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Review

A seasonal switch hypothesis for the neuroendocrine control of aggression

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Aggression is a well-studied social behavior that is universally exhibited by animals across a wide range of contexts. Prevailing knowledge suggests gonadal steroids primarily mediate aggression; however, this is based mainly on studies of male–male aggression in laboratory rodents. When males and females of other species, including humans, are examined, a positive relationship between gonadal steroids and aggression is less substantiated. For instance, hamsters housed in short 'winter-like' days show increased aggression compared with long-day housed hamsters, despite relatively low circulating gonadal steroids. These results suggest alternative, non-gonadal mechanisms controlling aggression. Here, we propose the seasonal switch hypothesis, which employs a multidisciplinary approach to describe how seasonal variation in extra-gonadal steroids, orchestrated by melatonin, drives context-specific changes in aggression.

Highlights

Considerable research has focused on how gonadal steroids, especially testosterone, modulate central nervous system control of aggression. Here, we outline a novel, extra-gonadal mechanism underlying the androgenic regulation of aggression.

The seasonal switch hypothesis postulates that the pineal hormone melatonin acts on the adrenal glands, and possibly the brain, to modulate androgen release and its subsequent conversion to regulate aggressive behavior.

This model extends our understanding of the neural and neuroendocrine mechanisms controlling aggressive behavior and violence across vertebrate species and environmental contexts.

Hormones and aggression: a historical perspective

The taproots of behavioral endocrinology, and the study of hormones and **aggression** (see Glossary) more narrowly, can be traced back to the seminal work of Arnold Berthold [1]. In 1849, Berthold, a German physiologist at the University of Göttingen, removed the testes of male chickens and noted a marked decrease in secondary sex characteristics and male-typical behaviors, including aggression. Notably, transplantation of one testis into a castrated animal restored male sexual and inter-male aggressive behaviors (Figure 1A). Thus, from its inception, the study of hormones and aggression has been tightly coupled with blood-borne gonadal secretions, primarily testosterone. Accordingly, early researchers toiled under the central premise that circulating testosterone, binding directly to androgen receptors (ARs), modulates neural circuits regulating aggression.

But what do we mean by 'aggression'? Although aggression has been described in a variety of ways, it has traditionally been defined as an overt behavior with the intention to inflict physical damage upon another individual [2]. Aggression is widely exhibited across animal taxa and social contexts and enables individuals to compete for access to or defend resources (e.g., territories, food, mates) [3]. Consequently, many species are highly aggressive during the breeding season, when competition for access to these resources is considerable and the ability to acquire a mate and defend territory is vital for reproductive success. Because circulating gonadal steroids are elevated during this time of the year, these hormones have received the lion's share of research on the endocrine control of aggression for decades [4,5]. Many studies have demonstrated that castration decreases inter-male aggression in a reproductive context and that this response can be reversed by exogenous testosterone administration [6–10]. The link between gonadal steroids and aggression is further supported by studies of inter-male aggression in nonseasonal domesticated rodents, such as laboratory rats (*Rattus norvegicus*) and mice (*Mus musculus*). In these species, removing the gonads substantially decreases circulating testosterone and aggression [11].

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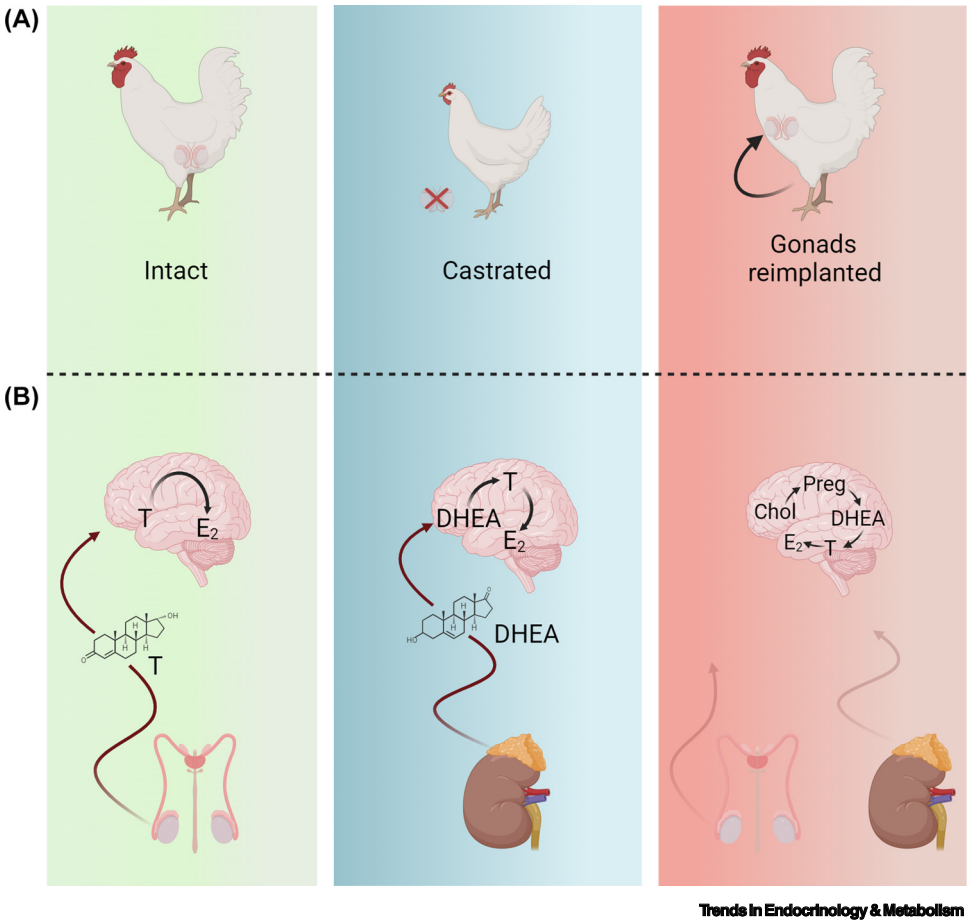

Figure 1. Berthold and beyond. (A) When a testis was transplanted into castrated male chickens at a new site (among the intestines), these animals showed normal male aggressive behavior. Upon dissection, Berthold found that the transplanted testes had established many new vascular connections. From these results, it was concluded that the testes release a substance into the bloodstream [testosterone (T)] that affects the entire organism, including the nervous system. (B) Since Berthold's seminal study, steroids have been shown to act on the brain to modulate aggression via several pathways: gonadal T can act directly or via local conversion to estradiol (E_2); adrenal dehydroepiandrosterone (DHEA) can act via local conversion to T and/or E_2; or DHEA can be produced *de novo* in the brain and then be converted to T and/or E_2 locally. Figure generated using BioRender.

