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Review

DHEA effects on brain and behavior: Insights from comparative studies of aggression

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ABSTRACT

Historically, research on the neuroendocrinology of aggression has been dominated by the paradigm that the brain receives sex steroid hormones, such as testosterone (T), from the gonads, and then these gonadal hormones modulate behaviorally relevant neural circuits. While this paradigm has been extremely useful for advancing the field, recent studies reveal important alternatives. For example, most vertebrate species are seasonal breeders, and many species show aggression outside of the breeding season, when the gonads are regressed and circulating levels of gonadal steroids are relatively low. Studies in diverse avian and mammalian species suggest that adrenal dehydroepiandrosterone (DHEA), an androgen precursor and prohormone, is important for the expression of aggression when gonadal T synthesis is low. Circulating DHEA can be converted into active sex steroids within the brain. In addition, the brain can synthesize sex steroids de novo from cholesterol, thereby uncoupling brain steroid levels from circulating steroid levels. These alternative mechanisms to provide sex steroids to specific neural circuits may have evolved to avoid the costs of high circulating T levels during the non-breeding season. Physiological indicators of season (e.g., melatonin) may allow animals to switch from one neuroendocrine mechanism to another across the year. DHEA and neurosteroids are likely to be important for the control of multiple behaviors in many species, including humans. These studies yield fundamental insights into the regulation of DHEA secretion, the mechanisms by which DHEA affects behavior, and the brain regions and neural processes that are modulated by DHEA. It is clear that the brain is an important site of DHEA synthesis and action.

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1. Introduction

Aggression is an extremely important social behavior displayed across vertebrate species that serves a wide range of adaptive functions. Despite its importance, the neuroendocrine mechanisms that regulate this critical social behavior remain, in many respects, unknown. Aggressive behavior occurs when two or more individuals compete for a limited resource such as space, mates, or food. Attainment of the limited resource can facilitate reproductive success and survival. Aggression has been defined as an overt behavior with the intention of inflicting physical damage upon another individual [1]. Moyer [1] divided aggression into specific types, including predatory aggression, inter-male aggression, fear-induced aggression, irritable aggression, maternal aggression, territorial defense and instrumental aggression, based on the social context in which the behavior is elicited. Subsequently, a simplified classification of aggressive behavior was suggested in which aggression is divided into offensive and defensive aggression [2]. Offensive aggression describes behaviors that are used in attack, whereas defensive aggression refers to behaviors that do not involve an active approach to the opponent, but rather serve as a protection against an attack. In either classification system, while different types of aggression can share specific behavioral features, the underlying neuroendocrine mechanisms can differ markedly.

Aggressive behavior has been studied both in the laboratory and under natural conditions, in a wide range of species and contexts. The experimental conditions used, the types of aggression measured, and the species tested can vary greatly across studies [3]. This variation is an important consideration when comparing studies. Although a relatively large number of experimental paradigms have been developed to evaluate aggression in animal models, one of the most prevalent models for assessing offensive aggression in rodents is the resident-intruder model. This model involves introducing an "intruder" into the home cage (or territory) of an experimental subject that has been housed in this cage for several days to ensure territoriality [4]. Then the amount, latency, and duration of aggressive behaviors (e.g., chases, attacks, bites) are quantified. Similarly, in studies of birds, a simulated territorial intrusion (using a decoy and/or song playback) is commonly used to quantify territorial aggression in captive subjects or in free-living subjects in their natural habitat [5–7]. In rodent studies, a less-commonly employed but nonetheless useful model is the neutral arena model, which involves placing two animals in a novel "neutral" cage and recording the amount of aggression directed toward each animal [8]. The neutral arena model assesses the formation of a dominance relationship because territories have not been established at the time of testing.

Much of the research on the neuroendocrinology of aggression has focused on the gonadal androgen testosterone (T) as the primary factor regulating aggression, most often in males [9,10]. Far fewer studies have examined other physiological factors such as dehydroepiandrosterone (DHEA) or 17β-estradiol (E_2). It is evident that multiple hormones orchestrate complex social behaviors such as aggression. For example, circulating T is converted to E_2 by aromatase within specific neurons, and E_2 regulates male aggressive behavior in many cases [11,12]. Alternatively, the androgen precursor DHEA is synthesized in extra-gonadal organs, such as the adrenal glands, liver, and brain. Adrenal steroids, as well as neurally synthesized steroids (neurosteroids), may play important roles in regulating aggressive responses [13–15]. Collectively, these results have elucidated several possible pathways by which steroids can act on the brain to affect aggression as well as other social behaviors (Fig. 1). While numerous endocrine and neural factors affect social behavior, this review will focus on emerging evidence suggesting a key role for DHEA in the regulation of aggression, including a discussion of the potential mechanisms and sites of action.

It is important to note that there is a long evolutionary history that separates birds from mammals, and these divergent lineages may have evolved different mechanisms that account for variation across comparative studies. The evolutionary lineages giving rise to the Diapsida (reptiles and birds) and the Synapsida (mammals) diverged approximately 310 million years ago (MYA). Mammals are represented in the fossil record about 220 MYA, whereas birds appeared in the fossil record about 150–200 MYA, when they diverged from reptiles. This shows deep evolutionary divergence between the two classes of vertebrates discussed in this review. Further, within the mammalian clade, rodents and primates diverged about 60 MYA [16–18]. Nonetheless, the similar ecological problem faced by these different organisms – the need for aggressive behavior to defend a limited resource, even when circulating T levels are low – may have resulted in a broadly similar solution in terms of the underlying physiological mechanisms.

2. DHEA and avian aggression

Most of the approximately 9000 extant avian species show seasonal breeding, with distinct breeding and non-breeding seasons. 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 territorial aggression throughout the year [19]. Often the territoriality expressed during the reproductive and non-reproductive seasons is quantitatively and qualitatively similar [20,21]. 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 [11,12,20,22].

