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Review

Novel mechanisms for neuroendocrine regulation of aggression

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Abstract

In 1849, Berthold demonstrated that testicular secretions are necessary for aggressive behavior in roosters. Since then, research on the neuroendocrinology of aggression has been dominated by the paradigm that the brain receives gonadal hormones, primarily testosterone, which modulate relevant neural circuits. While this paradigm has been extremely useful, recent studies reveal important alternatives. For example, most vertebrate species are seasonal breeders, and many species show aggression outside of the breeding season, when gonads are regressed and circulating testosterone levels are typically low. Studies in birds and mammals suggest that an adrenal androgen precursor—dehydroepiandrosterone (DHEA)—may be important for the expression of aggression when gonadal testosterone synthesis is low. Circulating DHEA can be metabolized into active sex steroids within the brain. Another possibility is that the brain can autonomously synthesize sex steroids *de novo* from cholesterol, thereby uncoupling brain steroid levels from circulating steroid levels. These alternative neuroendocrine mechanisms to provide sex steroids to specific neural circuits may have evolved to avoid the "costs" of high circulating testosterone during particular seasons. Physiological indicators of season (e.g., melatonin) may allow animals to switch from one neuroendocrine mechanism to another across the year. Such mechanisms may be important for the control of aggression in many vertebrate species, including humans.

Keywords: Allopregnanolone; Brain; DHEA; Estrogen; Hamster; Melatonin; Neurosteroid; Songbird; Stress; Testosterone - KT

1. Introduction

One of the more important and intensely studied social behaviors exhibited by animals is aggression [19,20,75,109]. Aggression is a complex suite of behaviors that is displayed by virtually all organisms and serves a wide range of adaptive functions. In general, aggressive behavior is exhibited when the interests of two or more individuals are in conflict, typically involving critical limited resources (e.g., food, territories, and mates). Often, a submissive posture displayed by one animal avoids the need for physical aggression. Additionally, animals may engage in threat displays or ritualized combat, in which dominance is established without physical harm. If such displays are ineffective, however, physical aggression can result. In some cases, animals may fight simply to ascertain dominance status [64].

1.1. Definition

Aggression is a notoriously nebulous concept that has been defined and categorized in a multitude of ways. Aggression has traditionally been defined as overt behavior with the intention of inflicting physical damage upon another individual or "goal entity" [72]. A commonly employed classification scheme was described by Moyer, who divided aggression into specific subtypes based on differences in social conditions in which the behavior was observed [72]. These subtypes of aggression include:

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predatory aggression, inter-male aggression, fear-induced aggression, irritable aggression, maternal aggression, territorial aggression, and instrumental aggression. The primary tenet of Moyer's classification system is that, although these different forms of aggression share behavioral features, the environmental factors eliciting these behaviors and their biological substrates differ markedly. More recently, a simplified classification scheme has been suggested [9] in which aggression is divided into offensive and defensive aggression. Behaviors used in attack are referred to as offensive, whereas defensive aggression does not involve an active approach to the opponent. This latter classification system provides a useful framework with which to identify and describe aggressive behavior across many species.

1.2. Methodological considerations

Aggressive behavior has been studied under a wide range of experimental conditions. It is often difficult, therefore, to compare results across studies. A relatively large number of experimental models have been developed to test aggression (e.g., electric shock-induced aggression and conditioned aggression). One of the prevalent models for assessing offensive aggression has been the resident-intruder model. This test is intended to simulate territorial aggression and involves introducing an "intruder" into the territory of an experimental animal, and the amount and duration of aggressive behavior (e.g., chases, attacks, and bites) are recorded in a timed test. The neutral arena model is a test in which two animals are placed in a novel "neutral" environment, and the amount of aggression directed towards each animal is recorded. The neutral arena model allows assessment of the development of a dominance relationship.

It is important to consider other issues, such as the time of behavioral testing (e.g., day vs. night). Rodents are typically nocturnal and display more aggressive behavior during the night. In contrast, many birds and primates are diurnal, and behavioral testing is performed during the day. Moreover, given the robust effects of melatonin on aggression (see below), time-of-day and day length (photoperiod) effects might be substantial but greatly underappreciated. In many publications, the day length for laboratory-housed animals is either not reported or invariant (typically 12 h light: 12 h darkness). Endocrine regulation of aggression may differ under other day lengths.

1.3. Comparative studies

A majority of the research on the physiology of aggression has used laboratory rodent models, particularly inbred strains of rats and mice [6,13,14,26,132]. These models have provided, and continue to provide, important insights into the mechanisms of aggression. However, the mechanisms mediating aggression can differ across taxa [144], and comparative studies shed light on general principles and the evolution of endocrine mechanisms. Here, we will review findings from various taxa, with an emphasis on birds and rodents, to draw attention to common themes as well as noteworthy differences in the neuroendocrine regulation of aggression.

2. A view from Berthold: direct effects of gonadal testosterone

The study of hormones and aggression, and of hormones in general, can be traced back to the work of Arnold Berthold in 1849 [95]. Berthold removed the testes of young male chickens and found a decrease in some secondary sex characteristics and male-typical behaviors. Specifically, castrated males did not crow, did not try to mate with females, and did not fight aggressively with other males. Importantly, transplantation of a testis into castrated animals restored male sexual and aggressive behaviors. When a testis was transplanted into castrated animals at a new site (among the intestines), these animals showed normal male aggressive behavior. Upon dissection, Berthold found that the transplanted testes had established many new vascular connections. From these results, Berthold concluded that the testes release a substance into the bloodstream that affects the entire organism, including the nervous system.

Thus, from its very beginning, the study of hormones and aggression was focused on blood-borne gonadal secretions, primarily testosterone, and early researchers worked under the premise that circulating testosterone binds directly to neural androgen receptors to modulate relevant neural circuits (Fig. 2A). This conceptual framework has greatly influenced subsequent studies up to the present day. It is clear that gonadal testosterone is important for the expression of male aggressive behavior. However, an exclusive focus on gonadal testosterone is simplistic and potentially misleading. More recent work suggests that the brain does not simply receive testosterone from the gonads, but can metabolize circulating testosterone, metabolize circulating testosterone precursors, or even synthesize testosterone autonomously (Fig. 2B–D). Other recent studies indicate that additional hormones, both steroidal and non-steroidal, regulate aggression, either independently of or in conjunction with testosterone. Such mechanisms might be particularly important in non-breeding males, developing animals, and/or females.