Whereas these studies support Berthold's original findings of a role for gonadal steroids in controlling aggressive behavior (Figure 1A), this widely accepted relationship is based primarily on studies of male–male aggression in a relatively limited number of species, many of which are domesticated or nonseasonal. Indeed, prior research has shown that lower circulating testosterone is not always linked with decreased aggression, especially when seasonal and nondomesticated species are examined (e.g., [12,13]). For example, several species across taxa do not display reduced aggression after castration during the breeding season, including prairie voles (*Microtus ochrogaster*), Syrian hamsters (*Mesocricetus auratus*), Siberian hamsters (*Phodopus sungorus*), blind mole rats (*Spalax ehrenbergi*), saddle-back tamarins (*Saguinus fuscicollis*), European starlings (*Sturnus vulgaris*), red-sided garter snakes (*Thamnophis sirtalis*), Siamese fighting fish (*Betta splendens*), and three-spined stickleback (*Gasterosteus aculeatus*) [12–20]. These findings indicate that, although gonadal steroids may modulate breeding aggression, extra-gonadal factors must also be important because removing the gonads is ineffective at reducing aggression in many species (Figure 1B).

Glossary

Aggression: an overt behavior to inflict physical damage upon another individual. Aggression is widely exhibited across animal taxa and social contexts and enables individuals to compete for access to or defend resources (e.g., food, mates).
Agonistic behavior: adaptive behaviors displayed during conflict between members of the same species. These include aggressive, submissive, and defensive behaviors.
Aromatase: an enzyme that catalyzes the conversion (aromatization) of androgens into estrogens.
3β-Hydroxysteroid dehydrogenase (3β-HSD): an enzyme that catalyzes the biosynthesis of the androgen androstenedione from dehydroepiandrosterone (DHEA) in the adrenal gland.
17β-Hydroxysteroid dehydrogenase (17β-HSD): an enzyme that catalyzes testosterone biosynthesis from androstenedione.
Dehydroepiandrosterone (DHEA): a steroid hormone precursor produced primarily in the adrenal glands and, to a lesser extent, in the gonads and brain. It functions as a metabolic intermediate in the biosynthesis of additional androgens and estrogens.
Demedullation: a procedure in which the catecholamine-secreting region of the adrenal gland, the adrenal medulla, is selectively removed.
Melatonin: an indoleamine hormone produced primarily in the pineal gland that is released during darkness and regulates both sleep–wake cycles and seasonal responses.
Neurosteroids: steroids that are synthesized *de novo* from cholesterol or produced from steroid precursors in the brain, which can act via genomic and nongenomic mechanisms on neural circuits to regulate physiological and behavioral responses.
Photoperiod: (day length); the period each day during which an organism receives illumination. Short winter days trigger regression of the reproductive system and other morphological, physiological, and behavioral changes in most temperate zone animals.
Pinealectomy: surgical removal of the pineal gland, thus eliminating endogenous melatonin production.
Recrudescence: regrowth of short-day regressed gonads following exposure to long days (or prolonged

Beyond Berthold: extra-gonadal steroids as regulators of aggression

A closer look at the endocrine regulation of behavior reveals a more nuanced relationship between gonadal steroids and aggression, particularly in seasonally breeding species. Whereas some animals show robust, positive correlations between testosterone and aggression, others display an inverse relationship between gonadal steroids and aggressive behavior, exhibiting elevated aggression during the nonbreeding season despite gonadal regression and low circulating gonadal hormones. These findings suggest that these species faced additional selective pressures that favored the evolution of alternative mechanisms, independent of gonadal steroids, to control aggressive behavior year-round [21,22]. Such species have been fundamental for identifying the role of extra-gonadal steroids (e.g., adrenal steroids and **neurosteroids**) in modulating seasonal aggression.

Because most seasonally breeding animals use **photoperiod** (day length) to anticipate changes in the annual cycle and alter their physiology and behavior accordingly, most studies investigating the mechanisms of seasonal plasticity in aggression have used either natural or experimentally induced changes in the light cycle. In laboratory settings, animals are typically housed in light cycles that simulate seasonal variation in their natural habitat; long days are characteristic of the summer breeding season, whereas short days reflect the winter nonbreeding season. Conversely, field studies rely on ambient changes in season, enabling researchers to examine naturally occurring variations in the neuroendocrine regulation of aggression.

There is considerable evidence that aggressive behavior during the nonbreeding season occurs in the absence of gonadal steroids. 'Functionally castrating' male Syrian hamsters by maintaining them in short days increases resident–intruder aggression compared with long-day housed hamsters [23]. After prolonged maintenance in short days, hamsters undergo gonadal **recrudescence** and these short-day increases in aggressive behavior disappear, returning to long-day levels by ~20 weeks [23]. These results suggest that aggression is inversely related to serum testosterone, at least in male Syrian hamsters. Several field studies published to date also support laboratory data demonstrating elevated nonbreeding aggression [24] or complete uncoupling of the relationship between aggression and seasonal changes in testosterone [25].

