Aggressive Behavior

Jérôme P Plumier, Graduate Program in Neuroscience and Djavad Mowafaghian Centre for Brain Health, The University of British Columbia, Vancouver, BC, Canada
Cecilia Jalabert, Departamento de Neurofisiología Celular y Molecular, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay
Kathleen M Munley, Department of Integrative Biology and Physiology, University of California Los Angeles, Los Angeles, CA, United States
Gregory E Demas, Department of Biology, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior, Indiana University, Bloomington, IN, United States
Kiran K Soma, Department of Psychology, Department of Zoology, and Djavad Mowafaghian Centre for Brain Health, The University of British Columbia, Vancouver, BC, Canada

This is an update of Cecilia Jalabert, Kathleen M. Munley, Gregory E. Demas, Kiran K. Soma, Aggressive Behavior, Editor(s): Michael K. Skinner, Encyclopedia of Reproduction (Second Edition), Academic Press, 2018, Pages 242–247, ISBN 9780128151457, https://doi.org/10.1016/B978-0-12-801238-3.64591-9.

Abstract

Aggression is displayed by virtually all animals and is critical for the acquisition and maintenance of limited valuable resources. In breeding contexts, males often compete for access to mates, and aggression is promoted by gonadal testosterone. Aggression also occurs in non-breeding contexts, when the gonads can be regressed and circulating testosterone levels can be low or non-detectable. In some species, non-breeding aggression is promoted by the local synthesis of sex steroids in the brain. Physiological indicators of season, such as melatonin, might allow animals to switch from one neuroendocrine mechanism to another across the annual cycle.

Key Points

- Aggression occurs in multiple contexts and is critical for reproductive success.
- The neural circuitry regulating aggression emerged early in animal evolution and is highly conserved across taxa.
- Aggression is modulated by steroid hormones, which may originate from peripheral tissues, such as the gonads or adrenal glands, or be locally produced in the brain.
- Dehydroepiandrosterone (DHEA), a precursor of testosterone (T) and 17β-estradiol (E_2), can modulate aggression in non-breeding contexts.
- Studies suggest that aggression in primates, including humans, may be regulated by similar neuroendocrine mechanisms.

Introduction

Aggression is an important social behavior. It includes both direct physical conflicts between two or more individuals and threatening behaviors displayed to avoid physical confrontations (Nelson, 2006). Aggression is displayed by virtually all animals and serves a range of functions, such as the acquisition and defense of limited resources (e.g., mates, territories, and food). However, aggressive encounters are costly in terms of time, energy, predation risk, and injury risk. Animals must evaluate the costs and benefits of competing for resources when deciding if they should fight. In this way, aggressive interactions impact the establishment of dominance hierarchies that govern access to a limited resource. For example, in the context of mate choice,

competitors may compare strength and establish dominance in front of a potential mate. In solitary or territorial species, aggression often dictates the exclusive use of a resource, but in gregarious species, aggression establishes dominance and preferential access to a resource. Consequently, aggressive interactions directly impact survival and reproductive success.

Historically, studies of aggression have focused on male–male competition for mates. However, aggression is not exclusive to males and does not only occur during competition for a mate. Female–female contests, although less studied, are also present in nature. As in males, preferential access to a resource is advantageous for females. Traditionally, aggression has been defined as an overt behavior with the intention to inflict physical damage upon another individual. Different classifications of aggressive interactions have been proposed, and they have been defined based on the context in which they occur: (1) territorial aggression; (2) disputes over food; (3) aggression to establish dominance relationships; (4) parental aggression; (5) aggression for sexual competition; (6) antipredator aggression; and (7) irritable aggression (Nelson, 2006; Soma *et al.*, 2008).

The neuroendocrine bases of aggressive behavior are conserved across vertebrates and have primarily been studied under breeding contexts. These studies have focused on male–male interactions and the role of gonadal steroid hormones, especially testosterone, in regulating aggression. The objective of this chapter is to provide a brief overview of aggressive behavior, including the role of aggression in reproductive contexts and the neuroendocrine mechanisms that regulate aggressive behavior, with a particular focus on gonadal and extra-gonadal steroids. In addition, we discuss the neural circuits that underlie aggression and how androgens modulate these circuits in vertebrates, including primates.

Aggression in Reproductive Contexts

Numerous studies across many species have demonstrated that aggression and reproduction influence one another. For example, mating elevates aggressive behavior towards novel same-sex conspecifics in some vertebrates and invertebrates. Aggression also plays an important role in reproduction, most commonly via intraspecific aggression, which is often observed in reproductive contexts.

Intraspecific aggression, which can be further classified into intrasexual and intersexual aggression, has been studied extensively in males. Male-male intrasexual conflicts can affect reproduction by impacting access to mates, such as via the establishment of social hierarchies that provide dominant males with greater access to females or via the hinderance of competitors' courtship displays. Moreover, male intrasexual aggression can affect reproduction after mating via mate guarding as a means of paternity assurance (Rubenstein, 2022). In many species, male-male aggression serves as an indicator of mate "quality" for females when choosing a partner, and these species often display sexual dimorphism in body size, which is reduced in species where both males and females exhibit aggression related to competition over non-sexual resources (Lischinsky and Lin, 2020).