3. Neural aromatization of gonadal testosterone

3.1. Metabolism of testosterone in the brain

Approximately 30 years ago, it became clear that many effects of circulating testosterone on the nervous system are mediated by local metabolism within the brain (Fig. 2B) [74]. For example, testosterone can be metabolized to 17β-estradiol by the enzyme P450 aromatase or to 5α-dihydrotestosterone by 5α-reductase [2,34,99]. In a variety of vertebrates, aromatase is highly expressed in the preoptic

area, hypothalamus and amygdala, all regions involved in the regulation of aggressive behavior (see recent reviews [3,33,126]).

3.2. Brain aromatase and avian aggression

Studies in breeding male Japanese quail (*Coturnix japonica*) illustrate the key role of brain aromatase in the expression of aggressive behavior [101]. To assess aggressive behavior, males were allowed to view a stimulus bird for 2 min [100]. Males were killed either 90 s or 24 h after behavioral tests to measure *in vitro* androgen metabolism in several brain regions. Individual differences in aggressive behavior were positively correlated with aromatase activity in the hypothalamus [100]. However, aggression was not correlated with brain 5α- or 5β-reductase activities or circulating testosterone or estradiol levels [100]. Furthermore, treatment of male quail with an aromatase inhibitor or estrogen receptor antagonist decreases aggression, but a 5α-reductase inhibitor or androgen receptor antagonist has no effect [102]. Similar results have been obtained in studies of songbirds [108,138].

3.3. Brain aromatase and mammalian aggression

Much of the recent evidence implicating estrogens in the regulation of male rodent aggression has been obtained using genetic knockout techniques in inbred mice. For example, male aromatase knockout (ARKO) mice that lack a functional aromatase enzyme display marked reductions in aggression [65,122]. Long-term treatment with estradiol partially restores aggressive behavior in male ARKO mice [122]. Note that plasma estradiol levels in male wild-type mice are extremely low, suggesting that estradiol production in the brain is directly related to aggression. These results suggest that the effects of androgens on inter-male aggression are due, at least in part, to neural conversion of circulating testosterone to estradiol and the subsequent action of estradiol on estrogen receptors within the brain.

In rodents, at least two isoforms of intracellular estrogen receptors have been identified (ERα and ERβ), and these receptors can exert different effects on aggression [78]. For example, studies using estrogen receptor KO (ERKO) mice that lack functional ERα demonstrate that inter-male aggression is markedly reduced and male-typical offensive attacks are rarely displayed by male ERKO mice [81]. Moreover, both castrated wild-type and ERKO mice display low levels of aggression; testosterone replacement increases aggression in castrated wild-type males but not in castrated ERKO males [82]. In contrast to ERKO mice, male mice that lack functional ERβ (BERKO) display normal or slightly elevated levels of aggressive behavior [80]. These results suggest that ERα facilitates male–male aggression, whereas ERβ may provide a "brake" on aggression. Consistent with this hypothesis, individual variation in ERα immunoreactivity in the lateral septum, ventral bed nucleus of the stria terminalis, and anterior hypothalamus of inbred CD-1 mice is positively correlated with aggressive behavior [125].

In contrast to inbred mice, outbred mice in the genus *Peromyscus* show a different pattern. In male California mice (*Peromyscus californicus*) under long-days (14 h light: 10 h dark), aromatase activity in the bed nucleus of the stria terminalis is negatively correlated with aggression [124]. Moreover, an aromatase inhibitor increases aggressive behavior [124]. A more complex picture emerges from recent studies of male beach mice (*Peromyscus polionotus*) [127]. In this species, under long-days (16 h light: 8 h dark), estradiol reduces aggression, possibly via genomic mechanisms. In contrast, under short-days (8 h light: 16 h dark), estradiol rapidly (within 15 min) increases aggression, likely via non-genomic mechanisms [127]. Thus, a single environmental variable (photoperiod) dramatically reverses the behavioral effect of estradiol and also its mechanism of action. Because nearly all studies of inbred and knockout mice use an invariant photoperiod of intermediate length (12 h light: 12 h dark), such hormone–photoperiod interactions are probably greatly underappreciated. Photoperiod may reverse the behavioral effects of estradiol treatment by changing the ratio of ERα and ERβ in select brain regions [129].

4. Adrenal steroids and aggression

The adrenal gland is a complex organ composed of both steroidogenic and chromaffin tissue. In most mammals, the steroidogenic tissue forms a cortical layer (adrenal cortex) that surrounds an inner medullary component composed of chromaffin tissue (adrenal medulla) [39]. In other vertebrates, including birds and reptiles, the two tissues are intermingled [39]. The adrenocortical tissue synthesizes several classes of steroids that have been implicated in the control of aggressive behavior: glucocorticoids (e.g., corticosterone), androgens (e.g., dehydroepiandrosterone or DHEA), and progestins (e.g., progesterone). These steroids may act directly on the brain or act indirectly after local conversion to other steroids. The chromaffin tissue produces catecholamines (e.g., epinephrine and norepinephrine), which also affect aggressive behavior [43], but here we will focus on the adrenal glucocorticoids and DHEA.

4.1. Glucocorticoids

Glucocorticoids are involved in coordinating behavioral and physiological responses to acute and chronic stressors and play an important role in social aggression [43]. The effects of glucocorticoids on aggressive behavior reported by experimenters can be contradictory and seem dependent on the species, length of glucocorticoid treatment, and type of behavioral test.

In birds, field studies of wild song sparrows (*Melospiza melodia*) indicate that chronic exposure (several days) to high corticosterone levels suppresses aggression [146]. In

another songbird, the great tit (*Parus major*), short-term simulated territorial intrusions (30–60 min) that elicit vigorous aggressive responses also increase plasma corticosterone levels, but not testosterone levels [133]. It is unclear if these rapid increases in plasma corticosterone facilitate or inhibit aggression in the short-term.