Several studies have focused on non-breeding aggression in song sparrows (*Melospiza melodia*), a common small North American songbird [11,12,20,23,24]. In certain populations, male song sparrows are highly territorial during the spring (breeding season) and also autumn/winter (non-breeding season) [21]. However, during the non-breeding season the testes are completely regressed (≤1 mm in length) and plasma T levels are very low or non-detectable [25]. Furthermore, castration of non-breeding male song sparrows has no effect on territorial aggression in autumn [26]. 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 non-steroidal aromatase inhibitor fadrozole in the non-breeding season [11]. Chronic fadrozole treatment strongly

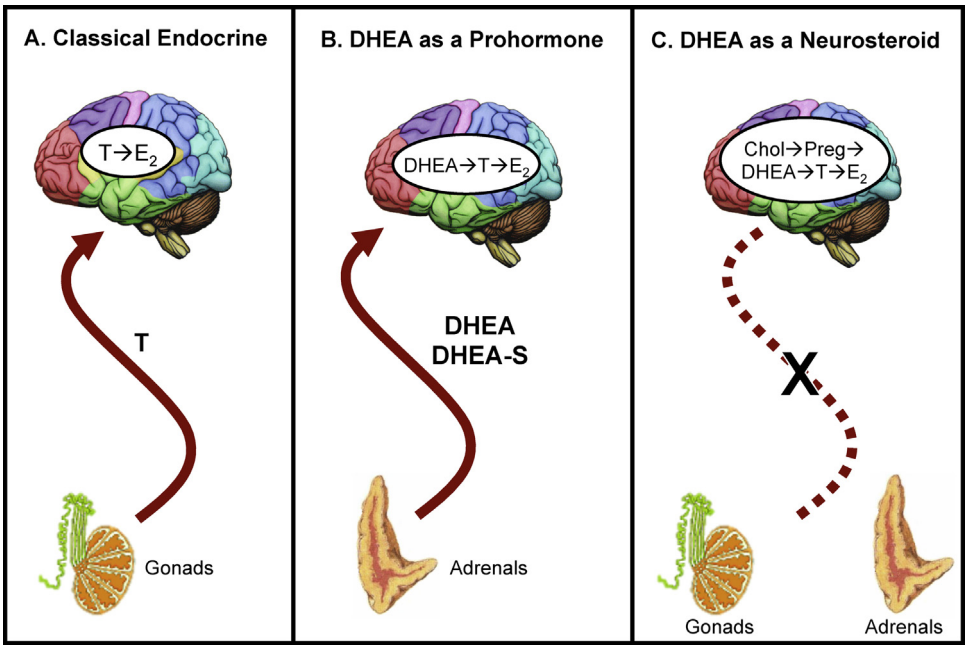

Fig. 1. Steroids can act on the brain to modulate aggression via several pathways: (A) Gonadal testosterone (T) can act directly or via local conversion to estradiol (E_2); (B) Adrenal dehydroepiandrosterone (DHEA) can act via local conversion to T and/or E_2; (C) DHEA can be produced in the brain and then be converted to T and/or E_2.

decreases aggressive behavior in non-breeding song sparrows [11]. Moreover, the effects of fadrozole are rescued by E_2 replacement [11]. These data suggest that sex steroids, in particular estrogens, are necessary for the expression of male aggressive behavior in the non-breeding season, even though plasma sex steroid levels are non-detectable at this time of year [11]. Similar results were obtained in two other field experiments, one of which demonstrated effects of acute (~24 h) fadrozole treatment in the non-breeding season [12,27]. Other studies demonstrate that aromatase, ERα and ERβ are expressed at very high levels in specific regions of the song sparrow brain [25,28].

The source of androgen substrate for brain aromatase in the non-breeding season could indirectly be circulating DHEA [20]. Whereas DHEA cannot be directly aromatized, DHEA can be metabolized by the enzyme 3β-HSD to androstenedione, an aromatizable androgen. In contrast to T and E_2, DHEA is detectable and elevated in the circulation of non-breeding song sparrows [20,29–35]. Further, seasonal changes in circulating DHEA levels generally match seasonal changes in aggression; both are reduced during the annual molt (August/September), when song sparrows replace their feathers [20,32]. More recently, the initial data on plasma DHEA levels collected by radioimmunoassay were confirmed by liquid chromatography–tandem mass spectrometry [36].

DHEA concentrations in the adrenals and regressed testes of non-breeding song sparrows are much higher than DHEA concentrations in the plasma, suggesting that both of these organs could secrete DHEA into the general circulation [20,33]. However, note that restraint stress and GnRH challenges do not increase systemic DHEA levels [20]. More recent studies in song sparrows suggest that the liver can have high concentrations of DHEA [34] but further studies are required to determine whether the liver can synthesize and secrete DHEA into the general circulation. In this regard, note that studies in mice and zebra finches (*Taeniopygia guttata*) suggest that fasting induces hepatic DHEA synthesis and secretion [37–39]. In recent work with captive song sparrows, we found that an acute fast (6 h) increases aggressive behavior in the breeding and non-breeding seasons and increases systemic DHEA levels in the breeding season (H.B. Fokidis et al., unpublished results).

Furthermore, DHEA concentrations in the song sparrow brain are very high (3–20 times higher than plasma concentrations, depending on the brain region), and these data are consistent with neural synthesis of DHEA as a neurosteroid [33] (S.A. Heimovics et al., unpublished results). Further, in the non-breeding season, a 30-min simulated territorial intrusion does not affect DHEA levels in plasma from the brachial vein (indicative of systemic levels in the general circulation) but does increase DHEA levels in plasma from the jugular vein exiting the brain (enriched with neurally synthesized steroids) [34]. Taken together, these data suggest that, in addition to being synthesized in the periphery, DHEA is synthesized de novo from cholesterol in the brain. Local production of DHEA is plausible given that the avian brain expresses the proteins required for neurosteroid production, including StAR, cytochrome P450 side-chain cleavage (P450scc or CYP11A1) and cytochrome P450 17α-hydroxylase/17,20-lyase (P450c17 or CYP17A1) [6,40–43].

Treatment of non-breeding male song sparrows with a physiological dose of DHEA increases territorial singing and the size of HVC, a telencephalic brain region involved in the production of song [44]. In adult song sparrows, DHEA treatment also increases the number of neurons in HVC, the incorporation of newly born cells into HVC, and the number of immature new neurons in HVC [31,45]. DHEA treatment is also effective in blocking some of the negative effects of chronic corticosterone treatment on the adult songbird brain [31,45]. These are some of the largest reported effects of DHEA on adult neuroplasticity, and similar to the effects of T and E_2 on song behavior and HVC [46]. However, DHEA treatment does not affect other territorial behaviors or, importantly, T-dependent secondary sexual characteristics [44]. Other studies demonstrate that treatment with DHEA, unlike T, does not suppress immune function in song sparrows [47].