Female-female aggression can also affect reproduction (Pandolfi *et al.*, 2021; Rosvall *et al.*, 2020). In many mammals, females form robust hierarchical relationships in which dominant individuals have greater or sole access to mates. Females of some hamster and mole rat species, for example, inhibit the reproductive capacity of female conspecifics through frequent attacks, which induces chronic stress and compromises fertility (Rubenstein, 2022). In cooperatively breeding meerkats (*Suricata suricatta*), dominant breeding females suppress reproduction of competing females by evicting them from their social group. These stressful evictions lead to reduced conception and increased abortion rates among subordinate females (Rubenstein, 2022). Females of other classes of vertebrates also exhibit aggression, which helps them acquire breeding territories or defend their offspring (Pandolfi *et al.*, 2021).

Intraspecific aggression encompasses more than same-sex conflicts. Due to sex differences in parental investment and gamete availability, the evolutionary interests of each sex rarely converge entirely (Rubenstein, 2022). Females, who are often more selective when choosing a mate due to greater parental and gamete investment, may be coerced to reproduce by aggressive males or be brought into sexual receptivity by infanticide.

Individuals may also exhibit aggressive behaviors to discourage additional reproductive partners. In monogamous species with substantial paternal investment, such as prairie voles (*Microtus ochrogaster*), males sometimes attack sexually-receptive novel females to maintain a pair bond with their partner (Pandolfi *et al.*, 2021).

Although males more commonly display intersexual aggression, females may show aggression towards males in some reproductive contexts, most of which involve maternal aggression (Pandolfi *et al.*, 2021; Rubenstein, 2022). Female intersexual aggression, however, can also be exhibited during mate choice. For example, convict cichlids (*Amatitlania siquia*) display size-assortative mating patterns, with each sex seeking out the largest available mate. Prior to breeding, females aggressively defend themselves against courtship attempts from smaller males in anticipation of finding a larger, more size-matched mate (Pandolfi *et al.*, 2021). Thus, similar to intrasexual aggression, intersexual aggression can facilitate or hinder mating.

Endocrine Mechanisms of Aggression

Gonadal Steroids

Traditionally, blood-borne gonadal steroids have been the focus of neuroendocrine studies of aggression (**Fig. 1**). The effects of gonadal hormones in development and behavior was first documented in male chickens (*Gallus domesticus*) in the mid-19th

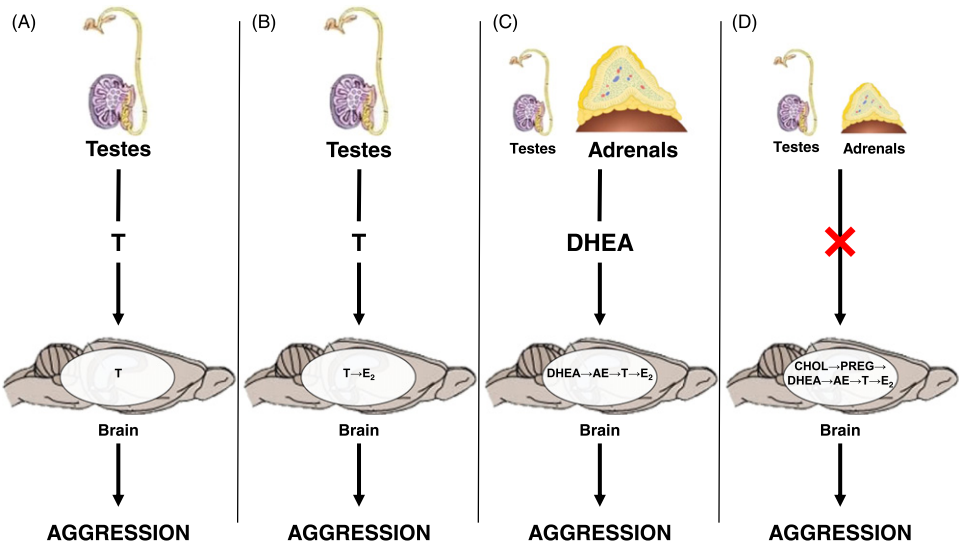

Fig. 1 Pathways by which steroids could affect aggression. (A) Gonadal testosterone (T) acts directly on the brain; (B) gonadal T is converted locally to 17β-estradiol (E_2); (C) adrenal dehydroepiandrosterone (DHEA) is converted locally to T and/or E_2; (D) neurosteroids are produced locally *de novo* from cholesterol (CHOL) via conversion to pregnenolone (PREG), DHEA, androstenedione (AE), T, and E_2 in the absence of gonadal and adrenal steroid production.

century by Arnold Berthold (Demas *et al.*, 2023; Soma *et al.*, 2008). In his classic study, Berthold removed the testes of sexually immature male chickens and found that castrated males, called capons, exhibited a decrease in the development of certain secondary sex characteristics, such as wattles and a prominent comb, and a decrease in male-typical behaviors, such as aggression and mating. When the testes were transplanted into capons, however, they exhibited normal morphological and behavioral characteristics. Berthold also observed that the testes developed additional vasculature following transplantation, suggesting that a blood-borne factor secreted by the testes is essential for proper morphological, behavioral, and physiological development in roosters. This compound, which Berthold termed "das productive Verhältnis der Hoden," is now known as the androgen testosterone (T). Berthold's experiment was the first to provide evidence that gonadal T regulates aggression in males.