While the adaptive function of short-day aggression remains unknown, it has been suggested that some animals, especially those inhabiting harsh winter environments, become aggressive during the nonbreeding season to gain access to and defend limited food resources [26]. Despite these intriguing findings, the precise hormonal mechanisms underlying short-day increases in territorial aggression remain largely undiscovered.

By far, most studies on the hormonal regulation of seasonal aggression have focused on male–male aggression. Photoperiodic changes in aggression, however, have been demonstrated in females of at least two species. Female Syrian and Siberian hamsters maintained in short days display significantly more aggression than long-day hamsters [27–31]. **Pinealectomy**, which eliminates **melatonin** and renders animals physiologically 'blind' to day length, blocks this short-day increase in aggression [27]. In contrast, short-term treatment of long-day hamsters with exogenous 'short-day-like' melatonin increases aggression in female [28] and male Syrian hamsters [32], suggesting that melatonin could also serve as the physiological 'signal' for nonbreeding season aggression. In further support of this hypothesis, ovariectomy of long-day female hamsters does not result in short-day-like levels of aggression, nor does it block increased aggression in short days [28]. Although many hormones and neuromodulators regulate aggressive behavior, we will focus our subsequent discussion on one class of hormones investigated more thoroughly in

exposure to short days, which is referred to as spontaneous recrudescence).

Simulated territorial intrusion (STI): experimental test of territorial aggression that involves placing a caged animal or group of conspecific animals within a territory and playing back tape-recorded vocalizations through a speaker placed alongside the cage.

Social behavior network: a collection of reciprocally connected regions in the basal forebrain, hypothalamus, and midbrain of vertebrates that regulate social behaviors, including aggression, and are sensitive to steroid hormones.

neuroendocrine studies of seasonal aggression: extra-gonadal steroid hormones, with a particular focus on the adrenal androgen **dehydroepiandrosterone (DHEA)**.

The seasonal switch hypothesis

Based on the findings from our work on the neuroendocrine control of seasonal aggression, primarily in rodents [21,33,34], as well as previous findings in birds [22], we propose a multidimensional mechanism for regulating aggressive behavior: (i) a 'bottom-up' regulation of central circuits controlling aggression via adrenally derived hormone secretion and subsequent conversion to other biologically active steroids, and (ii) a 'top-down' regulation through the direct actions of the pineal hormone melatonin on brain steroid receptors and neural circuits controlling aggression (Figure 2). Because melatonin is predominately produced at night, melatonin secretion is extended during the long winter nights relative to long summer days. We propose that this increased duration of melatonin production initiates 'a seasonal switch' from gonadal to adrenal regulation of aggression. Given that exogenous melatonin induces aggression in several rodent

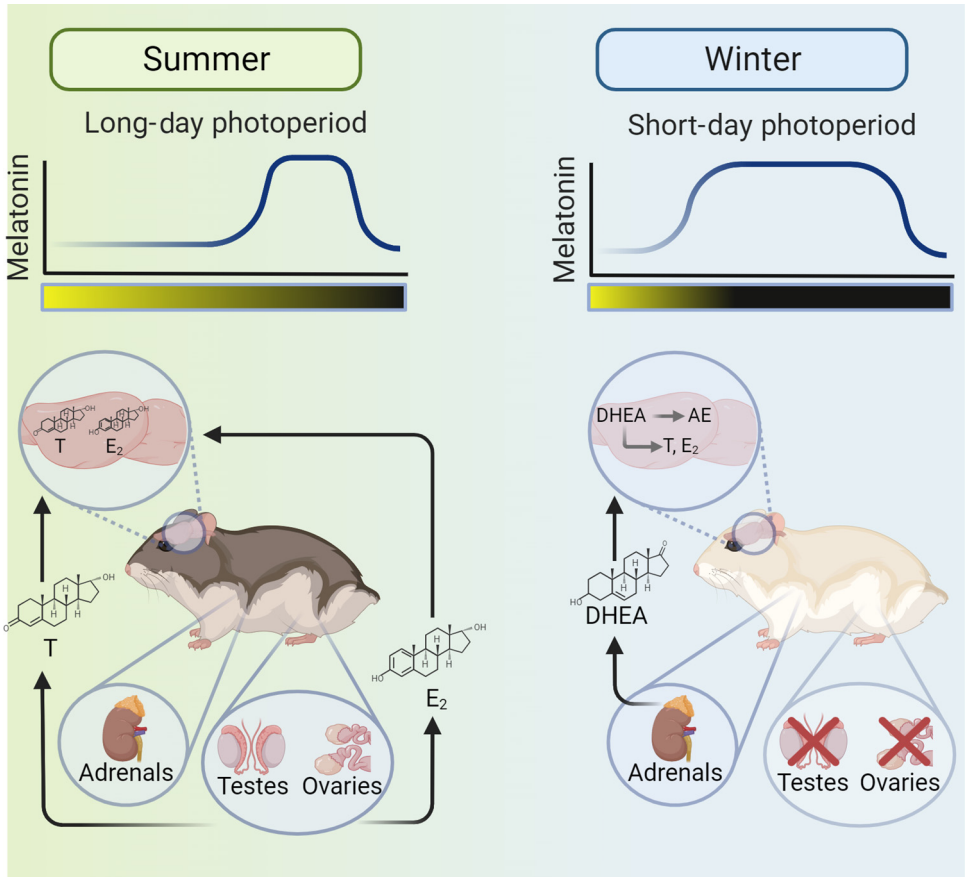

Figure 2. A seasonal switch. Schematic illustrating potential mechanisms underlying a 'seasonal switch' from gonadal to adrenal regulation of aggression. In this model, pineal melatonin acts peripherally on MT_1 melatonin (MT_1) receptors in the adrenal glands to upregulate the release of the androgen dehydroepiandrosterone (DHEA), as well as the steroid converting enzymes 3β-hydroxysteroid dehydrogenase (3β-HSD), which converts DHEA to androstenedione (AE), and 17β-HSD, which converts AE to testosterone (T). We also propose that melatonin acts centrally on MT_1 receptors to catalyze the conversion of androgens into estradiol (E_2) by upregulating the enzyme aromatase. Lastly, we predict that central melatonin upregulates steroid receptor expression (e.g., estrogen receptors) in brain regions controlling aggression, triggering the well-established phenotype of increased aggression in short-day hamsters. Figure generated using BioRender.