Further investigations examined the metabolism of DHEA to active sex steroids within the songbird brain [46,48,49]. To do so, brain tissue was 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. ^{3}H-androstenedione can be metabolized subsequently to ^{3}H–T or ^{3}H-estrogens. In captive

adult zebra finches, brain tissue readily metabolizes ^{3}H-DHEA to ^{3}H-androstenedione, which is in turn aromatized to ^{3}H-estrone. Importantly, trilostane, a 3β-HSD inhibitor, blocks the production of ^{3}H-androstenedione, and fadrozole, an aromatase inhibitor, blocks the production of ^{3}H-estrogens. Song sparrow brain tissue also robustly converts DHEA to androgens and estrogens [35]. Brain 3β-HSD activity is higher during the non-breeding season than the breeding season, consistent with a greater role for local steroid synthesis in the non-breeding season. Moreover, aggressive interactions strongly and rapidly (within 30 min) upregulate brain 3β-HSD activity in the non-breeding season [35]. Taken together, these data support the hypothesis that non-breeding song sparrows combine peripheral and neural DHEA synthesis with neural DHEA metabolism to androgens and estrogens.

Recent data suggest that neurally formed estrogens can rapidly affect aggressive behavior and relevant brain circuits. We non-invasively administered E_2 to breeding and non-breeding male song sparrows in captivity. Remarkably, in non-breeding subjects only, E_2 treatment rapidly increased aggression toward an "intruder" in a neighboring cage within 20 min of administration (S.A. Heimovics et al., unpublished results). This is a timeframe that is incompatible with a genomic mechanism of action. To identify possible underlying neural mechanisms, in a separate study, we administered E_2 and after 15 min looked for rapid changes in the levels of 3 different phosphoproteins: phosphorylated extracellular signal-regulated kinase (pERK), phosphorylated tyrosine hydroxylase (pTH), and phosphorylated cAMP response element binding protein (pCREB) [50]. We examined a wide range of brain regions involved in social behavior. Of note, pCREB levels in the medial preoptic nucleus (POM) were rapidly decreased by E_2 in the non-breeding season only [50]. These data suggest that POM neurons may tonically inhibit aggression and that E_2 may cause rapid disinhibition in the non-breeding season. The G protein-coupled receptor GPER-1 (or GPR30) is a membrane-bound receptor for E_2 [51], and we have immunohistochemical evidence for GPER-1 in the POM of song sparrows (C. Ma et al., unpublished results).

Studies in other avian species have examined the role of DHEA in male and female aggressive behavior. For example, the spotted antbird (*Hylophylax naevioides*) is a tropical species in Central America that exhibits year-round territorial aggression [52]. Despite the presence of year-round territorial aggression, these birds generally have low or non-detectable levels of plasma T, even during the breeding season [53]. Nonetheless, experiments have shown that T or its estrogenic metabolites do play a role in male territoriality [53]. A study examined male and female antbirds during the non-breeding season [52]. The results indicate that both sexes exhibit robust aggressive behavior during the non-breeding season, and in both sexes, plasma DHEA levels are detectable and higher than plasma T and E_2 levels [52]. 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 [52].

These data suggest a shift from systemic to local sex steroid production and signaling in the brains of non-breeding song sparrows and perhaps other birds. This shift may have evolved in order to avoid the costs of chronically elevated steroid hormones in the blood. For example, systemic T treatment in the non-breeding season suppresses cell-mediated and humoral immune responses in European starlings [54]. Elevated circulating T also decreases body mass and fat stores, which are essential for surviving snow storms and the low overnight temperatures during the non-breeding season. Systemic T also stimulates the development of secondary sexual characteristics and activates reproductive behaviors, which are energetically expensive and inappropriate in the non-breeding season. From an evolutionary perspective, the regulation of non-breeding aggression may have become dissociated from systemic steroid signaling in order to reduce the exposure of peripheral tissues and other brain areas to T and E_2. Importantly, this insight was made possible by field studies of wild birds in their natural habitat, which complement studies of rodents in controlled laboratory settings.

3. DHEA and mammalian aggression

Mammalian studies of aggression have predominantly focused on the role of T in males. These studies have revealed regulation by T in some mammalian species [55–59] but not others [10,60,61], suggesting that there are species-specific adaptations. Nonetheless, comparative studies can shed light on common themes and general principles. In fact, it is increasingly clear that DHEA is an important regulator of aggression, especially in rodent species other than rats and mice [10,60,61]. Like birds, studies of mammalian species that display seasonal changes in gonadal hormones and aggression have been useful for expanding this working paradigm to female aggression and aggression in non-reproductive contexts and have subsequently revealed novel mechanisms of aggression.

3.1. DHEA and rodent aggression

3.1.1. DHEA synthesis and metabolism

DHEA and DHEA-sulfate (DHEA-S) are not secreted in appreciable amounts by the adrenal cortices of laboratory rats and mice [62–66], but they are clearly secreted by the adrenal cortices of other rodents, such as hamsters and squirrels [67–72]. Circulating DHEA can cross the blood–brain–barrier and be metabolized to active androgens and estrogens within the brain, as the rodent brain expresses critical steroidogenic enzymes such as aromatase, 3β-HSD, and 17β-HSD [73–78]. In addition, the rodent brain is capable of de novo steroid synthesis from cholesterol [13,14,63,64,79–81]. The concept of "neurosteroids" (i.e., brain-derived steroids) was first introduced to describe the high levels of DHEA and purported DHEA-S seen in the rat brain, even after castration and adrenalectomy [62,66]. It is now clear that DHEA and other steroids (e.g., allopregnanolone) can be synthesized de novo from cholesterol within the rodent brain and can act locally on specific neural substrates to regulate behavior [15]. For example, in mice, male–male aggression is associated with changes in neurosteroid synthesis [82]. While DHEA is found throughout the adult rodent brain, it is still not entirely clear how DHEA is synthesized, given that a key DHEA-synthetic enzyme (P450c17 or CYP17A1) is detected in some studies [83–85] but not detected in other studies (reviewed in: [80]). Alternative mechanisms of brain DHEA synthesis, independent of P450c17 activity, have been proposed, but this issue remains unclear [86,87].