Since the publication of Berthold's work, numerous studies have provided evidence that circulating gonadal steroids, such as T and 17β-estradiol (E_2), promote aggression by binding directly to androgen receptors (ARs) and estrogen receptors (ERs) in the brain to modulate neural pathways relevant to aggressive behavior (Cunningham *et al.*, 2012; Soma *et al.*, 2008).

In seasonally-breeding vertebrates, sex steroids are particularly important in facilitating aggression during the breeding season, when aggressive behavior is crucial for acquiring a mate and maintaining territories (Wingfield *et al.*, 1990). Among seasonally-breeding species, the gonads recrudesce before the breeding season and regress following the termination of breeding, and circulating sex steroid concentrations are high during the breeding season and basal or non-detectable during the non-breeding season (Demas *et al.*, 2007; Wingfield *et al.*, 2019).

While gonadal steroids are key modulators of aggressive behaviors, recent work indicates that aggression is not exclusively regulated by these hormones. There is now strong evidence that the brain is capable of metabolizing circulating gonadal steroids and steroid precursors, such as dehydroepiandrosterone (DHEA), and even synthesizing androgens and estrogens *de novo* from cholesterol (Demas *et al.*, 2023; Munley *et al.*, 2018) (**Fig. 1**). Furthermore, other steroidal and non-steroidal hormones have been shown to modulate aggression, including glucocorticoids, a class of steroids known for their metabolic and immunomodulatory effects.

Extra-Gonadal Steroids

DHEA is a steroid produced by steroidogenic enzymes, including CYP17A1, which is secreted by the gonads and adrenal glands in some species and also locally produced in the brain. Once produced, DHEA travels through circulation, in some species after sulfation into DHEA-sulfate (DHEA-S), and crosses the blood-brain barrier. Once DHEA reaches a target organ or tissue, it can bind with very low affinity to steroid receptors, including AR, ERs, and glucocorticoid receptors. Alternatively, in tissues that express the appropriate steroidogenic enzymes, such as 3β-hydroxysteroid dehydrogenase/Δ5–Δ4 isomerase (3β-HSD), 17β-hydroxysteroid dehydrogenase, and CYP19A1 (aromatase), DHEA can be locally converted to more potent steroids, such as T and E_2, which can then bind with high affinity to AR and ERs, respectively (Demas *et al.*, 2023; Soma *et al.*, 2015).

The role of DHEA in controlling aggressive behavior has primarily been studied in songbirds and rodents that exhibit high levels of aggression year-round (Demas *et al.*, 2023; Munley *et al.*, 2018; Soma *et al.*, 2015). Both males and females of these species can exhibit territorial aggression outside of the breeding season, even though the gonads are regressed and circulating sex

steroid levels are low. For example, aggressive behaviors in non-breeding male song sparrows (*Melospiza melodia*) are qualitatively and quantitatively similar to those of breeding males (Soma *et al.*, 2008), while male and female Syrian and Siberian hamsters (*Mesocricetus auratus* and *Phodopus sungorus*, respectively) show higher aggression toward conspecifics when they are not in breeding condition (Demas *et al.*, 2023; Munley *et al.*, 2018). Interestingly, these species display elevated circulating, gonadal, and/or adrenal DHEA levels and show seasonal variation in the activity of 3β-HSD, an enzyme that converts DHEA to androstenedione, in the adrenal glands, suggesting that DHEA promotes non-breeding aggression (Munley *et al.*, 2022). Moreover, there is emerging evidence that non-breeding songbirds and rodents display locally elevated DHEA and androgen levels and increased AR and ER expression in brain regions that modulate aggression (Demas *et al.*, 2007; Munley *et al.*, 2023). Thus, seasonally-breeding animals use two different neuroendocrine mechanisms to sustain year-round territorial aggression. Breeding animals rely on circulating gonadal steroids to promote aggression, whereas reproductively quiescent animals use peripherally-derived and brain-derived DHEA as alternative sources of neural androgens during the non-breeding season.

Research in the past two decades shows that androgens regulate non-breeding aggression via conversion to estrogens by the enzyme aromatase in the brain (Demas *et al.*, 2007; Quintana *et al.*, 2021). In songbird and rodent species, aggression is positively correlated with brain aromatase activity and expression. Moreover, male-male aggression in castrated rodents is increased by E_2 administration, whereas aggression is greatly reduced in rodents with non-functional ERs. Finally, castrated songbirds and rodents given T show decreased aggression following aromatase inhibition. Thus, aggression is modulated by E_2, whose origin differs between contexts and seasons.