species [30,32,35–39], we suggest that melatonin acts directly on the adrenals to regulate DHEA synthesis, its local conversion to testosterone and estradiol, and, ultimately, mediates aggressive behavior through their actions in the brain. In this model, pineal melatonin acts on peripheral MT_1 melatonin receptors in the adrenal glands to upregulate the release of the androgen DHEA, as well as the steroid-converting enzymes **3β-hydroxysteroid dehydrogenase (3β-HSD)**, which converts DHEA to androstenedione, and **17β-hydroxysteroid dehydrogenase (17β-HSD)**, which converts androstenedione to testosterone. We further propose that melatonin acts centrally on MT_1 melatonin receptors to catalyze the conversion of androgens into estradiol by upregulating the enzyme **aromatase**. Lastly, we predict that central melatonin upregulates steroid receptor expression [e.g., estrogen receptors (ERs)] in brain regions controlling aggression, triggering the now well-established phenotype of increased aggression in short-day hamsters.

This hypothesis has been developed primarily from studies in Siberian hamsters, a seasonal species that has served as an ideal model to address extra-gonadal mechanisms of aggression [21]. Siberian hamsters and humans share an evolutionarily conserved neural circuit for transducing photoperiodic information into a biological signal (i.e., changes in the pattern and duration of melatonin secretion). Furthermore, Siberian hamsters are 'nature's knockout', possessing only one functional melatonin receptor subtype, the MT_1 melatonin receptor [40,41], allowing the actions of melatonin on aggression to be attributed solely to MT_1. In contrast, most rat and mouse strains do not produce sufficient melatonin [42,43] and many lack 17β-hydroxylase [44], the enzyme necessary to synthesize adrenal androgens. Siberian hamsters secrete significant amounts of adrenal DHEA, with similar circulating concentrations to those observed in humans. Importantly, unlike most rodents, where females limit aggression to pregnancy and lactation, female hamsters display substantial aggression across social contexts. Male and female hamsters show short-day and melatonin-induced aggression [29,30,35–37,45], which facilitates investigating natural aggression in both sexes. In hamsters and humans, DHEA and aggression are positively correlated [37,46,47]; thus, the parallels between hamster and human melatonin signaling and adrenal physiology make hamsters an excellent system to experimentally test the link among melatonin, DHEA, and aggression. Our published evidence demonstrates that adrenal overexpression of the MT_1 receptor partially increases aggression but does not fully emulate the short-day phenotype. These results suggest that the actions of melatonin on the adrenal glands are important in regulating increased aggression, although additional neuroendocrine mechanisms assuredly contribute to changes in behavior [36]. Thus, we further propose that melatonin acts on aggression neural circuits to mediate the conversion of testosterone to estradiol and ER expression. Collectively, this represents an alternative neuroendocrine mechanism controlling aggression and provides an essential tool for exploring the etiology of aggression.

Extra-gonadal steroid hormones

In contrast to research examining the hormonal basis of breeding aggression, there is little evidence that gonadal steroids regulate nonbreeding aggression. Such results are particularly apparent in seasonally breeding species with equal or higher levels of aggressive behavior during the nonbreeding season, despite low circulating gonadal steroids. For example, testosterone does not affect aggression in castrated male long-tailed hamsters (*Tscherskia triton*) housed in short days [48]. Moreover, male and female Syrian and Siberian hamsters show higher levels of aggression in short compared with long days [23,27,29,49]. Gonadectomy of long-day hamsters does not result in short-day-like levels of aggression, nor does it block short-day-induced increases in aggression [18,28,29]. Testosterone implants do not elevate aggression in male and female Siberian hamsters [18,29], suggesting that gonadal steroid hormones do not mediate photoperiodic effects on aggression. Field studies also support a weak relationship between

gonadal steroids and nonbreeding aggression. Male rat-like hamsters (*Cricetulus triton*) show increased aggression during the nonbreeding season, despite low levels of testosterone [24], and male wood rats (*Neotoma fuscipes*) display seasonal changes in aggression, independent of circulating testosterone [25]. In addition, aggression and testosterone are positively correlated during the breeding season in male ring-tailed lemurs (*Lemur catta*), yet are uncorrelated during the nonbreeding season [50]. Collectively, these laboratory and field studies suggest that alternative neuroendocrine processes, independent of gonadal steroids, control nonbreeding aggression in several seasonally breeding animals.

In recent years, it has become increasingly clear that extra-gonadal steroids, in both the periphery and brain, regulate seasonal aggression in vertebrates [21,22]. DHEA and neurosteroids have emerged as important modulators of nonbreeding aggression, primarily from studies conducted in songbirds and rodents. Within the brain, the hormonal regulation of aggression has mostly been examined within the **social behavior network**, a group of reciprocally connected nuclei in the basal forebrain, hypothalamus, and midbrain of vertebrates that are sensitive to steroid hormones [51,52]. Of these regions, the anterior hypothalamus (AH), bed nucleus of the stria terminalis (BNST), lateral septum (LS), medial amygdala (MeA), periaqueductal gray (PAG), preoptic area (POA), and ventromedial hypothalamus (VMH) and their non-mammalian homologs are associated with aggressive behavior and, thus, have been a major focus of studies examining the role of neurosteroids in mediating seasonal aggression. Both adrenal and neural steroids likely regulate aggressive behavior during the nonbreeding season, particularly in seasonally breeding animals that display high levels of aggression year-round.