Pharmacological inhibition of steroid sulfatase, the enzyme that converts DHEA-S to DHEA, increases aggression in male mice [88]. In addition, DHEA-S administration acutely increases aggression in a neutral arena test [88]. More recently, the neural expression levels of steroid sulfatase, sulfotransferase, and sulfatase-modifying factors were associated with inter-strain differences in mouse aggression [89]. Taken together, these results suggest an important role for DHEA-S in rodent aggression.

3.1.2. Possible mechanisms of action

DHEA has very low affinity for the androgen receptor (AR) and estrogen receptors (ERα and ERβ) [90]. Thus, very high local levels of DHEA would be required to activate brain AR or ER to affect behavior. It has been suggested that some neurosteroids were ligands for the ancestral ER and progesterone receptor, based on structure–function analyses [91].

As described above, the rodent brain expresses aromatase, 3β-HSD, and 17β-HSD, and thus it can convert circulating DHEA and/or neurally synthesized DHEA into active androgens and estrogens in a region-specific manner [81,83–86,92–95] Locally produced androgens and estrogens can then bind with high affinity to intracellular AR or ER as well as membrane-associated AR or ER (e.g., GPER-1) in neurons and glia. This is likely a key mechanism by which DHEA affects aggressive behavior in rodents.

In addition, DHEA may have neural effects that do not require prior conversion to androgens or estrogens. For example, DHEA can modulate γ-aminobutyric acid (GABA) neurotransmission via binding to $GABA_A$ receptors [14,63,64,79,96,97]. DHEA also modulates other neurotransmitter receptors, including N-methyl-D-aspartate (NMDA) receptors and sigma receptors [13,14,63,64,79,80,96–99]. Recent work suggests that DHEA directly binds to nerve growth factor receptors [100–102], consistent with the idea that DHEA is a neurotrophic factor and involved in neurogenesis and neuronal survival [97,103].

3.1.3. Seasonal changes in endocrine function

Much of the recent work on DHEA and rodent aggression has been conducted in a seasonal context, taking advantage of endocrine changes that occur naturally in the field or in the laboratory in response to experimental manipulations of photoperiod [10,60,61]. Note that laboratory rats and mice do not show large changes in reproductive function in response to photoperiod manipulations and are typically housed under 12 h of light (12L:12D) [104–107]. For such reasons, the importance of photoperiod and seasonality in neuroendocrine function and behavior in mammals is widely underappreciated [10,60,61,104,105].

There are over 2000 species of rodents (~40% of the total number of extant mammalian species). Most of the rodent species that live in the temperate zone are seasonal breeders, maintaining reproductive function during summer and suppressing it during winter. Photoperiod is the main environmental cue used by rodents (and most other species) to appropriately time reproduction [108]. For example, in hamsters, reproductive activity occurs during long "summer-like" days (e.g., >12.5 h of light), whereas reproductive suppression, including profound regression of the gonads and marked decreases in circulating T and E_2 levels, occurs during short "winter-like" days (e.g., <12.5 h of light) [108]. Short-day exposure decreases circulating T levels in male hamsters but can increase circulating DHEA levels [68].

3.1.4. Seasonal aggression in males

Male Syrian hamsters (*Mesocricetus auratus*) in short days display *increased* territorial aggression compared with subjects in long days, despite gonadal regression and low circulating T levels in short-day animals [68,109,110]. Short-day exposure, however, does not affect the frequency of flank marking, a form of social communication thought to be androgen-dependent [111]. In males on short days, flank marking continues to be displayed at high levels during social encounters and in response to conspecific odors, even though circulating levels of T are low [9,68,111,112]. These findings support the idea that factors other than T regulate flank marking, as well as overt aggression, in this species. After prolonged maintenance in short days (>15 weeks), hamsters typically undergo spontaneous gonadal recrudescence (i.e., increased gonad mass and circulating T levels), despite continued maintenance on short days. In such animals, levels of aggression decrease and resemble those of long-day animals by ~21 weeks [109].

The Siberian hamster (*Phodopus sungorus*) is another seasonally breeding and well-studied rodent species. Like Syrian hamsters, short-day male Siberian hamsters are considerably more aggressive than long-day subjects [110,113]. Specifically, male Siberian hamsters housed in short days (8L:16D) for 10 weeks display a greater number of attacks during a resident-intruder test and have a lower latency to initial attack, relative to subjects in long days (16L:8D). Note that short-day subjects have regressed testes and low circulating levels of T. Prolonged maintenance in short days (20 weeks) resulted in spontaneous gonadal recrudescence, in which gonad mass and circulating T levels returned to long-day levels [113]. Gonadally recrudesced subjects displayed less aggression than gonadally regressed subjects, even though both of these groups experienced the same short photoperiod; levels of aggression in gonadally recrudesced hamsters were similar to those of long-day hamsters [113]. Furthermore, when short-day male Siberian hamsters were implanted with capsules containing T, aggression *decreased* compared with short-day control animals [113], suggesting that short-day increases in aggression are *inversely* related to serum T concentrations.

In Siberian hamsters, serum DHEA levels are elevated under short days, when aggression is also elevated, however, neither short-term nor long-term treatments with exogenous DHEA increase aggression in either long-day or short-day subjects, suggesting that endogenous DHEA levels are not limiting [71,72]. It remains possible that neural conversion of DHEA to androgens or estrogens is the limiting step and that giving exogenous DHEA does not increase the levels of biologically active steroids (e.g., T, E_2) in the brain. Thus, elevated DHEA might be necessary but not sufficient to elicit increased aggression in this and other species.