Among seasonally-breeding vertebrates, physiological indicators of season are critical for signaling animals to shift from one mechanism to another across the annual cycle. In particular, the hormone melatonin plays an essential role in initiating the physiological changes necessary for this "seasonal switch" in the neuroendocrine regulation of aggressive behavior (Demas *et al.*, 2023). Melatonin is secreted by the pineal gland, a structure located between the cerebellum and cerebral cortex in mammals. Melatonin secretion is high during the night and low during the day; therefore, changes in day length, or photoperiod, result in changes in the pattern and duration of melatonin secretion. For example, some species of seasonally-breeding rodents, such as Siberian hamsters, breed during the summer, when there is a longer photoperiod. During the summer, the duration of melatonin secretion is short compared to the winter. Circulating melatonin binds to melatonin receptors in the gonads and adrenal glands, resulting in a decrease in gonadal steroid synthesis and an increase in adrenal DHEA synthesis (**Fig. 2**).

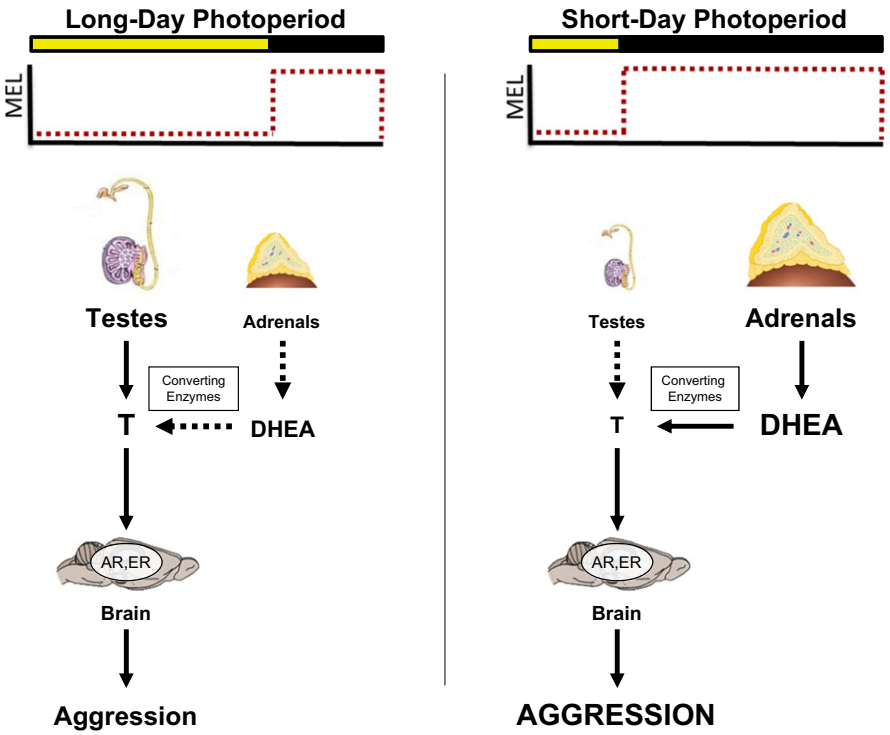

Fig. 2 Theoretical model describing the relationships among melatonin (MEL) secretion, seasonal changes in serum testosterone (T) and dehydroepiandrosterone (DHEA) levels, and aggression in male Siberian hamsters. During the summer, long-day photoperiods (LD) result in a short duration of MEL secretion compared to the short-day photoperiods (SD) of the winter. During LDs, T is secreted from the testes, whereas during SDs, DHEA is secreted by the adrenal glands. Dotted lines and smaller font sizes symbolize less abundant levels of hormones than solid lines and larger font sizes. T can either directly bind to neural androgen receptors (ARs) or can be locally converted to 17β-estradiol and bind to neural estrogen receptors (ERs). Differences in AR and ER binding and/or abundance in the brain result in changes in aggression, and in hamsters, there is higher aggression during SDs than LDs.

There are several potential benefits of using DHEA or neurosteroids as a source of androgens during the non-breeding season (Demas *et al.*, 2023; Munley *et al.*, 2018; Soma *et al.*, 2008). For example, maintaining high levels of aggression year-round may allow individuals to gain access to limited food resources and to defend their territories. Furthermore, the regulation of aggressive behaviors via DHEA might be less energetically costly than sustaining high levels of circulating T. During the breeding season, much energy is devoted to reproductive physiology, such as maintaining the gonads and spermatogenesis, often at the expense of other physiological processes. Chronic elevation of active androgens may induce immunosuppression, a reduction in fat stores, and reproductive instead of survival-oriented behaviors in the non-breeding season (Rubenstein, 2022; Soma *et al.*, 2015; Wingfield *et al.*, 2019). Thus, by using an androgen precursor (e.g., DHEA), which can be locally and rapidly converted to androgens, an individual can exhibit year-round aggression without incurring the costs of maintaining high circulating T levels.