The agonistic adrenal

As mentioned earlier, DHEA is an androgen secreted primarily by the adrenal glands, with lesser secretion by the liver, the gastrointestinal tract, gonads, and the brain [53]. Although DHEA itself can bind with low affinity to AR and ERs (ERα and ERβ), it predominantly serves as a prohormone that can be metabolized into more potent androgens (e.g., testosterone) and estrogens (e.g., 17β-estradiol) in tissues that express the appropriate steroidogenic enzymes [54]. Importantly, DHEA (and its sulfated form DHEA-S) passes through the blood–brain barrier and can be converted to other androgens and estrogens within the brain. Thus, it is likely that the local metabolism of circulating or brain-synthesized DHEA into more potent androgens and estrogens is responsible for controlling the neural circuits relevant to aggression during the nonbreeding season.

There is an established link between peripheral DHEA and nonbreeding aggression [21,34]. For example, in songbirds that display territorial aggression year-round, nonbreeding males have lower plasma testosterone and estradiol but higher plasma DHEA than breeding males [55–57]. Furthermore, circulating DHEA levels correlate positively with aggressive vocalizations displayed during a **simulated territorial intrusion (STI)** [57]. DHEA administration also elevates STI-induced aggressive behavior and song production [58,59], suggesting that DHEA drives territorial aggression during the nonbreeding season in some avian species.

Our work in Siberian hamsters further supports a link between adrenal DHEA and aggressive behavior. Male and female hamsters exhibit lower circulating gonadal steroids, but higher circulating DHEA and elevated aggression when housed in short days that mimic the nonbreeding season [18,29,30,38]. Short-day hamsters also show decreases in serum DHEA and testosterone after aggressive encounters, consistent with increased metabolism to testosterone and estradiol (Figure 3) [35]. Furthermore, housing hamsters in short days elicits structural changes specifically to the zona reticularis of the adrenal glands (the region responsible for producing adrenal androgens), but not other regions of the adrenals (Figure 4). Interestingly, and perhaps surprisingly, the

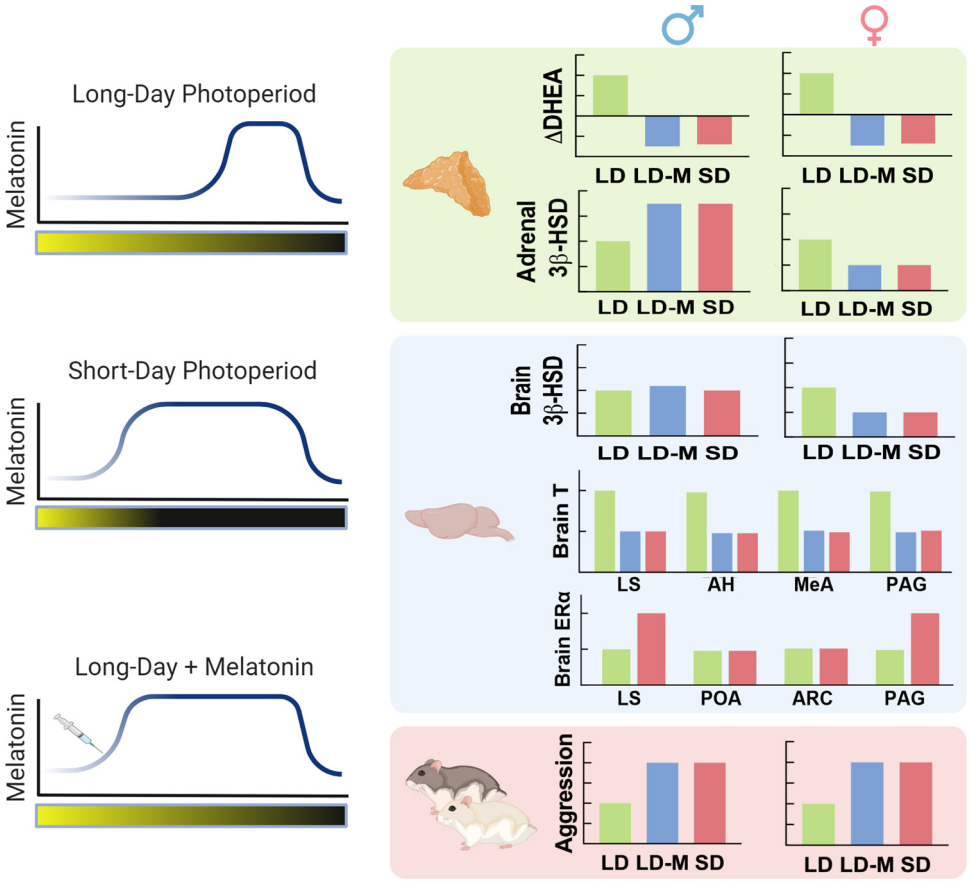

Figure 3. Melatonin and seasonal plasticity. (Left) Maintenance in short days or timed injections of the pineal hormone melatonin regulates a seasonal switch in the neuroendocrine regulation of aggression in Siberian hamsters via modulation of steroid hormones. (Right) Changes in serum dehydroepiandrosterone (DHEA) levels following an aggressive interaction, sex-specific changes in adrenal and central 3β-hydroxysteroid dehydrogenase (3β-HSD) activity, neural testosterone (T) concentrations in the lateral septum (LS), anterior hypothalamus (AH), medial amygdala (MeA), and periaqueductal gray (PAG) of male hamsters, short-day increases in estrogen receptor (ER) immunoreactivity in the LS and PAG, but not the preoptic area (POA) or arcuate nucleus (ARC) of female hamsters, and attack duration of long-day (LD), short-day (SD), and LD hamsters given timed melatonin (LD-M). Stylized data are modified from previous studies with permission from the authors. Figure generated using BioRender.

zona reticularis is smaller in short-day hamsters compared with long-day hamsters, perhaps owing to increased DHEA release (thus, less storage of the hormone within the adrenal cells). Functionally, adrenal glands cultured from short-day hamsters show significantly elevated DHEA release *in vitro* in response to melatonin compared with adrenals from long-day hamsters [30], suggesting a direct effect of melatonin on the adrenals to stimulate DHEA release. In addition, short-day-housed hamsters have elevated serum DHEA compared with long-day-housed hamsters and concentrations are significantly correlated with aggression. Moreover, short-day females have higher adrenal DHEA content and exhibit an increase in serum DHEA concentration following an adrenocorticotropic hormone challenge compared with long-day females [30]. Notably, the role of DHEA in controlling nonbreeding aggression occurs independently of other adrenal hormones (i.e., glucocorticoids, catecholamines); short-day males that receive adrenalectomies display reduced levels of aggression, yet adrenal **demedullation**, in which the catecholamine-secreting adrenal medulla is removed, produces no change in aggressive behavior [38].