To further test the hypothesis that changes in DHEA levels or DHEA metabolism regulate aggression in male Siberian hamsters, serum DHEA levels were assessed prior to and in response to an aggressive interaction [72]. DHEA and T concentrations were also measured during the day (noon) and the night (midnight). Although there were no significant differences in serum DHEA concentrations between these times, there was a trend toward reduced circulating levels of DHEA at midnight [72]. In contrast, in male Syrian hamsters, there are robust diel changes in circulating DHEA levels, and DHEA levels peak 30 min prior to lights-off and remain elevated during the night [70]. Further, in Siberian hamsters, post-aggression DHEA levels were lower than pre-aggression DHEA levels, but only in animals tested during the night and not during the day [72]. A different pattern of results was found for serum T levels. Post-aggression T levels were higher than pre-aggression T levels, but again only during the night. Consistent with these results, aggression was greater during the night, when circulating levels of melatonin are at their peak. These data suggest that circulating DHEA may be converted to active sex steroids within the brain and thereby influence aggressive behavior. The enzyme 3β-HSD catalyzes the conversion of DHEA to androstenedione, which can then be converted by 17β-HSD to T. Aggressive encounters at night may cause rapid increases in 3β-HSD or 17β-HSD activity in the brain or periphery.

An alternative mechanism underlying short day increases in aggression involves nitric oxide (NO). Reduced NO levels are associated with short day increases in aggression, and aggression is negatively correlated with neuronal nitric oxide synthase (nNOS) expression in brain regions known to regulate aggression [114]. It has also been shown that adrenalectomy blocks nNOS [115] and short day increases in aggression [116], suggesting that nNOS is regulated by adrenal hormones. In another study, however, serum DHEA levels were not altered in short days or with pharmacological blockade of nNOS [117]. These data suggest that an interplay among steroids, nNOS, and NO may be involved in the regulation of aggression, but these interactions are still not clear. Unlike other species, the adaptive function of "winter" aggression in hamsters is not known, due to limited availability of life history information for these species. Presumably, protection of a territory during times of reduced food availability would ensure overwinter

survival (e.g., as in red squirrels [67]), but this hypothesis remains to be tested.

3.1.5. Seasonal aggression in females

In Syrian hamsters, unlike most rodent species, females are more aggressive than males [118,119]. Photoperiodic changes in aggression have been demonstrated in female Syrian hamsters [69,120,121]. Female hamsters were housed in long days (14L:10D) or short days (6L:18D) for 12 weeks, and then both offensive and defensive aggression were tested [121]. Female hamsters maintained in short days displayed less defensive aggression than those in long days, and thus had a higher ratio of offensive to defensive aggression than long-day animals [121]. To further examine the physiological mechanisms mediating short-day aggression in females of this species, the effects of short days on circulating levels of adrenal steroids were assessed [69]. Short-day females were more aggressive than long-day females, had lower serum cortisol and DHEA levels, but higher serum DHEA-S levels [69]. Further, exogenous E_2 reduced aggression in long-day but not short-day hamsters [69]. These interesting data suggest that DHEA-S may play a role in promoting female aggression in this species.

In female Siberian hamsters, aggression is increased during the non-breeding season. Increased secretion of DHEA by the adrenal glands during the non-breeding season may be involved, but this has not been directly tested. In a pilot study of long- and short-day female Siberian hamsters, an ACTH challenge was administered and serum DHEA and cortisol levels were measured after 30, 60, and 120 min. These values were compared to baseline levels before the ACTH challenge. In both long- and short-day females, cortisol levels are significantly elevated at 30 and 60 min, and then return to baseline by 120 min (Fig. 2). Interestingly, DHEA levels are significantly elevated at 30 and 60 min, but only in short-day females and not in long-day females (Fig. 2). As expected, aggression is significantly elevated in short- compared to long-days females (Fig. 2). This effect of photoperiod is specific to aggression; other social behaviors including ano-genital investigation, facial investigation, and grooming do not differ between photoperiods (Fig. 2; N. Rendon and G. Demas, unpublished data). These data demonstrate that short-day females are more aggressive and have a more sensitive HPA axis, at least with respect to DHEA secretion, than long-day females, consistent with a role for DHEA in female aggression.

In female and male red squirrels (*Tamiasciurus hudsonicus*), circulating DHEA levels at baseline and in response to ACTH challenges were examined in the field under natural conditions in northern Canada [67]. Both females and males of this species are highly aggressive during both the breeding and non-breeding seasons, in order to defend food stores on their territories that are essential for overwinter survival. Red squirrels display considerably higher circulating levels of DHEA than those seen in laboratory rats and mice [67]. During the breeding season (summer), females have much higher circulating DHEA levels than males. In both females and males, serum DHEA levels rapidly increased following ACTH challenges, suggesting that circulating DHEA is secreted by adrenocortical cells. While aggression was not specifically addressed, these findings demonstrate that DHEA levels are elevated at times of high territorial aggression in the field.

3.1.6. Pineal melatonin and seasonal aggression

In virtually all mammals, photoperiodic responses are mediated by changes in the pineal indolamine melatonin. Melatonin is secreted by the pineal gland into the general circulation predominantly during darkness, whereas light inhibits pineal melatonin secretion [108]. Thus, changes in day length result in changes in the pattern of melatonin secretion. It is the precise pattern of melatonin secretion, and not the amount of melatonin per se, that provides a biochemical "code" for day length [108].