Neural Circuits of Aggression

The regulation of social behaviors, such as aggression, primarily depends on neural circuits. One neural circuit that has been extensively studied is the social behavior network (SBN), a collection of interconnected brain regions or nodes located in the forebrain, midbrain, and hindbrain (Lischinsky and Lin, 2020). In mammals, the SBN consists of six nodes: the extended medial amygdala (medial amygdala and bed nucleus of stria terminalis), lateral septum, preoptic area, anterior hypothalamus, ventromedial hypothalamus, and periaqueductal gray. Because there are many reciprocal projections among nodes of the SBN, each node within this network controls multiple social behaviors, including sexual behavior, parental behavior, and aggressive behavior. When the SBN receives and evaluates external stimuli, it integrates them with internal physiological information and produces an appropriate response with a distinctive activity pattern, thereby producing behavior that is adaptive for a specific context. For example, across nodes, there is a particular pattern of neural activation for sexual behavior, and the same nodes show a different pattern of neural activation for aggressive behavior.

Social behavior emerged early in animal evolution, playing a key role in determining individual survival and fitness. Therefore, its neural control is under strong evolutionary pressures. Neuroanatomical and functional studies that have assessed the distribution, connectivity, and neurochemistry of the SBN have found that this neural circuit is highly conserved across vertebrates and plays similar roles in the regulation of these behaviors (Lischinsky and Lin, 2020). Similarly, the neural circuits and hormones involved in modulating these behaviors are highly conserved in all vertebrate lineages, despite the diversity of social behaviors regulated by this network (e.g., aggression, parental care). Birds, reptiles, amphibians, and teleost fishes all contain nodes of the SBN that are homologous with mammalian counterparts and have similar activation patterns in similar social contexts. The conservation of these nodes enables comparative studies in different species to establish general principles in vertebrates (Lischinsky and Lin, 2020).

More recent work suggests that a broader social decision-making network (SDMN) that encompasses both the SBN and the mesocorticolimbic system regulates social behaviors (O'Connell and Hofmann, 2012). However, its morphological homologs in other vertebrates, such as fishes and amphibians, are less well-defined. The mesocorticolimbic reward system is composed of several interconnected nodes, including the ventral tegmental area (VTA) and nucleus accumbens (NAc). The VTA contains dopaminergic neurons that project to the NAc and other forebrain regions. Signaling from these dopaminergic neurons regulates several behaviors, including activational aspects of motivation, preparatory behavior, and appetitive behavior. Additionally, this system is involved in positive reinforcement, a fundamental aspect for the expression of appetitive-approach behaviors. Like the SBN, the SDMN appeared early in evolution and is also highly conserved across vertebrates (O'Connell and Hofmann, 2012).

Every node of the SBN and SDMN expresses sex steroid receptors, indicating that these brain regions are sensitive to steroids and that hormones play key roles in modulating the activity of these networks and regulating social behaviors (Seib *et al.*, 2023). Sex steroids, such as androgens and estrogens, act on the central nervous system by binding to their intracellular receptors (e.g., ARs and ERs). Upon binding, these receptors modulate gene expression and intracellular signaling cascades. This genomic mechanism of action allows steroid hormones to modulate the activity of different brain regions and act indirectly, but not deterministically, on the execution of a behavior (Adkins-Regan, 2013). For instance, sex steroids can change a stimulus response threshold, such as lowering the threshold (and thus increasing the likelihood) of an aggressive response toward a competitor, but do not typically trigger aggression itself. The genomic effects of steroid hormones on the central nervous system require one hour to several days to develop and produce persistent changes in physiology and behavior (McCarthy *et al.*, 2009).

Sex steroids can also exert short-term (within 30 min) non-genomic effects on behavior, which are often mediated by plasma membrane receptors or by the allosteric modulation of neurotransmitter receptors (Quintana *et al.*, 2021). For example, ERs, such as ERα and ERβ, can be associated with the plasma membrane and rapidly regulate intracellular signaling pathways. Another membrane-associated ER is the G-protein-coupled estrogen receptor-1 (GPER-1), which is also present in the brain. Estrogens rapidly influence aggressive behaviors in songbirds and rodents via intracellular signaling in the SDMN. These rapid effects are more prominent during short-day photoperiods in both mice and song sparrows. Interestingly, E_2 administration rapidly increases aggression exclusively during the non-breeding season in both deer mice (*Peromyscus maniculatus*) and song sparrows. These data suggest that steroids act via non-genomic mechanisms to maintain non-breeding aggression in some seasonally-breeding species.

Furthermore, androgens and estrogens produced by the testes and ovaries are under neural influence via the hypothalamic–pituitary–gonadal (HPG) axis. Within the HPG axis, the hypothalamus integrates neuroendocrine input and environmental stimuli to regulate the release of gonadotropin-releasing hormone (GnRH). In turn, GnRH secretion stimulates the synthesis and

release of luteinizing hormone and follicle-stimulating hormone from the anterior pituitary gland into the bloodstream, which then stimulate the secretion of gonadal sex steroids. Circulating sex steroids reach virtually every cell in the body, including cells in the central nervous system, where they bind to sex steroid receptors and regulate cells in the SBN and SDMN (Balthazart *et al.*, 2018).

