradiol from pregnenolone by cytochromes P45017alpha and P450 aromatase localized in neurons. *Proc Natl Acad Sci U S A* 101:865–70.
- Jasnow, A. M., K. L. Huhman, T. J. Bartness, and G. E. Demas. 2000. Short-day increases in aggression are inversely related to circulating testosterone concentrations in male Siberian hamsters (*Phodopus sungorus*). *Horm Behav* 38:102–10.
- Jasnow, A. M., K. L. Huhman, T. J. Bartness, and G. E. Demas. 2002. Short days and exogenous melatonin increase aggression in male Syrian hamsters (*Mesocricetus auratus*). *Horm Behav* 42:13–20.
- Labrie, F. 2003. Extragonadal synthesis of sex steroids: Intracrinology. *Ann Endocrinol (Paris)* 64:95–107.
- Labrie, F., A. Belanger, J. Simard, V. Luu-The, and C. Labrie. 1995. DHEA and peripheral androgen and estrogen formation: Intracrinology. *Ann NY Acad Sci* 774:16–28.
- Labrie, F., V. Luu-The, C. Labrie, and J. Simard. 2001. DHEA and its transformation into androgens and estrogens in peripheral target tissues: Intracrinology. *Front Neuroendocrinol* 22:185–212.
- Lu, S. F., Q. Mo, S. Hum, C. Garippam, and N. G. Simon. 2003. Dehydroepiandrosterone upregulates neural androgen receptor level and transcriptional activity. *J Neurobiol* 57:163–71.
- Lynch, J. W., T. E. Ziegler, and K. B. Strier. 2002. Individual and seasonal variation in fecal testosterone and cortisol levels of wild male tufted capuchin monkeys, *Cebus apella nigratus*. *Horm Behav* 41:275–87.
- Maninger, N., O. M. Wolkowitz, V. I. Reus, E. S. Epel, and S. H. Mellon. 2009. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). *Front Neuroendocrinol* 30:65–91.
- Marques, D. M., and E. S. Valenstein. 1977. Individual differences in aggressiveness of female hamsters: Response to intact and castrated males and to females. *Anim Behav* 25:131–9.
- Mellon, S. H., and H. Vaudry. 2001. Biosynthesis of neurosteroids and regulation of their synthesis. *Int Rev Neurobiol* 46:33–78.
- Miczek, K. A., J. F. DeBold, A. M. van Erp, and W. Tornatzky. 1997. Alcohol, GABAA-benzodiazepine receptor complex, and aggression. *Recent Dev Alcohol* 13:139–71.
- Miczek, K. A., E. Weerts, M. Haney, and J. Tidey. 1994. Neurobiological mechanisms controlling aggression: Preclinical developments for pharmacotherapeutic interventions. *Neurosci Biobehav Rev* 18:97–110.

- Mo, Q., S. F. Lu, S. Hu, and N. G. Simon. 2005. DHEA and DHEA sulfate differentially regulate neural androgen receptor and its transcriptional activity. *Brain Res Mol Brain Res* 126:165–72.
- Mohle, U., M. Heistermann, R. Palme, and J. K. Hodges. 2002. Characterization of urinary and fecal metabolites of testosterone and their measurement for assessing gonadal endocrine function in male nonhuman primates. *Gen Comp Endocrinol* 129:135–45.
- Moyer, K. E. 1971. *The Physiology of Hostility*. Chicago: Markham.
- Nelson, R. J. 1990. Photoperiodic responsiveness in house mice. *Physiol Behav* 48:403–8.
- Newman, A. E., S. A. MacDougall-Shackleton, Y. S. An, B. Kriengwatana, and K. K. Soma. 2010. Corticosterone and dehydroepiandrosterone have opposing effects on adult neuroplasticity in the avian song control system. *J Comp Neurol* 518:3662–78.
- Newman, A. E., D. S. Pradhan, and K. K. Soma. 2008. Dehydroepiandrosterone and corticosterone are regulated by season and acute stress in a wild songbird: Jugular versus brachial plasma. *Endocrinology* 149:2537–45.
- Newman, A. E., and K. K. Soma. 2009. Corticosterone and dehydroepiandrosterone in songbird plasma and brain: Effects of season and acute stress. *Eur J Neurosci* 29:1905–14.
- Nicolas, L. B., W. Pinoteau, S. Papot, S. Routierm, G. Guillaumetm, and S. Mortaud. 2001. Aggressive behavior induced by the steroid sulfatase inhibitor COUMATE and by DHEAS in CBA/H mice. *Brain Res* 922:216–22.