Glucocorticoids play an important role in regulating aggressive behavior in adult rodents. It is particularly important to note that the duration of glucocorticoid (or stressor) exposure seems to be critical in determining their effects on aggression, and that the effects of stress and glucocorticoids differ. For example, in adult rats, acute restraint stress reduces aggressive behavior, whereas chronic restraint stress increases aggressive behavior [151]. In contrast, acute injections of corticosterone promote aggressive behavior [41], and acute reduction of corticosterone (via an injection of metyrapone) decreases aggression in rats. Chronic reduction of corticosterone (via adrenalectomy with low glucocorticoid replacement), can produce abnormally aggressive behavior [42] (but see [23,61,71,86]). Note that adrenalectomy causes high ACTH levels, which may affect behavior via extra-adrenal sites [11,61,71].

In addition, glucocorticoids exert powerful effects on the development of aggression. For example, juvenile Syrian hamsters that were exposed to repeated social defeat by an adult, and thus daily increases in plasma cortisol, showed an accelerated transition from play fighting to adult-like aggression [148]. Similar findings result from exposure to the synthetic glucocorticoid dexamethasone early in puberty [150]. The cortisol regulation of this shift from juvenile to adult-like agonistic behavior seems to be via type II corticosteroid receptors/glucocorticoid receptors [149]. A glucocorticoid receptor antagonist prevents cortisol treatment from speeding the transition from play fighting to adult aggression [149]. Interestingly, studies of children with aggressive antisocial behavior have found that individuals with conduct disorder have lower resting levels of cortisol than controls [107,134] (but see [104]). It has also been suggested that glucocorticoid deficiencies are involved in psychopathological violence [51]. Collectively, these results suggest an important role for glucocorticoids in the development of aggressive behavior.

Glucocorticoids play an integral role in the development of social hierarchies. Baseline levels of glucocorticoids can predict dominance status and aggressive behavior. Adult mice with low baseline levels of corticosterone are more likely to become dominant than mice with high baseline corticosterone levels [31]. Similarly, mice with short attack latencies have lower baseline levels of corticosterone than mice with long attack latencies [57,84]. Furthermore, following an aggressive encounter, defeated individuals often have elevated glucocorticoid levels [10,93], which can affect future aggressive interactions [53]. Subordinate individuals in well-established dominance hierarchies often have chronically elevated baseline levels of glucocorticoids [97].

Interestingly, glucocorticoid regulation of aggression may be coordinated by other signals, such as melatonin from the pineal gland. In adult mice, Syrian hamsters, and Siberian hamsters, melatonin injections increase aggression [55]; however, this effect of melatonin is abolished by adrenalectomy [23,86]. In contrast, adrenal demedullation, which reduces adrenal catecholamines but not adrenocortical steroids, has no effect on melatonin-induced aggression [23]. Together, these studies suggest that adrenocortical hormones mediate the effects of melatonin on aggression, but do not discriminate between adrenal glucocorticoids and adrenal DHEA.

4.2. Dehydroepiandrosterone

DHEA and its sulfated ester (DHEAS) are produced in large amounts by the adrenal cortex in humans and hamsters, but not in laboratory rats and mice [17,89,137]. In humans, adrenal DHEAS is the most abundant circulating steroid hormone [58,120,141]. DHEA is considered an inert sex steroid precursor and binds with low affinity to intracellular androgen receptors, estrogen receptors, progesterone receptors, mineralocorticoid receptors, and glucocorticoid receptors [70,141]. Also, there is little evidence for a classical intracellular steroid receptor that is specific for DHEA [1,141]. Although DHEA itself may be largely inert, it can be rapidly metabolized within target tissues into potent androgens and estrogens, such as androstenedione, testosterone, estrone, and estradiol (Fig. 1). The metabolism of DHEA occurs in tissues, such as the brain, that contain the appropriate steroidogenic enzymes (Fig. 2C) [5,40,60].

Most avian species show seasonal breeding, with distinct breeding and non-breeding seasons [37]. Recent investigations of avian species that exhibit year-round territorial aggression have found that non-breeding aggression can be independent from circulating T levels. The males and females of many species of birds exhibit high levels of

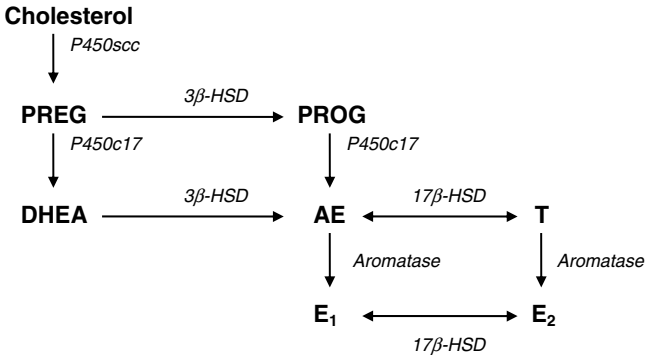

Fig. 1. A simplified diagram of sex steroid synthesis. *Steroids*: PREG = pregnenolone; PROG = progesterone; DHEA = dehydroepiandrosterone; AE = androstenedione; T = testosterone; E_1 = estrone; E_2 = 17β-estradiol. *Enzymes*: *P450scc* = Cytochrome P450 side chain cleavage; *P450c17* = Cytochrome P450 17α-hydroxylase/C17,20 lyase; *3β-HSD* = 3β-hydroxysteroid dehydrogenase/isomerase; *17β-HSD* = 17β-hydroxysteroid dehydrogenase; *Aromatase* = Cytochrome P450 aromatase.