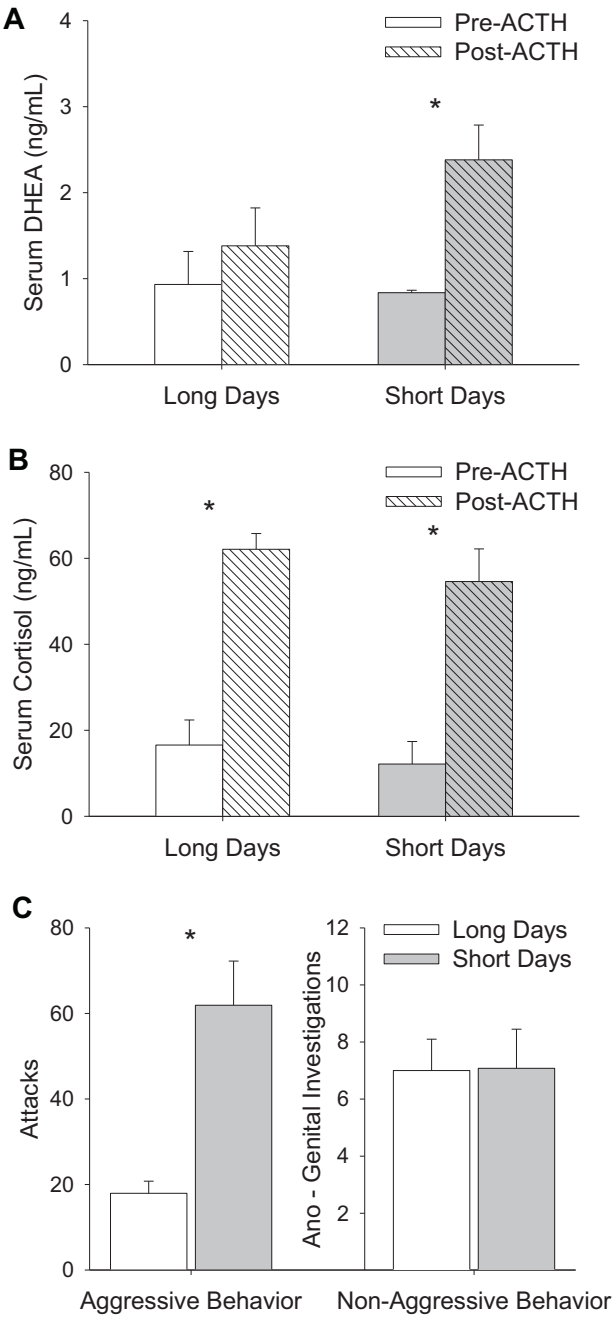

Fig. 2. HPA axis reactivity and aggression in female Siberian hamsters in long days and short days at 2 h into the light phase. (A) At 30 min after an ACTH challenge, serum DHEA was significantly elevated in short-day females but not long-day females. (B) At 30 min after an ACTH challenge, serum cortisol was significantly elevated in both groups. (C) Aggression was significantly higher in short-day females than long-day females, but non-aggressive behaviors (ano-genital investigation and other social behaviors) were not different. N.M. Rendon and G.E. Demas, unpublished results.

In male Syrian hamsters, timed daily melatonin injections (that mimic short-day patterns of melatonin) to long-day subjects increase aggression. Because these melatonin injections occurred for only 10 days, testes mass and circulating levels of T were unaffected, supporting the idea that photoperiodic changes in aggression are independent of gonadal steroids [110]. In female Syrian hamsters, pinealectomy decreases aggression in short-day subjects, whereas melatonin treatment increases aggression in long-day subjects [121]. Ovariectomy, in contrast, has no effect on aggression. In a subsequent study of female Syrian hamsters,

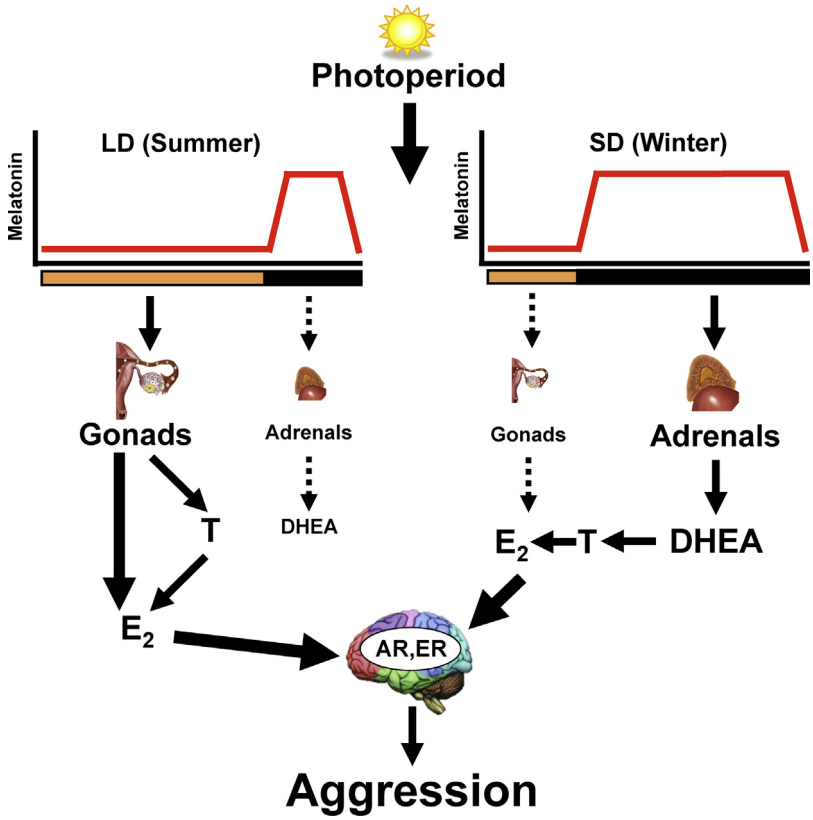

Fig. 3. Theoretical model regarding DHEA and seasonal changes in aggression in Siberian hamsters. Different photoperiods in long days (LD) and short days (SD) produce different melatonin profiles. These melatonin profiles modulate many physiological systems, including those that regulate aggression. During LD, sex steroid hormones are predominantly from a gonadal source (*solid lines*), and during SD, switch to a predominantly adrenal source (*solid lines*). *Dotted lines* symbolize less abundant levels than *solid lines*, showing that serum E_2 is higher in LD than SD, and that adrenal DHEA is lower in LD than SD. During SD, DHEA can act on the brain by serving as a prohormone and being converted to active androgens or estrogens, which can bind to their respective receptors. Further, DHEA may act as a neurosteroid by being produced de novo in the brain.

a higher percentage of subjects showed aggression in short days than in long days [120]. Short-day aggression was attenuated by pinealectomy, but treatment with E_2 (alone or in combination with progesterone) had no effect on aggression. These results also support the hypothesis that photoperiodic changes in aggression are mediated by pineal melatonin, but independent of gonadal steroids, in this species. Future studies should examine the effects of melatonin administration on circulating DHEA levels in Syrian hamsters.