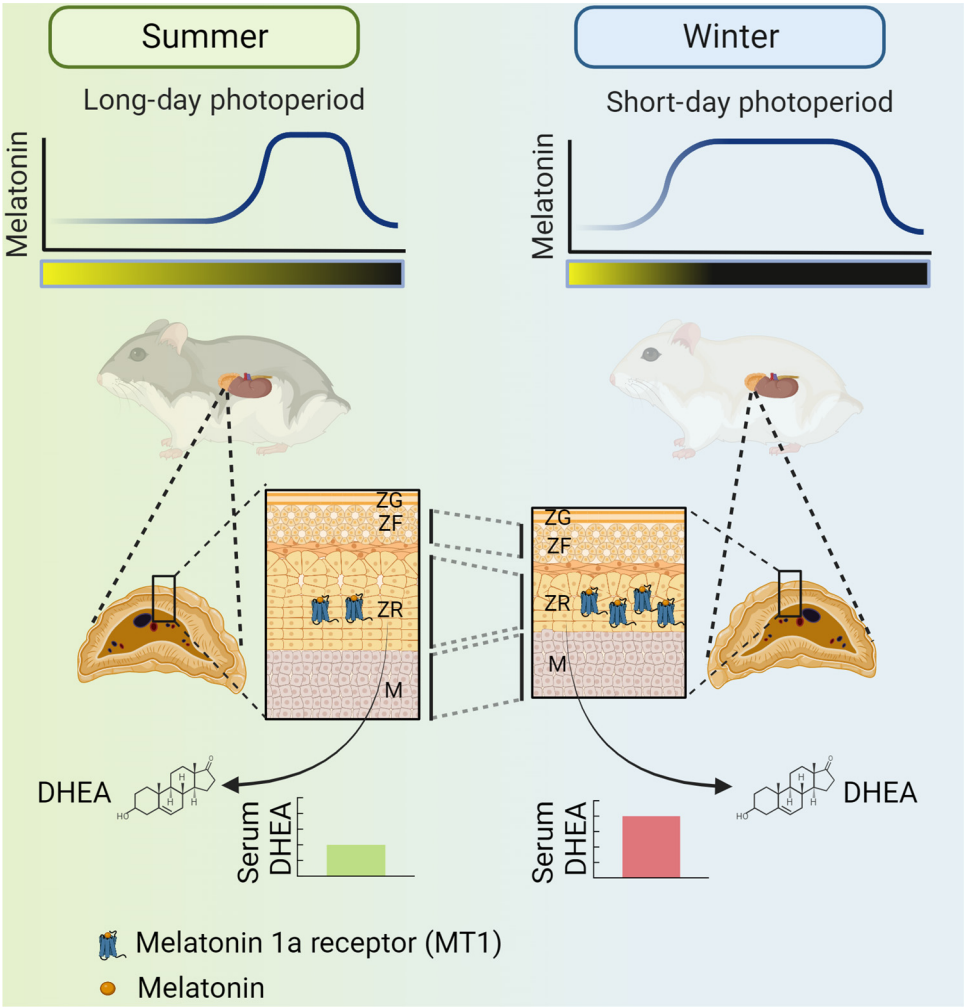

Figure 4. The agonistic adrenal. Proposed actions of the seasonal switch within the adrenal glands. Hamsters housed in short days undergo an increase in the duration of pineal melatonin secretion, acting directly on MT_1 melatonin receptors in the adrenal glands to increase circulating DHEA. In support of this idea, short days confer structural changes in the adrenals specific to the androgen-producing zona reticularis, short-day-housed hamsters have increased basal DHEA, and exogenous melatonin increases *in vitro* DHEA release in cultured adrenal glands. We also predict that maintenance in short days increases expression and/or sensitivity of MT_1 receptors, consistent with important peripheral actions of melatonin to regulate behavior. Figure generated using BioRender.

Furthermore, short-day photoperiods do not affect serum or adrenal cortisol content, nor does cortisol treatment influence male aggression [60]. These findings indicate that DHEA is a primary driver of increased nonbreeding aggression in this species.

Although the aforementioned research supports a role for adrenal DHEA in regulating aggressive behavior during the nonbreeding season, we note that similar relationships between DHEA and aggression are not observed in all vertebrates. For example, in male European starlings, aggressive non-courtship and vocalization behavior is displayed during the nonbreeding season, despite lower circulating DHEA [61]. Moreover, DHEA administration does not increase aggression in male European nuthatches (*Sitta europaea*), a species in which both males and females defend

a single territory year-round [62]. There is also considerable evidence of a lack of a relationship between DHEA and aggression in laboratory mice. As mentioned earlier, many laboratory rodents lack 17β-hydroxylase [44], the enzyme necessary to synthesize adrenal androgens, and many have undetectable levels of circulating DHEA (e.g., [63]), yet display aggression. In addition, castrated male mice show lower levels of aggression towards lactating female mice when given exogenous DHEA [64,65]. Similarly, DHEA reduces aggressive behavior towards intact, ovariectomized, and lactating females when administered to ovariectomized female mice [66,67]. Thus, these data demonstrate that aggression is controlled independently of DHEA in some nonseasonal and seasonally breeding animals.