- Ostner, T., P. M. Kappeler, and M. Heistermann. 2002. Seasonal variation and social correlates of androgen excretion in male redfronted lemurs (*Eulemur fulvus rufus*). *Behav Ecol Sociobiol* 52:485–95.
- Ozsoy, S., and E. Esel. 2008. Hypothalamic-pituitary-adrenal axis activity, dehydroepiandrosterone sulphate and their relationships with aggression in early and late alcohol withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry* 32:340–7.
- Pajer, K., R. Tabbah, W. Gardner, R. T. Rubin, R. K. Czambel, and Y. Wang. 2006. Adrenal androgen and gonadal hormone levels in adolescent girls with conduct disorder. *Psychoneuroendocrinology* 31:1245–56.
- Paterson, A. T., and C. Vickers. 1981. Melatonin and the adrenal cortex: Relationship to territorial aggression in mice. *Physiol Behav* 27:983–7.
- Perché, F., J. Young, P. Robel, N. G. Simon, and M. Haug. 2000. Prenatal testosterone treatment potentiates the aggression-suppressive effect of the neurosteroid dehydroandrosterone in female mice. *Agg Behav* 27:130–8.
- Pieper, D. R., and C. A. Lobo. 2000. Characterization of serum dehydroepiandrosterone secretion in golden hamsters. *Proc Soc Exp Biol Med* 224:278–84.
- Pieper, D. R., C. A. Lobo, E. M. Lichten, and J. Malaczynski. 1999. Dehydroepiandrosterone and exercise in golden hamsters. *Physiol Behav* 67:607–10.
- Pinna, G., E. Costa, and A. Guidotti. 2005. Changes in brain testosterone and allopregnanolone biosynthesis elicit aggressive behavior. *Proc Natl Acad Sci U S A* 102:2135–40.
- Pinxten, R., E. De Ridder, J. Balthazart, L. Berghman, and M. Eens. 2000. The effect of castration on aggression in the nonbreeding season is age-dependent in male European starlings. *Behaviour* 137:647–61.
- Pradhan, D. S., A. E. Newman, D. W. Wacker, J. C. Wingfield, B. A. Schlinger, and K. K. Soma. 2010. Aggressive interactions rapidly increase androgen synthesis in the brain during the non-breeding season. *Horm Behav* 57:381–9.
- Rehman, K. S., and B. R. Carr. 2004. Sex differences in adrenal androgens. *Semin Reprod Med* 22:349–60.
- Sapolsky, R. M., J. H. Vogelman, N. Orentreich, and J. Altmann. 1993. Senescent decline in serum dehydroepiandrosterone sulfate concentrations in a population of wild baboons. *J Gerontol* 48:B196–200.
- Schlegel, M. L., J. F. Spetz, P. Robel, and M. Haug. 1985. Studies on the effects of dehydroepiandrosterone and its metabolites on attack by castrated mice on lactating intruders. *Physiol Behav* 34:867–70.
- Schlinger, B. A., D. S. Pradhan, and K. K. Soma. 2008. 3beta-HSD activates DHEA in the songbird brain. *Neurochem Int* 52:611–20.
- Scotti, M.-A., J. Belén, G. E. Jackson, and G. E. Demas. 2008. The role of testosterone and DHEA in the mediation of seasonal territorial aggression in male Siberian hamsters (*Phodopus sungorus*). *Physiol Behav* 95:633–40.
- Scotti, M. L., A. E. M. Newman, K. L. Schmidt, T. N. Bonu, K. K. Soma, and G. E. Demas. 2009. Aggressive encounters differentially affect circulating androgen levels in male Siberian hamsters (*Phodopus sungorus*). *Horm Behav* 56:376–81.
- Simon, N. G. 2003. Hormonal processes in the development and expression of aggressive behavior. In *Hormones, Brain and Behavior*, ed. D. W. Pfaff, A. P. Arnold, A. M. Etgen, S. E. Fahrbach, and R. T. Rubin, 339–2. New York: Academic Press.

- Simon, N. G., J. R. Kaplan, S. Hu, T. C. Register, and M. R. Adams. 2004. Increased aggressive behavior and decreased affiliative behavior in adult male monkeys after long-term consumption of diets rich in soy protein and isoflavones. *Horm Behav* 45:278–84.
- Soma, K. K. 2004. Steroid regulation of territorial behavior in wild songbirds. *Horm Behav* 46:135.