In male Siberian hamsters, treatment of long-day animals with short-day like levels of melatonin also mimics photoperiodic changes in aggression. Long-day hamsters were given daily injections of melatonin 2 h before lights-off, for 10 days, to mimic short-day levels of melatonin, and these subjects displayed elevated aggression when compared with control subjects [116]. As with previous studies, these results were not likely due to changes in gonadal steroids, as serum T levels were unaffected by this injection protocol. More recently, we tested the hypothesis that the pattern of melatonin secretion mediates short-day increases in aggression in female Siberian hamsters. Aggression and circulating levels of DHEA, T and E_2 were examined in long-day and short-day females. Two additional groups of females were housed in long days that received daily "timed" injections of melatonin (2 h before lights-off for 10 weeks) or daily "mis-timed" injections (in the middle of the light phase, which do not mimic a short-day pattern of melatonin). Following 10 weeks of treatment, animals housed in short days or receiving timed melatonin injections displayed reproductive regression and increased aggression. These groups also displayed elevated serum DHEA levels but reduced serum E_2 levels, compared with long-day hamsters. Further, the short-day group and timed melatonin injection group, but not the long-day group or mis-timed melatonin injection group, showed increased serum E_2 levels following an aggression trial, when compared to baseline E_2 levels. Serum DHEA levels were not affected by an aggression trial, but nonetheless circulating DHEA might have provided the substrate for E_2 synthesis (N. Rendon and G. Demas, unpublished results). These data suggest a role for melatonin in female aggression, in DHEA secretion, and also in behaviorally induced E_2 synthesis (Fig. 3).

The effects of melatonin on rodent aggression may be due to direct actions on neural substrates (e.g., hypothalamus, limbic system) or indirect actions via the HPA axis and adrenal hormones [122]. In support of the latter hypothesis, changes in both the size and function of the adrenal gland are associated with changes in aggression [123]. In house mice, males housed in long days and treated with melatonin display increased territorial aggression but decreased adrenal mass compared to saline-treated animals [123]. The increases in aggression displayed by melatonin-treated animals, however, can be blocked by adrenalectomy [123]. Further, pharmacological blockade of ACTH release attenuated melatonin-induced increases in aggression [123]. It is possible that blockade of ACTH release reduced DHEA secretion, but DHEA was not measured in this study. These results are particularly intriguing given that house mice are generally reproductively non-responsive to photoperiod manipulations [106], and further, because melatonin-deficiency observed in house mice may be explained by lack of the gene encoding the HIOMT enzyme, responsible for catalysis of the last step of melatonin synthesis [104].

More recently, research has implicated changes in adrenocortical hormones in mediating melatonin-induced aggression in Siberian hamsters. As described previously, long-day hamsters treated with short-day like levels of melatonin display increased aggression, comparable to levels seen in short-day hamsters [116]. Adrenal demedullation, which eliminates adrenal catecholamines (i.e., epinephrine) but leaves adrenocortical steroids (i.e., cortisol, DHEA), had no effect on melatonin-induced aggression [116]. Collectively, these results support the hypothesis that the effects of exogenous melatonin on aggression are mediated by adrenocortical steroids. However, it is currently not known which class of steroid hormones may mediate this effect, as DHEA and cortisol have both been implicated in aggression in rodents [122,124–127]. Importantly, in laboratory rats and mice, corticosterone is the predominant adrenal glucocorticoid, and these species secrete little to no adrenal DHEA. In contrast, in hamsters, as in humans, cortisol is the predominant adrenal glucocorticoid [128], and both hamsters and humans secrete adrenal DHEA and DHEA-S [69–72,128,129].

Melatonin also facilitates DHEA secretion from adrenal glands in vitro, in both hamsters and mice [60,130]. Specifically, incubation of cultured adrenal glands for 2 h with a combination of ACTH and melatonin results in higher concentrations of DHEA in the culture media compared with ACTH alone. These results suggest that melatonin plays a permissive role in adrenal DHEA secretion. Circulating DHEA may, in turn, be converted to active sex steroids within the brain to influence aggressive behavior. As discussed above, the enzyme 3β-HSD catalyzes the conversion of DHEA to androstenedione, which can then be converted to T. It is possible that increased aggression when melatonin levels are elevated (e.g., short days or nighttime) may be driven by increased adrenal DHEA secretion and subsequent rapid increases in 3β-HSD activity in the brain or periphery thus leading to increased T. Increased 3β-HSD activity would be consistent with the pattern of results in animals tested at nighttime (rapid decrease in DHEA and increase in T levels in serum) previously reported [71]. Taken together, studies of laboratory rats and mice, together with studies of "non-traditional" rodent models, show that DHEA has a central role in an important social behavior such as aggression, in both sexes and across different environments.

3.2. DHEA and non-human primate aggression

In the few non-human primate species that have been examined, the adrenal cortex secretes DHEA and DHEA-S in all cases, but changes in DHEA levels across life stages vary considerably from species to species [131]. The roles of DHEA and DHEA-S in primate aggression are largely unknown. Measurement of fecal androgen metabolites, a common way hormones are measured in non-human primates, may not give a complete picture of plasma androgens or their identities. Further, fecal androgen metabolite levels are dramatically altered by biotic factors such as diet [132]. In some non-human primates, aggression is unrelated to fecal T levels [133,134]. But of course, a lack of a correlation between aggression and fecal T does not necessarily mean that aggression is T-independent [132]. One study has assessed circulating DHEA-S levels in wild baboons [135]. DHEA-S concentrations were high in both male and female baboons and showed marked age-related decreases in both sexes; however, circulating levels of DHEA-S were not compared with aggression [135].

Recently, plasma DHEA-S and cortisol concentrations were assessed in young (6–8 yr) and old (20–27 yr) female rhesus macaques in conjunction with specific behaviors, including aggression [136]. Concentrations of DHEA-S were higher in aggressive young animals than non-aggressive young animals. In older monkeys, high levels of DHEA-S were associated with lower levels of depressive-like behaviors, but not related to aggression [136]. Further, enzymes for DHEA synthesis and metabolism are expressed in several areas of the rhesus macaque brain, with an age-related decrease in hippocampal expression of CYP17A1, 3BHSD1/2 and steroid sulfatase [137,138].

3.3. DHEA and human aggression

Alterations in circulating DHEA and DHEA-S levels have been implicated in a range of psychiatric disorders in humans [139]. The zona reticularis of the human adrenal cortex secretes both DHEA and DHEA-S, but circulating levels of DHEA-S are generally 1000 times higher than those of DHEA. Further, circulating DHEA-S levels are 100–500 times higher than those of T and 1000–10,000 times higher than those of E_2 [140].