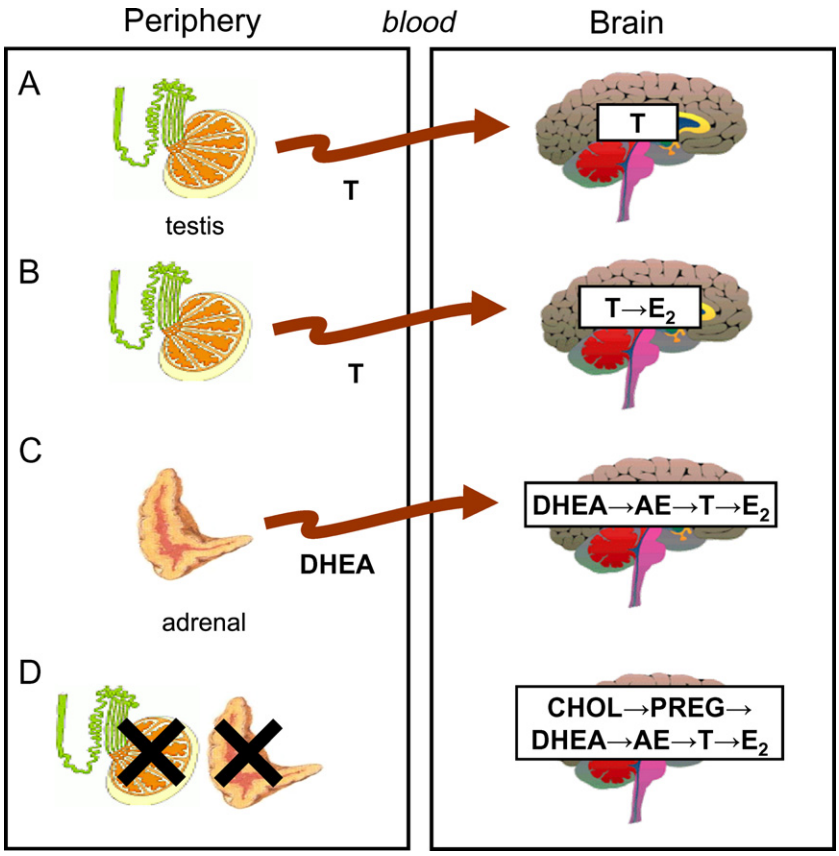

Fig. 2. Pathways by which sex steroids could affect aggression. (A) Gonadal testosterone (T) acts directly on the brain. (B) Gonadal T is converted locally to estradiol (E_2). (C) Adrenal dehydroepiandrosterone (DHEA) is converted locally to T and/or E_2. (D) T and E_2 are produced locally *de novo* from cholesterol (neurosteroids). Modified from Demas et al. [20].

territorial aggression throughout the year [117]. Often the territoriality expressed during the reproductive and non-reproductive seasons is quantitatively and qualitatively similar [118,147]. 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 [110,114,147].

Several studies have focused on non-breeding aggression in song sparrows (*Melospiza melodia morphna*) [113,114,118]. Male song sparrows are highly territorial during the spring (breeding season) and autumn/winter (non-breeding season) [143]. Note that the testes are completely regressed and plasma testosterone, androstenedione, estrone, and estradiol levels are basal during the non-breeding season [112,118]. Furthermore, castration of non-breeding sparrows has no effect on territorial aggression in autumn [142]. These data raised the hypothesis that aggression during the non-breeding season is not regulated by sex steroids.

To test this hypothesis, male song sparrows were treated with the aromatase inhibitor fadrozole in the non-breeding season [116]. Fadrozole strongly decreases aggressive behavior in non-breeding song sparrows [116]. Moreover, the effects of fadrozole are rescued by estradiol replacement [116]. These data suggest that sex steroids, in particular estrogens, are necessary for the expression of aggressive behavior in the non-breeding season, even though plasma sex steroids are non-detectable [114]. Similar results were obtained in two other field experiments [113,114].

The source of androgen substrate for brain aromatase in the non-breeding season could be circulating DHEA [118]. While DHEA cannot be directly aromatized, DHEA can be metabolized by 3β-hydroxysteroid dehydrogenase/isomerase (3β-HSD) to androstenedione, an aromatizable androgen (Fig. 1). In contrast to testosterone and estradiol, DHEA is detectable and elevated in the circulation of non-breeding birds (Fig. 3) [36,118]. DHEA concentrations in the adrenals and regressed testes of non-breeding birds are even higher than plasma levels, suggesting that both organs could secrete DHEA into the general circulation [118].

Treatment of non-breeding 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 song (Fig. 4) [119]. This is one of the largest reported effects of DHEA on adult neuroplasticity and is similar to the effects of testosterone and estradiol on song behavior and neuroanatomy [115]. However, DHEA treatment does not affect other territorial behaviors or, importantly, peripheral secondary sexual characteristics that are androgen-sensitive [119]. Other studies demonstrate that DHEA, unlike testosterone, does not suppress immune function in song sparrows [83].

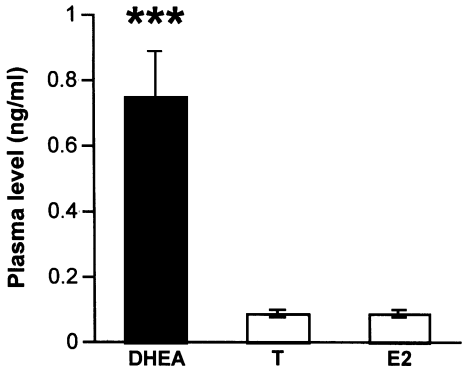

Fig. 3. Levels of DHEA, T, and E_2 (ng/ml) in plasma from wild male song sparrows in the non-breeding season. Redrawn from data in Soma and Wingfield [118]. $^{***}p < 0.001$, compared to plasma T and E2 levels.

Further investigations examined the metabolism of DHEA to active sex steroids within the songbird brain [111]. In one study, brain homogenates were incubated with ^{3}H-DHEA *in vitro*. The biochemical assay measures the conversion of ^{3}H-DHEA to ^{3}H-androstenedione by the enzyme 3β-HSD (Fig. 5). ^{3}H-androstenedione can be metabolized subsequently to ^{3}H-testosterone or ^{3}H-estrogens [111]. In captive adult zebra finches (*Taeniopygia guttata*), brain homogenates clearly metabolize ^{3}H-DHEA to ^{3}H-androstenedione, which is in turn aromatized to ^{3}H-estrone. Importantly, trilostane, a specific 3β-HSD inhibitor, blocks the production of ^{3}H-androstenedione, and fadrozole, a specific aromatase inhibitor, reduces the production of ^{3}H-estrone (Fig. 5B and C). In non-breeding song sparrows, the brain can also convert DHEA to androgens and estrogens (K. Soma, D. Wacker, J. Wingfield, B. Schlinger, unpublished results). Taken together, these data support the hypothesis that non-breeding song sparrows combine adrenal and/or gonadal DHEA synthesis with neural DHEA metabolism to maintain territorial behavior when gonadal testosterone secretion is low. Moreover, it remains possible that the brain itself is a significant site of DHEA synthesis in non-breeding song sparrows (see below).