- Soma, K. K., N. A. Alday, and B. A. Schlinger. 2002. 3β -HSD and aromatase in songbird brain: DHEA metabolism, aggression, and song. *Soc Neurosci Abstracts*.
- Soma, K. K., N. A. Alday, M. Hau, and B. A. Schlinger. 2004. Dehydroepiandrosterone metabolism by 3β -hydroxysteroid dehydrogenase/ $\Delta 5$ - $\Delta 4$ isomerase in adult zebra finch brain: Sex difference and rapid effect of stress. *Endocrinology* 145:1668–77.
- Soma, K. K., R. K. Bindra, J. Gee, J. C. Wingfield, and B. A. Schlinger. 1999. Androgen-metabolizing enzymes show region-specific changes across the breeding season in the brain of a wild songbird. *J Neurobiol* 41:176–88.
- Soma, K. K., V. N. Hartman, J. C. Wingfield, and E. A. Brenowitz. 1999. Seasonal changes in androgen receptor immunoreactivity in the song nucleus HVC of a wild bird. *J Comp Neurol* 409:224–36.
- Soma, K. K., B. A. Schlinger, J. C. Wingfield, and C. J. Saldanha. 2003. Brain aromatase, 5α -reductase and 5β -reductase change seasonally in wild male song sparrows: Relationship to sexual and aggressive behaviors. *J Neurobiol* 56:209–21.
- Soma, K. K., M.-A. Scotti, A. Neuman, and G. E. Demas. 2008. Novel mechanisms of steroid regulation of aggression. *Front Neuroendocrinol* 29:476–89.
- Soma, K. K., K. A. Sullivan, A. D. Tramontin, C. J. Saldanha, B. A. Schlinger, and J. C. Wingfield. 2000. Acute and chronic effects of an aromatase inhibitor on territorial aggression in breeding and nonbreeding male song sparrows. *J Comp Physiol A* 186:759–69.
- Soma, K. K., K. Sullivan, and J. Wingfield. 1999. Combined aromatase inhibitor and antiandrogen treatment decreases territorial aggression in a wild songbird during the nonbreeding season. *Gen Comp Endocrinol* 115:442–53.
- Soma, K. K., A. D. Tramontin, and J. C. Wingfield. 2000. Oestrogen regulates male aggression in the nonbreeding season. *Proc Roy Soc London B* 267:1089–96.
- Soma, K. K., and J. C. Wingfield. 1999. Endocrinology of aggression in the nonbreeding season. In *22nd International Ornithological Congress*, ed. N. Adams, and R. Slotow, 1606–20. Durban, South Africa: University of Natal.
- Soma, K. K., and J. C. Wingfield. 2001. Dehydroepiandrosterone in songbird plasma: Seasonal regulation and relationship to territorial aggression. *Gen Comp Endocrinol* 123:144–55.
- Soma, K. K., A. M. Wissman, E. A. Brenowitz, and J. C. Wingfield. 2002. Dehydroepiandrosterone (DHEA) increases territorial song and the size of an associated brain region in a male songbird. *Horm Behav* 41:203–12.
- van Goozen, S. H. M., W. Matthys, P. T. Cohen-Kettenis, J. H. H. Thijssen, and H. van Engeland. 1998. Adrenal androgens and aggression in conduct disorder prepubertal boys and normal controls. *Biol Psychiat* 43:156–8.
- van Goozen, S. H., E. van den Ban, W. Matthys, P. T. Cohen-Kettenis, J. H. Thijssen, and H. van Engeland. 2000. Increased adrenal androgen functioning in children with oppositional defiant disorder: A comparison with psychiatric and normal controls. *J Am Acad Child Adolesc Psychiat* 39:1446–51.
- Wingfield, J. C. 1994. Control of territorial aggression in a changing environment. *Psychoneuroendocrinology* 19:709–21.
- Wingfield, J. C., and T. Hahn. 1994. Testosterone and territorial behaviour in sedentary and migratory sparrows. *Anim Behav* 47:77–89.
- Wingfield, J. C., and K. K. Soma. 2002. Spring and autumn territoriality in song sparrows: Same behavior, different mechanisms? *Integr Comp Biol* 42:11–20.
- Young, J., C. Corpéchet, F. Perché, B. Eycheche, M. Haug, E. E. Baulieu, and P. Robel. 1996. Neurosteroids in the mouse brain: Behavioral and pharmacological effects of a 3 beta-hydroxysteroid dehydrogenase inhibitor. *Steroids* 61:144–9.