In addition to gonadal steroid synthesis, the brain itself is capable of locally synthesizing sex steroids. The brain possesses all necessary enzymes for steroidogenesis and can synthesize active sex steroids called neurosteroids (**Fig. 1**), either from circulating precursors or *de novo* from cholesterol (Soma *et al.*, 2008). Neurosteroids can regulate behavior via actions on the SDMN. In male song sparrows, several brain regions, such as the preoptic area, ventromedial hypothalamus, and bed nucleus of the stria terminalis, contain elevated levels of aromatase year-round except during molt, the only time of year when song sparrows are not aggressive. During molt, aromatase activity decreases in the nucleus taeniae of the amygdala, which is homologous to the mammalian medial amygdala. Like aromatase, the activity of the enzyme 3β-HSD varies with season and social context in male song sparrows: 3β-HSD activity is highest during the non-breeding season in multiple nodes of the SDMN, and an aggressive social interaction rapidly increases 3β-HSD activity. Moreover, Siberian hamsters exhibit seasonal and sex differences in the expression and activity of steroidogenic enzymes in the adrenal glands and brain, despite showing a similar aggressive phenotype during the non-breeding season. Specifically, non-breeding females exhibit reductions in 3β-HSD activity in the anterior hypothalamus relative to breeding females, whereas there is no difference in 3β-HSD activity in this brain region between breeding and non-breeding males (Munley *et al.*, 2022). Moreover, non-breeding hamsters show sex-specific changes in the expression of aromatase and 5α-reductase (an enzyme that converts testosterone to the potent androgen 5α-dihydrotestosterone) in several brain regions associated with aggression (Munley *et al.*, 2023). These local changes in neural steroidogenesis are further supported by studies demonstrating seasonal variation in neurosteroid levels in the brain of male Siberian hamsters and song sparrows (Jalabert *et al.*, 2021; Munley *et al.*, 2023). Together, these data suggest that seasonal plasticity in local neurosteroid production regulates aggressive behavior.

Androgens and Primate Aggression

Aggression has been a central topic of human and non-human primate research for many years (Lischinsky and Lin, 2020). Considerable research indicates the importance of environmental and social influences on the development and expression of primate aggression. Dominance is the most well-known social influence on aggression, and dominance hierarchies are a major organizing principle in many primate societies. Although the hormonal mechanisms of primate aggression have been studied, less is known compared to rodents and songbirds. Most recent studies on the neuroendocrine regulation of primate aggression quantify androgens in feces or urine. While collection of such samples can be performed non-invasively, excreted levels frequently represent a small fraction of plasma levels. In general, high rates of aggression are positively correlated with elevated androgen concentrations in non-human primates. This correlation is observed in seasonal changes in androgens and aggression, sex differences in aggression, and increased aggression at puberty (De Almeida *et al.*, 2015; Soma *et al.*, 2015; Van Goozen *et al.*, 1998).

Many primates reproduce seasonally and offer insights into the relationship between androgens and aggression. In these species, circulating T concentrations often peak during the mating season. In non-seasonal breeders, T levels are not associated with a season, but rather with the presence of competing groups or solitary males, independently of an individual's social status (De Almeida *et al.*, 2015). Although exceptions exist, most research suggests that androgens do not necessarily drive aggression and dominance in non-human primates, but rather play a more complex modulatory role in maintaining aggressive behaviors and promoting aggression in already dominant males (De Almeida *et al.*, 2015). In Japanese macaques (*Macaca fuscata*), seasonal increases in circulating androgens precede seasonal increases in aggression by several months, suggesting that these steroids do not affect aggression in a simple causal way. Furthermore, experimental elevations of T do not reliably increase aggression. In rhesus monkeys (*Macaca mulatta*), injection of human chorionic gonadotropin stimulates T production, but has no consistent effect on rates of aggression. Rather, increased circulating T levels are associated with a heightening of existing behavior, which does not disrupt group stability (Gordon *et al.*, 1979). In contrast, injections of T propionate increase aggression in dominant male long-tailed macaques (*Macaca fascicularis*), but increase submission in subordinate males. When male marmosets (*Callithrix jacchus*) are castrated as neonates and tested as adults, they display high rates of aggression with female partners and low rates with male partners. Moreover, the effects of neonatal castration on aggressive behavior are reversed by T treatment in adulthood. Several studies have found that castration of adult males has little effect on aggressive behavior, suggesting that gonadal T is not required to maintain aggression in adults (Dixson, 1993).

In humans, aggression is often associated with T across all age groups, and competitive scenarios tend to increase T secretion in men. This increase in T levels may prime them for additional competitions, thus escalating aggression. Moreover, exposure to supraphysiological levels of androgens promote displays of aggression in adults and, if the exposure occurs in early life stages, may affect the development of aggressive behaviors (De Almeida *et al.*, 2015).

Some studies in non-human primates also suggest that aggressive behavior is independent of fecal T levels, but related to adrenal androgens (Soma *et al.*, 2015). Although the adrenal glands can secrete high levels of DHEA and DHEA-S, the role of adrenal DHEA and DHEA-S in primate aggression is largely unknown. One study assessed circulating DHEA-S levels in a population of wild baboons and found high DHEA-S concentrations in both males and females and marked age-related decreases in both sexes. DHEA-S levels were not compared with aggressive behaviors, however.