Other field studies have examined the spotted antbird (*Hylophylax n. naevioides*) [44,45]. The spotted antbird is a tropical species that exhibits year-round territorial aggression [44]. Despite the presence of year-round territorial aggression, these birds generally have low or non-detectable levels of plasma testosterone, even during the breeding season [45]. Nonetheless, experiments have shown that testosterone or its estrogenic metabolites do play a role in male territoriality [45]. A recent study examined male and female antbirds during the non-breeding season [44]. The results indicate that both sexes exhibit robust aggressive behavior during the non-breeding season, and in both

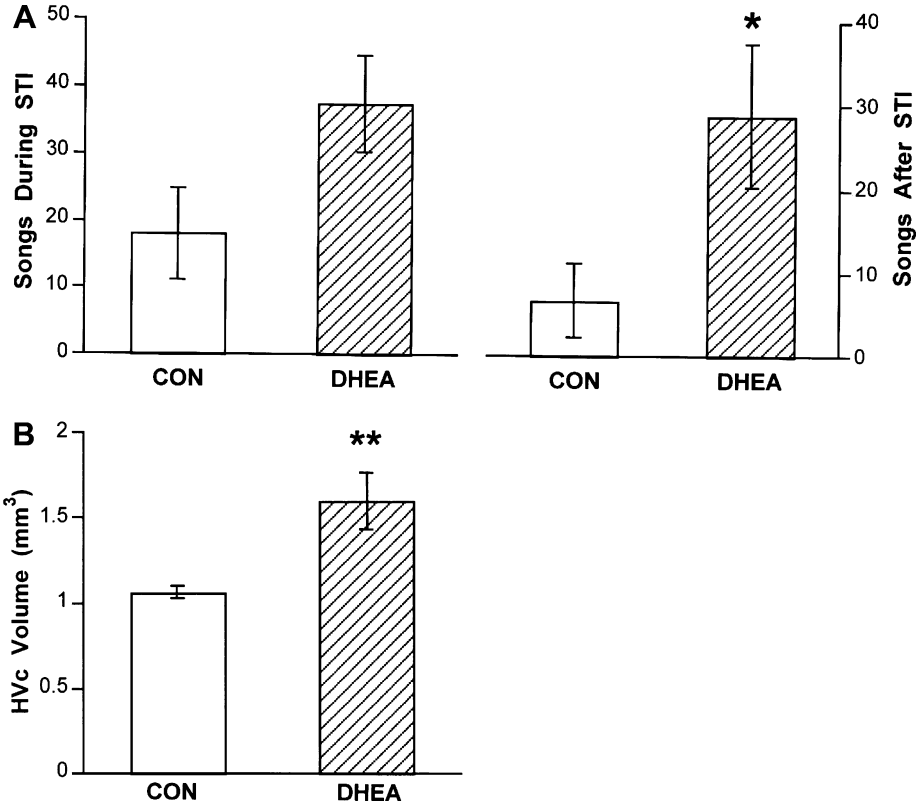

Fig. 4. Effects of DHEA treatment on wild male song sparrows in the non-breeding season. (A) Relative to controls (CON), DHEA treatment increases the number of aggressive songs given in response to a simulated territorial intrusion (STI), particularly the persistence of singing after termination of the STI. $^{*}p < 0.05$. (B) Relative to controls (CON), DHEA treatment also increases the volume of HVC, a telencephalic brain region involved in song production. From Soma et al. [119]. $^{**}p < 0.01$.

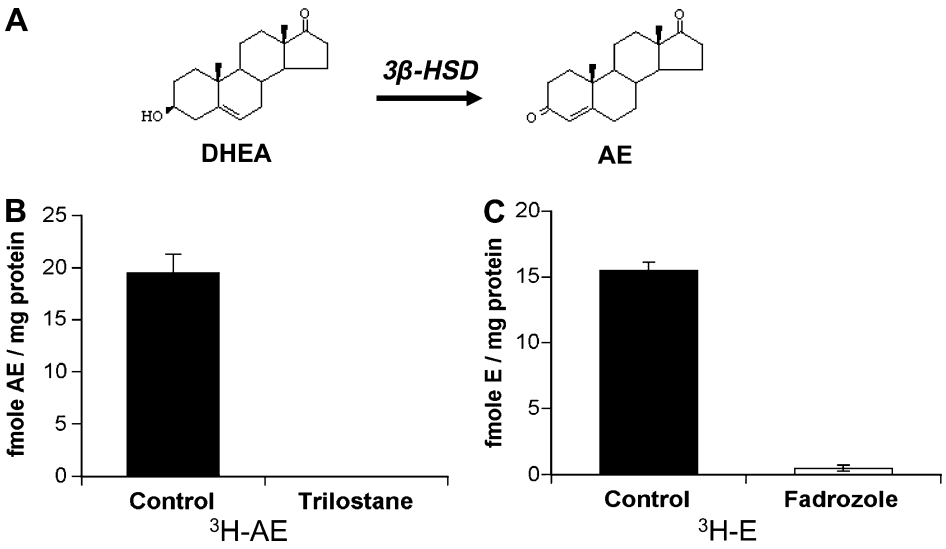

Fig. 5. (A) 3β-Hydroxysteroid dehydrogenase/isomerase (3β-HSD) catalyzes the oxidation and isomerization of DHEA into androstenedione (AE). Conversion of ^{3}H-DHEA into ^{3}H-AE (B) and then ^{3}H-estrogens (C) by homogenates of the adult zebra finch brain. Trilostane, a specific 3β-HSD inhibitor, abolishes ^{3}H-AE production (B), and fadrozole, a specific aromatase inhibitor, decreases ^{3}H-estrogen production by 97%. From Soma et al. [111].

sexes, plasma DHEA levels are detectable and higher than plasma testosterone and estradiol levels [44]. Additionally, plasma DHEA levels in males are positively correlated with aggressive vocalizations. Plasma DHEA, therefore, might serve as a precursor for brain synthesis of sex steroids throughout the year in these birds, in both males and females [44].

Non-gonadal steroids may also be important for aggression in captive rodents under laboratory conditions. For example, castration during adulthood has no effect on the aggressive behavior of male prairie voles (*Microtus ochrogaster*), California mice, or CD-1 mice, suggesting that gonadal steroids do not activate aggressive behavior in these species [22,125,128]. Another example is the dusky-footed wood rat (*Neotoma fuscipes*). Wood rats express high aggression during the breeding season; however, castration does not reduce aggression in the breeding or non-breeding seasons [16].