3.3.1. DHEA and aggression during childhood and adolescence

High serum DHEA and T levels are associated with increased aggression in children [141]. Several studies have focused on "conduct disorder," typically defined as a collection of symptoms including aggression directed toward people or animals, destruction of property, theft, and serious violations of rules. Pre-pubertal boys with conduct disorder have higher levels of plasma DHEA-S, but not T, than pre-pubertal boys without conduct disorder ([142]; but see: [143]). Also, DHEA-S concentrations were correlated with the intensity of aggression as rated by parents and teachers [142]. In another study, plasma DHEA-S concentrations were higher in boys with conduct disorder than in boys with attention-deficit/hyperactivity disorder (ADHD) or normal controls [144]. DHEA is also positively related to scores on the Brief Rating of Aggression by Children and Adolescents (BRACHA) scale in psychiatrically hospitalized boys between the ages of 7–9 [145]. Specifically, morning levels of both salivary DHEA and T were associated with the severity of the nearest aggressive incident [145]. Lastly, a study examined plasma levels of cortisol, DHEA and DHEA-S in delinquent adolescent boys diagnosed with conduct disorder. Hormone levels were correlated with aggression as determined by the Child Behavior Checklist and the Overt Aggression Scale [146]. Delinquent boys tend to have higher DHEA-S levels than control boys, but did not show any differences in DHEA or cortisol [146]. Collectively, these data suggest a relationship between DHEA-S and aggression in boys, in particular those with conduct disorder.

Adrenal androgen precursors may also affect aggression in girls. Adolescent and adult females with congenital adrenal hyperplasia, who were exposed to high levels of adrenal androgen precursors in the prenatal and early postnatal periods, have greater self-reported aggression ratings than control females [147]. Adrenal androgen precursor levels have also been measured in adolescent girls diagnosed with conduct disorder [148]. Specifically, in adolescent girls with either conduct disorder or no psychiatric disorder, serum samples were assessed for DHEA, DHEA-S, cortisol, as well as gonadal androgens and estrogens. Girls with conduct disorder scored higher on a clinical aggression scale and had a lower cortisol to DHEA ratio but did not differ from control girls on any other hormone measurement [148]. Furthermore, girls with aggressive conduct disorder had a lower cortisol to DHEA ratio than those with non-aggressive conduct disorder. Lastly, a study of 5–6 yr old boys and girls showed that boys displayed more physical, verbal, and indirect aggression than girls, but boys had lower levels of DHEA than girls. Further, boys with directive (i.e., more controlling) mothers displayed more physical aggression than the other boys and girls, showing how the environment can alter behavior [149].

3.3.2. DHEA and aggression during adulthood

More recently, it has been shown that serum DHEA concentrations correlate with criminal activity [150]. DHEA was assessed in individuals with personality disorders who were convicted of

serious violent crimes and compared to mentally healthy subjects convicted of non-violent crimes and to normal healthy control subjects. DHEA concentrations were elevated in criminals, regardless of the type of crime, compared with healthy control subjects [150]. Recent data also suggest that being the recipient of aggression might increase salivary DHEA-S levels [151]. Specifically, subjects who suffered from bullying at work showed elevated scores on tests of anxiety and depression and elevated DHEA-S, but not cortisol, concentrations [151]. However, aggressive behavior of the subjects that were bullied was not examined in this study.

There are important discrepancies among the studies reporting relationships between hormones and aggression in humans [141]. Further, whether a link between DHEA, DHEA-S and aggressive behavior exists in healthy adults and children remains to be determined. In addition, there is a need for experimental studies in humans to make clear conclusions about the role of DHEA in human aggression. Lastly, while the human brain does express the enzymes to metabolize circulating DHEA and DHEA-S, as well as to synthesize steroids de novo from cholesterol, there are many gaps in our knowledge regarding the behavioral functions of neurosteroids in humans [152,153].

4. Conclusions

In many cases across vertebrate taxa, aggressive behavior is positively correlated with circulating T levels. Furthermore, in male rodents, predominantly laboratory rats and mice, castration reduces aggression and T treatment restores aggression [56,154,155]. In birds, a positive correlation between aggression and plasma T levels has been documented during periods of social challenge, particularly during competition for mates [156] However, in many other cases, aggression is independent of or even negatively related to circulating T levels. Seasonal changes in aggression provide a valuable paradigm in which to study the neuroendocrine mechanisms of aggression. In many species, high rates of aggression in males occur outside the period of high circulating T levels [12,109,133]. The neuroendocrine mechanisms regulating aggression under these conditions remain unclear, but recent data provide some interesting possibilities. In some avian species, during the non-breeding season, local steroid synthesis in the brain may play a more important role in promoting territorial aggression [11,12]. In contrast to T, DHEA remains elevated in the blood, and neural conversion of DHEA to sex steroids is up-regulated during the non-breeding season [20,35]. In some rodent species, the neural metabolism of DHEA may also regulate same sex aggression in both males in females when circulating T and E_2 levels are low. Furthermore, melatonin might regulate aggression under these conditions by affecting DHEA secretion by the adrenals or DHEA metabolism by the brain [60,130]. Whether other physiological indicators of photoperiod (e.g., vitamin D_3) play a role in these seasonal changes remains unknown and should be examined.

Humans and non-human primates secrete relatively high levels of DHEA and DHEA-S from the adrenal cortices, but the role of DHEA in primate aggression has received little attention. Recent evidence, however, suggests that plasma DHEA-S levels are associated with conduct disorder, and in particular with the aggressive symptoms of conduct disorder in children [142,148]. While speculative, it is possible that adrenal DHEA and DHEA-S play greater roles in human behavior when circulating androgen levels are low (e.g., before puberty, during aging, hypogonadism, men receiving androgen deprivation therapy for prostate cancer).

The traditional focus on T in the regulation of aggressive behavior has limited our understanding of the diverse neuroendocrine mechanisms that regulate aggression and has contributed to the misperception that a complex social behavior is governed by a single hormone. This traditional focus has also restricted our ability to postulate about the evolution of these diverse mechanisms across taxa. Among several factors recently identified as regulators of aggression, DHEA has received considerable attention. These studies have begun to reveal the varied mechanisms by which DHEA affects the brain and behavior and the wide range of brain regions that are modulated by DHEA. It is increasingly clear that the brain, like the prostate gland and breasts, is an important target of DHEA.

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