Additionally, DHEA has been implicated in regulating human aggression, but has received only limited experimental attention. In humans, circulating levels of DHEA-S are generally 1000-fold higher than levels of DHEA, 100–500 times higher than T, and 1000–10,000 times higher than E_2. Moreover, dysregulation of circulating DHEA and DHEA-S have been implicated in a variety of psychiatric disorders (Soma *et al.*, 2015). Studies from rodents and songbirds suggest that androgens such as DHEA may regulate aggression in situations where aggression seems otherwise T-independent.

Adrenal DHEA appears to play a role in human aggression, as indicated by studies on "conduct disorders," which are typically defined as a collection of symptoms, including aggression directed toward people or animals, destruction of property, theft, and serious violations of rules. Prepubertal boys with conduct disorder have higher levels of plasma DHEA-S, but not T, than age-matched control boys. Also, DHEA-S concentrations are positively correlated with aggression intensity as rated by parents and teachers (Van Goozen *et al.*, 1998). In another study, plasma DHEA-S concentrations were found to be higher in boys with conduct disorder than in boys with attention-deficit/hyperactivity disorder (ADHD) or age-matched controls. Recent research has examined circulating levels of cortisol, DHEA, and DHEA-S 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. Delinquent boys had higher DHEA-S levels than control boys, but did not show any differences in DHEA or cortisol. Additionally, DHEA circulating levels were correlated with the severity of the most recent aggressive event in children patients of psychiatry hospital units, and with levels of aggression in healthy children (De Almeida *et al.*, 2015). Collectively, these data suggest a positive relationship between DHEA and/or DHEA-S and aggression, at least in male children and adolescents.

Adrenal androgen precursors may also contribute to the regulation of aggression in human females (Soma *et al.*, 2015). Adolescent and adult women with congenital adrenal hyperplasia who are exposed to high levels of DHEA-S in the prenatal and early postnatal periods have greater self-reported aggression ratings than controls. Moreover, a recent study showed that girls with conduct disorder score higher on a clinical aggression scale and have significantly lower cortisol to DHEA ratios compared to control girls, but do not differ in any other hormone measurement. Girls diagnosed with aggressive conduct disorder also have lower cortisol to DHEA ratios than those with non-aggressive conduct disorder (De Almeida *et al.*, 2015).

In addition to regulating aggression in adolescents, DHEA also modulates aggressive behaviors in adults. In a study of alcohol withdrawal, serum levels of DHEA-S and cortisol were quantified in adult alcohol-dependent or healthy control males. Subjects were also treated with dexamethasone, an exogenous steroid, to determine DHEA-S responsiveness. During late alcohol withdrawal, alcohol-dependent subjects display reduced basal and dexamethasone-induced levels of DHEA-S compared with control subjects. When alcohol-dependent subjects were separated into high and low aggression groups, lower basal DHEA-S levels were seen only during early alcohol withdrawal in high aggression individuals. In contrast, DHEA is lower only during late withdrawal in low aggression individuals relative to control subjects. Finally, dexamethasone-induced decreases in DHEA-S were observed during both early and late alcohol withdrawal, whereas lower DHEA levels were only seen during early withdrawal (Ozsoy and Esel, 2008). While the meaning of these results is not entirely clear, these data suggest an important link between DHEA and aggression in humans, at least under conditions of drug withdrawal. Whether a link between DHEA, DHEA-S and aggression exists in healthy adult and adolescent men and women remains to be determined. Regardless, additional research on DHEA and human aggression is warranted.

Conclusion

Aggression is displayed by virtually all organisms and enables individuals to compete for access to limited valuable resources, such as mates and food. Many studies have examined the endocrine and neural regulation of aggression, and this work highlights the importance of steroid hormones, such as testosterone, and brain circuits, such as the social behavior network. Aggression occurs in a range of physiological and social contexts and may be supported by different neuroendocrine mechanisms in different contexts. For example, gonadal sex steroids are important modulators of breeding aggression, but adrenal and brain-derived steroids are critical regulators of non-breeding aggression. Furthermore, sex steroids affect aggression via both genomic and non-genomic mechanisms, and the balance between these two modalities of action is context-dependent. Despite the variability of aggression across species, the neural circuits and endocrine mechanisms that regulate this important behavior are generally well-conserved. Thus, comparative studies in different vertebrate taxa can shed light on common biological mechanisms and general principles that govern aggression.

References

Adkins-Regan, E., 2013. Hormones and Animal Social Behavior. Princeton University Press.

