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Rapid effects of estrogens on behavior: environmental modulation and molecular mechanisms

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Abstract

Estradiol can modulate neural activity and behavior via both genomic and nongenomic mechanisms. Environmental cues have a major impact on the relative importance of these signaling pathways with significant consequences for behavior. First we consider how photoperiod modulates nongenomic estrogen signaling on behavior. Intriguingly, short days permit rapid effects of estrogens on aggression in both rodents and song sparrows. This highlights the importance of considering photoperiod as a variable in laboratory research. Next we review evidence for rapid effects of estradiol on ecologically-relevant behaviors including aggression, copulation, communication, and learning. We also address the impact of endocrine disruptors on estrogen signaling, such as those found in corncob bedding used in rodent research. Finally, we examine the biochemical mechanisms that may mediate rapid estrogen action on behavior in males and females. A common theme across these topics is that the effects of estrogens on social behaviors vary across different environmental conditions.

Keywords

estradiol; aggression; *Peromyscus*; nongenomic; photoperiod; melatonin; MAPK

1. Introduction

For decades it has been well established that a major pathway of steroid hormone action occurs after receptor binding and requires migration of the hormone-receptor dimer for subsequent regulation of gene transcription [1, 2] (Fig 1). The discovery of estrogen receptor

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genes and their associated hormone response elements provided new insights into how estrogen signaling induces changes in cell function [3, 4]. In general, these so-called genomic mechanisms are considered to be longer latency and to induce long term changes in cell function. Although the expression of some genes can occur within 15 minutes, biologically active protein expression typically does not occur until several hours later [5, 6]. This delayed cellular response presumably contributes to delayed behavioral responses. For example, it takes several weeks of testosterone treatment to restore sexual behavior to normal levels in castrated male Guinea pigs [7].

In seminal studies by Kelly and colleagues [8, 9], however, it was shown that estradiol could alter neuronal activity within seconds, which is usually considered as too rapid to be explained by a genomic mechanism. As interest in these “nongenomic” actions began to increase, it was shown that estradiol could indeed bind to synaptic plasma membranes [10]. This observation suggested that estrogen receptors were inserted in to the plasma membrane. ERα and ERß have since been observed at extranuclear sites such as dendritic spines, axons, and terminals [11-14]. Interestingly, estrogen receptors alpha (ERα) and beta (ERß) in the nucleus and in the cell membrane are synthesized from the same transcript [15]. Estrogen receptors are targeted for membrane insertion by palmitoylation [16], the covalent attachment of a fatty acid such as palmitic acid. This process makes a protein more hydrophobic, thus facilitating insertion in to the lipid bilayer of the membrane [17]. In the hippocampus [12, 18] and hypothalamus [19] palmitoylated estrogen receptors are stored in vesicles that can then be inserted in to the membrane by exocytosis. Rapid effects of ERα are mediated primarily by transactivation of metabotropic glutamate receptors [20]. In addition to ERα and ERβ, several novel receptors have been identified in cell membranes that have the ability to mediate rapid estrogen signaling [21]. A screen of G protein-coupled receptors showed that GPR30 was localized to the endoplasmic reticulum and mediated rapid effects of estradiol on intracellular signaling [22]. Immunohistochemistry studies identified GPR30 in both the membrane and cytoplasm of the forebrain, hypothalamus and midbrain [23, 24]. So far there is little direct evidence for GPR30 mediated effects on behavior (but see Anchan et al., 2014 and Hawley et al., 2014). An alternative membrane receptor (dubbed Gq-mER) has been identified in hypothalamic neurons that mediates rapid estrogen modulation of phospholipase C activity [25]. Hypothalamic neurons expressing mER coexpress POMC or dopamine, which regulate energy balance. Consistent with these observations, systemic injections of the Gq-mER selective agonist STX blocks metabolic disruptions induced by ovariectomy such as increased abdominal fat accumulation [26]. All of these membrane bound receptors have the potential to induce more rapid behavioral and neuronal modifications than originally seen via nuclear ligand-receptor interactions.

Estrogen receptors located on the cell membrane can interact with a variety of cellular processes to induce rapid neuronal and behavioral change, one of which is the mitogen activated protein kinase (MAPK) cascade (Fig 1). Membrane impermeable 17ß-estradiol conjugated with bovine serum albumin (BSA-E_2) has been shown to activate the MAPK cascade, including phosphorylation of extracellular signal-regulated kinase (ERK) [27]. Furthermore, these effects are not inhibited by ERα or ERß antagonists, suggesting that alternative membrane estrogen receptors may be driving these processes [28]. When estradiol or a GPR30 agonist was administered to osteocyte-like cells, MAPK expression

was increased, and this effect was not blocked by estrogen receptor antagonists [29], indicating that estradiol may be acting through GPR30 to affect the MAPK cascade. Knockout of either ERα or ERß, blocks activation of the MAPK cascade [30]. Thus MAPK is regulated by several estrogen sensitive receptors.