Other examples in which territorial aggression does not appear to be mediated by gonadal steroids are found in several species of hamsters [54,55]. In Syrian hamsters (*Mesocrecitus auratus*) and Siberian hamsters (*Phodopus sungorus*), males are in breeding condition and have high plasma testosterone levels during long-day photoperiods. However, in both male and female hamsters, territorial aggression is higher during short-day photoperiods, when the gonads are regressed (Fig. 6) [32,35,54]. In both species, melatonin treatment that mimics short-day melatonin patterns causes an increase in aggression (Fig. 7) [23,32,55]. Note that melatonin is a pineal hormone that is secreted at night, with longer durations of secretion under short-day conditions.

In addition, in both hamster species, gonadal hormones are not clearly involved in the regulation of aggression. For example, gonadectomy has no effect on aggression in female Syrian hamsters or male Siberian hamsters housed in long-days [32,54]. Additionally, testosterone treatment of male Siberian hamsters housed in short-days reduces aggression [54]. Thus, non-reproductive, gonadally regressed males with basal levels of circulating testosterone

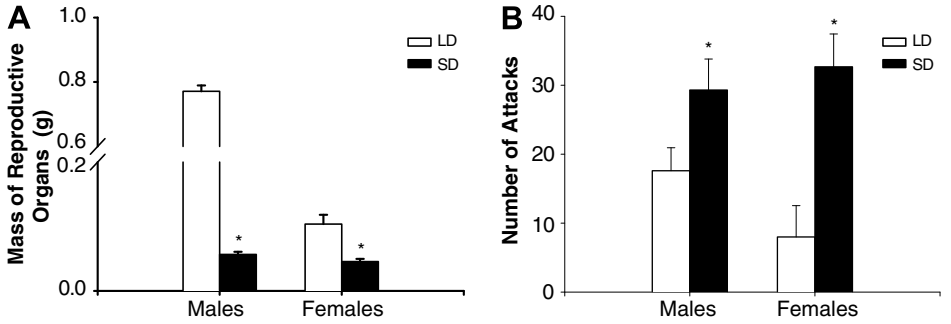

Fig. 6. (A) Both male and female Siberian hamsters housed in short "winter-like" days (Short-Day, SD) display a significant decrease in reproductive (i.e., gonadal) masses compared with animals housed in long "summer-like" days (Long-Day, LD). (B) Male and female hamsters display significantly elevated aggression in SD condition compared with LD condition. Adapted from Scotti et al. [106] and unpublished results.

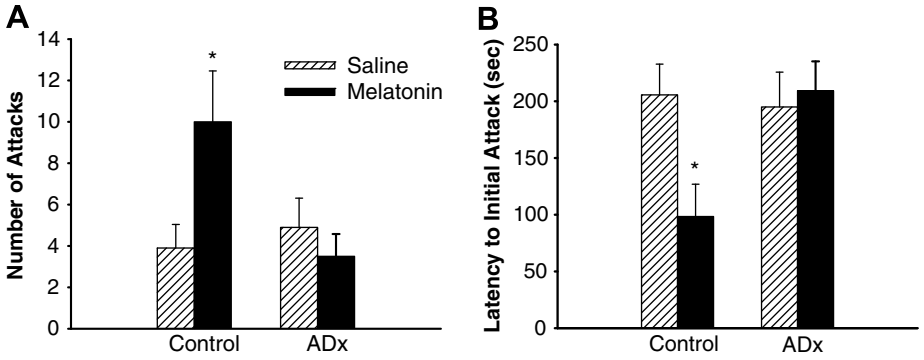

Fig. 7. (A) Treatment with exogenous melatonin significantly increases the number of attacks in male hamsters; this effect, however, is blocked by bilateral surgical adrenalectomy (ADx), relative to sham surgeries (Control). (B) Melatonin treatment decreases the latency to initial attack in control but not ADx hamsters. Adapted from Demas et al. [23].

are more aggressive than reproductive males with high levels of circulating testosterone. Furthermore, male Siberian hamsters that are photoperiodic non-responders (i.e., do not respond to short-days with gonadal regression) nonetheless show increases in aggression under short-days [140]. Short-day subjects, regardless of gonadal responsiveness to short photoperiod, all had reduced neuronal nitric oxide synthase, compared to long-day subjects [140]. Neuronal nitric oxide synthase is known to regulate aggressive behavior [21,76]. Taken together, these results suggest that photoperiodic regulation of aggression may be independent of, or inversely related to, circulating concentrations of gonadal sex steroids in these hamsters [54]. Adrenocortical steroids such as cortisol and DHEA are being investigated as potential mediators of seasonal aggression in these hamsters [105].

Interestingly, Syrian hamsters have very high circulating levels of DHEA and DHEAS, with serum levels of DHEAS up to 100 times higher than those in laboratory rats and mice [89]. In Syrian hamsters, serum DHEA and DHEAS levels are reduced by adrenalectomy, suggesting that a large percentage of circulating DHEA(S) is secreted by the adrenal glands, as in humans [89]. Gonadectomy does not reduce serum DHEA levels in male or female Syrian hamsters, and DHEAS concentrations are actually elevated in gonadectomized subjects [89].

It is possible that melatonin stimulates DHEA(S) secretion by the adrenal cortex in hamsters and other rodents. In mice, *in vitro* studies have demonstrated that administration of melatonin to isolated adrenal glands increases the secretion of DHEA into the medium [48]. Similar studies using hamster adrenals suggest that cortisol secretion does not increase after melatonin treatment [62]. The effects of melatonin on DHEA secretion by hamster adrenals, however, have not been reported and are the focus of ongoing studies. Collectively, these data raise the novel hypothesis that long melatonin pulses during the long nights of winter lead to greater adrenal secretion of DHEA, which is in turn metabolized to estrogens within the brain to facilitate the expression of non-reproductive aggression.