Steroid converting enzymes: catalysts of the switch

To date, two steroidogenic enzymes have been the primary focus of neuroendocrine studies of seasonal aggression: 3β-HSD, which converts pregnenolone to progesterone and DHEA to androstenedione, and aromatase, which converts testosterone to estradiol. Male song sparrows (*Melospiza melodia*) exhibit seasonal changes in 3β-HSD and aromatase in brain regions associated with aggressive behavior [68–70]. Although functional studies to link these changes in enzymatic activity with aggression have not been completed, these findings suggest that local changes in neural steroid metabolism may contribute to nonbreeding aggression in male song sparrows.

In rodents, seasonal plasticity in steroidogenic enzyme activity is species-specific. For example, in beach mice (*Peromyscus polionotus*), which display higher territorial aggression during the nonbreeding season, administering the aromatase inhibitor fadrozole decreases aggression in males housed in nonbreeding conditions but increases aggression in breeding males. Estradiol injections, however, prevent the effects of fadrozole on these behavioral phenotypes [71], suggesting that estradiol modulates aggressive behavior in a context-dependent manner. Conversely, there are no differences in the density of aromatase immunoreactive cells in the PAG and two brain regions that regulate reproduction (the paraventricular nucleus of the hypothalamus and ventral tegmental area) between long- and short-day female Siberian hamsters [45]. Siberian hamsters, however, exhibit seasonal and sex differences in adrenal and neural 3β-HSD activity and the expression of steroidogenic genes in the brain, despite showing a similar aggressive phenotype during the nonbreeding season. Specifically, short-day males and long-day males treated with exogenous melatonin have higher 3β-HSD activity in the adrenal glands than long-day control males. In contrast, short-day females exhibit reductions in 3β-HSD activity in the adrenal glands and AH relative to long-day females (Figure 3) [31]. These findings suggest that melatonin increases the activity of enzymes that convert DHEA to bioactive steroids, such as testosterone and estradiol, at least in males. Moreover, while short-day hamsters show similar changes in the expression of aromatase and 5α-reductase (an enzyme that converts testosterone to 5α-dihydrotestosterone) in the arcuate nucleus, a brain region that is linked with reproduction and energy balance, they show sex-specific patterns of gene expression in brain regions associated with aggression (medial POA, AH, and PAG) [72]. Taken together, these findings support a role for steroid-synthesizing and -metabolizing enzymes in controlling seasonal aggression and suggest that seasonal variation in steroidogenic enzyme activity is sex-specific in some rodents.

A role for the brain

Central steroid receptors: the 'keys' to aggression

Whereas the initial actions of the seasonal switch occur in the periphery, the brain also plays a critical role in regulating seasonal aggression. Seasonal variation in steroid receptors in brain regions associated with aggressive behavior is highly variable across species. For example, ERα expression in the POA and AR expression in the nucleus taeniae, the avian homolog of the MeA, are

higher during the nonbreeding season than during the breeding season in spotted antbirds (*Hylophylax naevioides*) [73], presumably due to increased sensitivity to low circulating steroids, which could drive year-round aggression. Conversely, breeding male song sparrows show higher AR expression in the POA than nonbreeding males, consistent with its role in regulating aggression during the breeding season. However, there are no differences in ERα and ERβ expression in brain regions associated with aggressive behaviors across the seasons [69], suggesting estrogen-dependent changes in aggression are not due to increased sensitivity during the nonbreeding season. In other bird species, inhibiting the androgenic and estrogenic actions of testosterone reduces territorial aggression in breeding but not nonbreeding males [74,75], pointing to non-steroid receptor-dependent mechanisms of aggression during the nonbreeding season.

Similar studies in seasonally breeding rodents have documented seasonal differences in the expression and abundance of ERs and characterized their potential role in controlling aggression. Male beach mice and deer mice (*Peromyscus maniculatus*) housed in nonbreeding conditions show increases in ERα abundance and expression in the BNST, but reductions in ERβ in the BNST and MeA relative to males housed in breeding conditions [76]. Furthermore, selective activation of ERα or ERβ increases aggression in short-day male beach mice, but is not related to changes in estrogen-dependent gene expression in the BNST or POA [71]. Similarly, nonbreeding aggression is positively correlated with ERα immunoreactivity and expression in brain regions associated with aggression in short-day male and female Siberian hamsters (i.e., PAG, POA, LS, MeA, and BNST) (Figure 3), but aggressive behavior is either negatively or not associated with ERα expression in brain regions associated with reproductive behavior (i.e., arcuate nucleus and the anteroventral periventricular nucleus of the hypothalamus) [72,77,78]. This dissociation suggests that ERα may regulate aggression independent of sex, but is dependent upon the season. Interestingly, there are no differences in ERα and ERβ immunostaining in the LS, POA, BNST, or MeA between seasonal phenotypes of male California mice (*Peromyscus californicus*), a species that displays increased aggression during the nonbreeding season, but does not exhibit gonadal regression [79,80]. Thus, these findings indicate that ERs regulate nonbreeding aggression in rodent species that are reproductively responsive to changes in photoperiod.

In addition to photoperiodic effects, the seasonal switch hypothesis proposes that there are melatonin-induced changes in a suite of steroid hormone actions, including changes in secretion, activity of converting enzymes, and tissue sensitivity (e.g., receptors), that collectively orchestrate a coordinated endocrine response to modulate aggression. Thus, increases in peripheral steroid release alone, endogenously or exogenously (via experimental manipulation of hormones), may not be sufficient to alter aggressive behavior without changes in converting enzymes or receptors. Future research is needed to test this intriguing idea via experiments that alter multiple aspects of endocrine action (e.g., exogenous hormone treatment coupled with tissue-specific overexpression of central steroid receptors).