De Almeida, R.M.M., Cabral, J.C.C., Narvaes, R., 2015. Behavioural, hormonal and neurobiological mechanisms of aggressive behaviour in human and nonhuman primates. Physiology & Behavior 143, 121–135

Balthazart, J., Choleris, E., Remage-Healey, L., 2018. Steroids and the brain: 50 Years of research, conceptual shifts and the ascent of non-classical and membrane-initiated actions. Hormones and Behavior 99, 1–8

Cunningham, R.L., Lumia, A.R., McGinnis, M.Y., 2012. Androgen receptors, sex behavior, and aggression. Neuroendocrinology 96, 131–140

Demas, G.E., Cooper, M.A., Albers, H.E., Soma, K.K., 2007. Novel mechanisms underlying neuroendocrine regulation of aggression: A synthesis of rodent, avian, and primate studies. In: Lajtha, A., Blaustein, J.D. (Eds.), Handbook of Neurochemistry and Molecular Neurobiology. Springer, pp. 337–372.

Demas, G.E., Munley, K.M., Jasnow, A.M., 2023. A seasonal switch hypothesis for the neuroendocrine control of aggression. Trends in Endocrinology & Metabolism 34, 799–812
Dixson, A.F., 1993. Sexual and aggressive behaviour of adult male marmosets (Callithrix jacchus) castrated neonatally, prepubertally, or in adulthood. Physiology & Behavior 54, 301–307
Van Goozen, S.H.M., Matthys, W., Cohen-Kettenis, P.T., Thijssen, J.H.H., Van Engeland, H., 1998. Adrenal androgens and aggression in conduct disorder prepubertal boys and normal controls. Biological Psychiatry 43, 156–158
Gordon, T.P., Rose, R.M., Grady, C.L., Berstein, I.S., 1979. Effects of increased testosterone secretion on the behavior of adult male rhesus living in a social group. Folia Primatologica 32, 149–160
Jalabert, C., Ma, C., Soma, K.K., 2021. Profiling of systemic and brain steroids in male songbirds: Seasonal changes in neurosteroids. Journal of Neuroendocrinology 33, e12922
Lischinsky, J.E., Lin, D., 2020. Neural mechanisms of aggression across species. Nature Neuroscience 23, 1317–1328
McCarthy, M.M., Wright, C.L., Schwarz, J.M., 2009. New tricks by an old dogma: Mechanisms of the organizational/activational hypothesis of steroid-mediated sexual differentiation of brain and behavior. Hormones and Behavior 55, 655–665
Munley, K.M., Rendon, N.M., Demas, G.E., 2018. Neural androgen synthesis and aggression: Insights from a seasonally breeding rodent. Frontiers in Endocrinology 9, 136
Munley, K.M., Sinkiewicz, D.M., Szwed, S.M., Demas, G.E., 2023. Sex and seasonal differences in neural steroid sensitivity predict territorial aggression in Siberian hamsters. Hormones and Behavior 154, 105390.
Munley, K.M., Trinidad, J.C., Demas, G.E., 2022. Sex-specific endocrine regulation of seasonal aggression in Siberian hamsters. Proceedings of the Royal Society B 289, 20220668.
Nelson, R.J., 2006. Biology of Aggression. Oxford University Press.
Ozsoy, S., Esel, E., 2008. Hypothalamic–pituitary–adrenal axis activity, dehydroepiandrosterone sulphate and their relationships with aggression in early and late alcohol withdrawal. Progress in Neuro-Psychopharmacology and Biological Psychiatry 32, 340–347.
O'Connell, L.A., Hofmann, H.A., 2012. Evolution of a vertebrate social decision-making network. Science 336, 1154–1157
Pandolfi, M., Scaia, M.F., Fernandez, M.P., 2021. Sexual dimorphism in aggression: Sex-specific fighting strategies across species. Frontiers in Behavioral Neuroscience 15, 136
Quintana, L., Jalabert, C., Fokidis, H.B., Soma, K.K., Zubizarreta, L., 2021. Neuroendocrine mechanisms underlying non-breeding aggression: Common strategies between birds and fish. Frontiers in Neural Circuits 15, 716605.
Rosvall, K.A., Bentz, A.B., George, E.M., 2020. How research on female vertebrates contributes to an expanded challenge hypothesis. Hormones and Behavior 123, 104565.
Rubenstein, D.R., 2022. Animal Behavior. Oxford University Press.
Seib, D.R., Tobiansky, D.J., Meitzen, J., Floresco, S.B., Soma, K.K., 2023. Neurosteroids and the mesocorticolimbic system. Neuroscience & Biobehavioral Reviews 153, 105356.
Soma, K.K., Rendon, N.M., Boonstra, R., Albers, H.E., Demas, G.E., 2015. DHEA effects on brain and behavior: Insights from comparative studies of aggression. The Journal of Steroid Biochemistry and Molecular Biology 145, 261–272
Soma, K.K., Scotti, M.-A.L., Newman, A.E., Charlier, T.D., Demas, G.E., 2008. Novel mechanisms for neuroendocrine regulation of aggression. Frontiers in Neuroendocrinology 29, 476–489
Wingfield, J.C., Goymann, W., Jalabert, C., Soma, K.K., 2019. Concepts derived from the challenge hypothesis. Hormones and Behavior 115, 104550.
Wingfield, J.C., Hegner, R.E., Dufty Jr., A.M., Ball, G.F., 1990. The "challenge hypothesis": Theoretical implications for patterns of testosterone secretion, mating systems, and breeding strategies. The American Naturalist 136, 829–846.