DHEA has been implicated in the regulation of aggression in rodents [121]. For example, in male mice that have been castrated to increase their aggression towards lactating females, DHEA treatment reduces this specific form of aggression [46,47,98,152]. Because mice treated with DHEA showed elevated levels of testosterone in brain tissue, a similar experiment was performed using a synthetic DHEA analog (DHEA-CH3) that cannot be converted to testosterone. DHEA-CH3 also reduced aggression towards lactating female mice [46]. Similarly, ovariectomized female mice show robust aggression towards intact, ovariectomized, or lactating females. This aggression was reduced by treatment with DHEA [4,12,87]. More recent investigations suggest that increases in male–male aggression can be induced by injections of DHEAS [77]. Moreover, subjects treated with COUMATE (4-methylcoumarin-7-*O*-sulfamate), which inhibits the steroid sulfatase enzyme that converts DHEAS to DHEA, are more aggressive than subjects that received DHEAS alone. Further, individuals that received COUMATE require less DHEAS to increase aggression [77]. These results suggest that steroid sulfatase in the brain modulates the effects of DHEAS on aggression [77].

DHEAS secretion by the zona reticularis of the adrenal cortex is pronounced in humans and some other primates [60]. Studies of the hormonal regulation of aggressive behavior in primates have also found that aggression may not be dependent on gonadal hormones. For example, seasonally breeding tamarins (*Saguinus fuscicollis*) show no evidence for seasonality in aggressive behavior, and gonadectomy has no effect on male or female aggression [24,27]. The role of DHEA in non-human primate aggression has received extremely little attention and is an important topic for future studies.

In humans, several studies suggest a role for DHEA in aggression. Prior to puberty, plasma testosterone levels are relatively low, but circulating DHEAS levels rise during adrenarche (~7 years of age). In prepubertal children with aggressive conduct disorder, aggression is correlated with plasma DHEAS, but not plasma testosterone [15,25,85,135,136]. Other work has focused on children with congenital adrenal hyperplasia (CAH), who have elevated plasma DHEAS levels. Adolescent CAH females are more aggressive than controls [8]. In one CAH patient,

treatment with a P450c17 inhibitor reduced circulating DHEAS levels and ameliorated aggressive behavior [49]. These results suggest an important link between DHEAS and human aggressive behavior.

5. Neurosteroids and aggression

Neurosteroids can be strictly defined as steroids that are synthesized *de novo* from cholesterol in the brain (Fig. 2D). Using this strict definition, estradiol produced in the brain from circulating testosterone would not be considered a neurosteroid, nor would brain estradiol indirectly produced from circulating DHEA. Neurosteroids may act via genomic and non-genomic mechanisms on neural circuits to regulate aggressive behavior [109].

Groundbreaking studies by Baulieu and colleagues first suggested that the brain can synthesize DHEA and other steroids from cholesterol [18]. Despite great advances in understanding the biochemistry and molecular biology of neurosteroid synthesis, much remains unknown regarding the physiological and behavioral functions of neurosteroids and the selective forces that favor the evolution of local steroid signaling.

Recent avian studies suggest that progestins, androgens, and estrogens can be synthesized entirely within the brain, during adulthood and development. In adult Japanese quail, the brain expresses P450scc, P450c17, 3β-HSD, and aromatase [130,131]. These studies integrate measurements of enzyme mRNA, protein, and activity with measurements of brain and plasma steroid levels. Other studies have focused on developing birds, particularly the zebra finch. In this species, there are large male-biased sex differences in song behavior and the telencephalic song control system [79]. Estrogen treatment of female zebra finches during development masculinizes song behavior and the song system [38]. Recent *in vitro* data suggest that neurosteroids, but perhaps not gonadal steroids, are important for the development in males of a projection from HVC to the robust nucleus of the arcopallium (RA) in the song circuit [52,103]. *In vivo* studies of developing zebra finches demonstrate neural expression of mRNAs for several steroidogenic enzymes, although no sex differences were detected in brain [63]. Taken together, these studies suggest that adult and developing birds are capable of producing neurosteroids, but importantly, no studies have yet directly linked neurosteroids with aggression in birds, and this is an aim of ongoing studies.

As with the research in birds described above, brain-derived steroids (i.e., neurosteroids) have been identified in the mammalian brain, although their role in mediating aggression has yet to be fully determined. Two specific neurosteroids that have been studied in the context of aggression are DHEA and allopregnanolone. The effects of DHEA on aggression have led to studies on the physiological mechanisms underlying this behavioral response, with much of the work focused on interaction of DHEA with GABA neurotransmission (reviewed in [109]). DHEA alters brain levels of pregnenolone sulfate (PREGS), another neurosteroid that inhibits GABA action via the $GABA_A$ receptor. Specifically, DHEA-induced changes in GABA activity appear responsible for the effects of DHEA on aggression. These results are consistent with previous findings demonstrating an inhibitory effect of GABA on aggression [67]. Although the precise mechanisms of action are still unknown, DHEA can modulate the actions of both GABA and glutamatergic NMDA receptors [59,66], and both of these neurotransmitter systems have been implicated in the control of aggression in the mammalian brain. Alternatively, DHEA may act via local conversion to sex steroids, which act on specific brain areas to regulate aggression, as has been described in birds [111]. Recent evidence suggests that DHEA and sex steroids can be produced locally within the mammalian brain. For example, expression of mRNA for key steroidogenic enzymes, including P450scc, P450c17, P450 aromatase, and 3β-HSD, has been identified in rat hippocampus [50,56,73]. Furthermore, hippocampal estradiol concentrations are significantly greater than those found in plasma, suggesting, at least in part, a neural origin for 17β-estradiol or 17α-estradiol [50,123]. As is the case for other neurosteroids, the role of neurally derived estrogens in mediating mammalian aggression remains to be explored.

Allopregnanolone is another neurosteroid that has been shown to play a role in regulating mammalian aggressive behavior [30,68,88,91]. Allopregnanolone is a metabolite of progesterone that acts via a non-genomic mechanism: positive allosteric modulation of $GABA_A$ receptors [7,94]. Studies have implicated the GABAergic system in the mediation of aggressive behavior [67,69]. For example, socially isolated mice display both reduced levels of allopregnanolone in various brain regions and increased aggressiveness, compared to group-housed individuals [91]. Treatment of socially isolated male and female mice with fluoxetine (i.e., Prozac), which affects allopregnanolone biosynthesis, increases brain allopregnanolone levels, and reduces aggressive behavior [90,92]. Similarly, treatment of socially isolated female mice with testosterone propionate decreases brain allopregnanolone and increases aggressive behavior [90]. On the other hand, in separate studies, acute low or moderate doses of allopregnanolone can increase the motivation to engage in aggressive behavior [28,29], so more work remains to be done. Collectively, these data suggest that the neurosteroid allopregnanolone may play an important role in the control of aggressive behavior.