Neurosteroids: the brain's own hormones

In addition to the peripheral secretion of steroid hormones, vertebrates can also synthesize steroids *de novo* from cholesterol in the brain [63,81]. The idea of 'neurosteroids', or brain-derived steroid hormones, was first introduced to describe the high levels of DHEA and DHEA-S detected in the brains of castrated and adrenalectomized rats [82,83]. It is now well established that DHEA, among other steroid hormones (e.g., allopregnanolone), can be synthesized *de novo* within the central nervous system and act locally on specific neural substrates to modulate social behaviors, such as aggression [3,84]. Thus, it is likely that both neurosteroids and neurally derived

androgens and estrogens (i.e., androgens and estrogens derived from circulating steroids) seasonally modulate the neural circuits regulating aggression [21,34].

Only a few studies have characterized seasonal variation in neurosteroid levels in two seasonally breeding species: song sparrows and Siberian hamsters. Male song sparrows exhibit seasonal changes in neurosteroid concentrations within the brain; nonbreeding males have lower testosterone and estradiol in the POA, AH, and nucleus taeniae, but have higher progesterone in the POA, AH, VMH, and nucleus taeniae than breeding males (Figure 3). There are no differences in the neural DHEA or corticosterone concentrations, however, between breeding and nonbreeding males [85–87]. Conversely, short-day male Siberian hamsters have lower DHEA, testosterone, and estradiol in the LS, AH, MeA, and PAG than long-day males. Yet, there are no differences in neural progesterone or cortisol concentrations between long- and short-day male hamsters. Interestingly, long- and short-day male hamsters also show distinct associations between neurosteroid levels and aggression. Whereas neural progesterone and DHEA positively correlate with aggression regardless of photoperiod, only short-day males exhibit negative correlations among neural testosterone, estradiol, and cortisol concentrations and aggressive behavior [37]. One possibility is that short-day decreases in specific neurosteroids (e.g., DHEA, testosterone) are driven by subsequent conversion to other biologically active steroids, which in turn regulate aggression. Data supporting this have been demonstrated in the periphery, with circulating DHEA decreasing and estradiol increasing following aggressive encounters, but only in the presence of melatonin [88]. Unlike the increases in circulating estradiol seen in this paradigm, decreased neural estradiol in short days provides an interesting challenge to this hypothesis and may relate to the rapid actions of neurosteroids on aggression relative to circulating steroids [89,90]. Regardless, additional studies are necessary to determine the role of neurosteroids in regulating aggression in hamsters and other seasonally breeding species.

A model for human aggression?

Although aggression has evolved as an adaptive response within specific contexts, aggression and violence have become pervasive across many human societies. Violence against self and others is often associated with neurological and psychiatric disorders, including mood disorders, anxiety, psychotic disorders, and impulse control or conduct disorders [91,92]. Current treatments for excessive or inappropriate aggression, however, are mainly ineffectual, owing to our limited understanding of the endocrinology and neurobiology of these disorders [93,94]. Prior studies suggest that aggression varies seasonally in humans; annual rhythms in violent crimes track seasonal variation in photoperiod and violent crimes show strong seasonal patterns in the northern hemisphere, whereas non-violent crimes exhibit no such pattern. Inverse rhythms in aggressive crimes occur in the southern hemisphere [95]. Other reports indicate peaks in violent acts during the winter, including suicide [96,97]. Thus, there is an essential yet underappreciated link among mental illness, seasonality, and violence, particularly for suicide, suggesting that biochemical signals mediating seasonality also influence aggressive behavior. Unfortunately, in most clinical studies, the effects of season are only controlled as covariates and not directly examined [98]. Because melatonin largely regulates seasonal responses in all mammalian species, including humans, we suggest melatonin may serve as a key mechanism in regulating seasonal changes in aggression. In support of this idea, a recent randomized, double-blind, placebo-controlled study demonstrated that exogenous melatonin increases human reactive aggression [99]. Given these findings, perhaps it is especially troubling that over-the-counter melatonin use to improve sleep has nearly doubled over the past decade and often exceeds the recommended dose of 5 mg/day [100]. We hope that the seasonal switch hypothesis will provide a useful experimental framework for future studies addressing this critical knowledge gap by providing a better

understanding of how the pineal hormone melatonin coordinates neuroendocrine modifications contributing to aggressive behavior.

Concluding remarks and future perspectives

While growing research has examined seasonal changes in nonaggressive social and affective behaviors and a potential role for melatonin in mediating changes in these behaviors, much less is known about these mechanisms relative to aggressive behavior. Thus, additional research on seasonal and melatonin-dependent variation in nonaggressive social and nonsocial behaviors (e.g., reward and affective behaviors) and their interaction with other neuroendocrine substrates (e.g., gonadal, adrenal, and neural steroids) is warranted. Ongoing and future research will address important lingering questions regarding the precise causal relationships between changes in adrenal steroids and aggression, the specific mechanisms by which melatonin regulates changes in steroid hormone actions and subsequent changes in behavior, as well as potential sex differences in the neuroendocrine regulation of seasonal aggression (see Outstanding questions). Continued studies testing the seasonal switch hypothesis will be critical for characterizing the neuroendocrine mechanisms by which melatonin modulates plasticity in social and nonsocial behaviors. A greater understanding of how melatonin orchestrates seasonal plasticity in behavior can provide insight into how this hormone influences emotional states.

Outstanding questions

What are the precise mechanisms by which melatonin acts at the level of the adrenal glands to increase DHEA output and coordinate the seasonal switch?

What is the role of centrally acting melatonin on brain circuits regulating aggression?

Do locally derived neurosteroids contribute to seasonal aggression?

What is the role of melatonin in regulating seasonal aggression in diurnal species, including humans?

Are there sex differences in the neuroendocrine mechanisms underlying seasonal aggression?

What role do factors other than steroid hormones play in orchestrating a seasonal switch in aggression?

Do seasonal changes in melatonin coordinate changes in social and affective behaviors beyond **agonistic behaviors**?

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Declaration of interests

No interests are declared.

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