6. Conclusions

Although much research has traditionally focused on the role of testosterone in the regulation of aggression, recent findings in a variety of species and in different experimental paradigms ranging from field to laboratory studies have proven this idea to be too simplistic. It is becoming increasingly clear that steroids other than testosterone

(e.g., DHEA, allopregnanolone) and also non-steroidal hormones (e.g., melatonin) play important roles in the regulation of aggressive behavior, either by acting independently of or in conjunction with testosterone. Moreover, there is clear evidence that steroid hormones, in addition to their traditional role as transcription factors, can exert rapid, non-genomic effects. These latter effects are likely mediated, at least in part, via actions on plasma membrane-bound receptors [139] or via allosteric modulation of neurotransmitter systems [92]. A more complete understanding of these non-genomic mechanisms of steroid action may help explain the rapid, dynamic changes in aggressive behavior displayed by a variety of animals [96].

Much less is known regarding the adaptive value of these alternative mechanisms (Fig. 2C and D) for the neuroendocrine control of aggression, although some general themes are beginning to emerge [145]. In a seasonal context, reliance on hormones other than gonadal sex steroids, such as adrenal DHEA, may allow for increased aggression at times when gonadal production of testosterone is low (e.g., winter). Maintenance of high levels of aggression during the non-breeding season may be particularly beneficial for individuals to gain access to limited food resources or to maintain territories in some species. Furthermore, the modulation of aggression via alternative mechanisms allows an individual to maintain aggression during specific life history stages without incurring the "costs" of high circulating testosterone (e.g., suppression of immune function, increased metabolic rate) (Fig. 8). For example, an individual can maintain high circulating levels of a testosterone precursor, such as DHEA, rather than testosterone itself during specific life history stages. This inert precursor can be converted to sex steroids locally via a few enzymatic steps when and where necessary. The utility of these mechanisms (Fig. 2C and D) is that they allow an animal to avoid the potential costs of constitutively high levels of testosterone in the blood, while still allowing for rapid "on demand" production of sex steroids in relevant neural circuits.

Although it is clear that testosterone plays an important role in the regulation of aggression across many vertebrate taxa, the recent findings discussed in this review indicate that

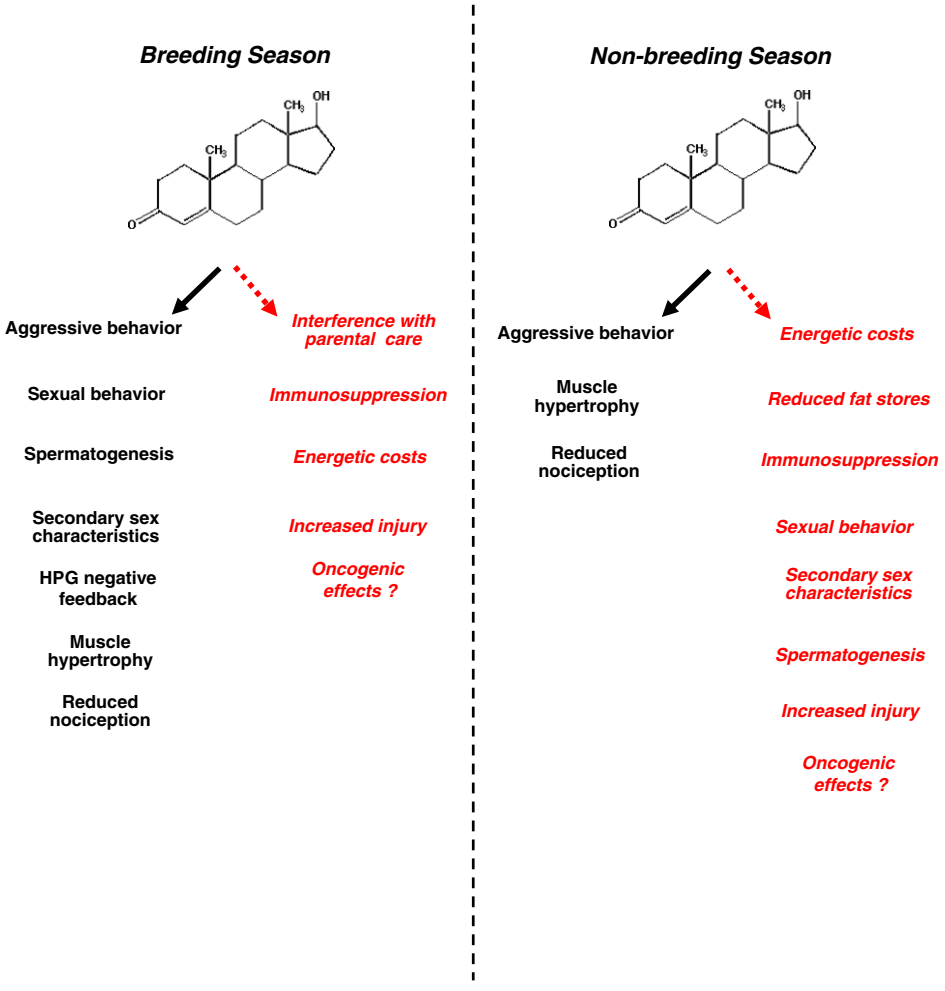

Fig. 8. Actions and costs of high circulating testosterone in the breeding season and non-breeding season. Within each season, actions are on the left, and potential costs are on the right. In the breeding season, a major cost of high circulating testosterone can be interference with parental care. In the non-breeding season, interference with parental care is not an issue, but a major cost of high circulating testosterone is increased energy expenditure (metabolic rate). From Soma [110].

the neuroendocrine regulation of aggression is more complex and more plastic than previously thought. A myriad of other steroid and peptide hormones play integral roles in the control of aggression. These hormones can act in concert with gonadal steroids, act as precursors for sex steroids, or act independently of steroids to regulate aggressive behavior. We still know relatively little about the endocrine bases of aggression across different environmental and life history contexts and across different species, but a comparative approach will be useful for identifying general themes as well as species-specific adaptations.

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