There is growing evidence that rapid nongenomic action by estrogens have important effects on behavior. Initially these effects were demonstrated under standardized laboratory conditions. However, it has become clear that the effects of estrogens on behavior are highly dependent on the environment. One of the best examples of this interaction is the interaction between day length (photoperiod) and aggressive behavior [31]. In rodents estrogens act via nongenomic mechanisms under short day photoperiods while in song sparrows nongenomic estrogen action on aggression is observed in winter but not spring. [134] Photoperiodic changes in the environment can be utilized as a prominent cue of temperature change and resource availability in nontropical locations. Photoperiod can also modulate physiological conditions that are associated with aggressive behaviors, which is a behavior that can be associated with territory, resource, and mate defense [32-34].

In the current review we examine the evidence for rapid effects on estrogens on behavior, and consider the importance of the environment. Estrogens have important effects on aggressive behavior, as well as other related social behaviors such as copulation and communication. Although we primarily focus on rodents, we also consider evidence from quail and songbirds, which have higher levels of estrogen production in the brain and are good models for communication. The best described environmental factor modulating rapid action of estradiol is photoperiod [31], but we also consider growing evidence that phytoestrogens and endocrine disruptors can impact molecular pathways that are estradiol sensitive. Finally, we consider the role of ERK and CREB as potential mediators of rapid estrogen action. Rather than acting as an on-off switch, estradiol dependent circuits integrate important environmental signals, such as photoperiod, to regulate behavior.

2. Rapid Effects of Estrogens on Behavior

Estrogens are known to have important effects on a wide variety of social behaviors. Indeed, most species have high concentrations of nuclear estrogen receptors in the social behavior network, a group of interconnected hypothalamic and limbic nuclei [35-37]. Nuclear estrogen receptors are assumed to be irrelevant for rapid estrogen action, yet there is strong evidence that estrogens regulate a wide range of social behaviors via nongenomic mechanisms. One such behavior is aggression, which is tightly coupled with reproductive behavior [32-34] and can be critical for maintaining territorial resources necessary for mating opportunities as well guarding potential mates [38, 39]. Estrogens also modulate individual recognition, which can determine whether an individual decides to engage and aggression. It is also clear that systems regulating visual or auditory displays, which are often utilized during aggressive encounters, are similarly modulated by rapid estrogen action. Thus it is not surprising that estrogens can rapidly affect many behaviors related to aggression such as sexual behavior, communication, and learning, all of which are examined below in the context of mediating social interactions.

2.1 Aggression

Rapid effects of estradiol on aggression have been observed primarily in animals under winter-like photoperiods. In most species of rodents that have been studied, aggression levels are elevated under winter-like short day photoperiods. In some species short photoperiods alter the expression of estrogen receptors in the lateral septum (LS) and the posterior bed nucleus of the stria terminalis (pBNST), suggesting that changes in receptor expression could play an important role in mediating the effects of short days on aggression. For example, under short day photoperiods, male old-field mice (*Peromyscus polionotus*) and deer mice (*Peromyscus maniculatus*) were more aggressive than mice housed under long day photoperiods [40]. Furthermore, the number of ERα-ir cells and ERα mRNA expression in the LS were increased under short days, and the number of ERα-ir cells was correlated with aggressive behavior. In contrast, ERß-ir cells and ERß mRNA expression in the pBNST were downregulated in short days [40]. These results were consistent with knock out studies, which demonstrated that ERαKO mice and ERßKO mice have different aggression phenotypes [41, 42]. Those mice lacking ERαdemonstrated reduced aggression, while mice lacking ERß higher levels of aggression as compared to wild type mice. Similar results were seen in Siberian hamsters (*Phodopus sungorus*) housed in short day photoperiods. Males were more aggressive and had more ERα-ir cells in the BNST and medial amygdala when housed under short days compared to long days [43]. Results from studies on California mice (*Peromyscus californicus*), however, were not consistent with the hypothesis that changes in receptor expression underlie the effects of photoperiod on aggression. California mice housed under short day photoperiods also show an increase in aggression relative to California mice housed under long days [44, 45]. Unlike other species of *Peromyscus* or Siberian hamsters, however, there were no differences in ERα-ir or ERß-ir cells in the LS, BNST, medial preoptic area (MPOA), medial amygdala, paraventricular nucleus, or ventromedial hypothalamus [45]. Unlike these other species, male California mice do not undergo reproductive suppression in short days [46]. These studies suggest that photoperiod induced changes in nuclear estrogen receptors are more closely linked to short-day induced decreases in circulating testosterone, and that they are not directly responsible for the effects of short days on aggression. Also important was the observation that short-day induced increases in aggression occurred independently of gonadal regression in California mice. This observation was consistent with previous work showing that a small population of Siberian hamsters that do not inhibit testes size under short days show elevated aggression levels [47]. This indicates that effects of photoperiod are independent of changes in gonadal hormones, raising the possibility that behaviorally active estrogens are synthesized in the brain.

To more directly examine the effects of ERα and ERß on aggression under different photoperiodic conditions, ERαand ERß specific agonists were administered to old-field mice housed in both short and long day photoperiods [48] (Fig 2). First, mice were housed in either short days or long days and then gonadectomized. Simultaneously, all mice were implanted with an osmotic minipump containing vehicle or fadrozole, a selective aromatase inhibitor. Fadrozole alone decreased aggression in short day mice tested in resident intruder tests, but facilitated aggression in long day mice. If estradiol was added to the minipump, fadrozole had no effect on aggression. Other groups of mice received either the ERα agonist

propylpyrazole-triol (PPT) or the ERß agonist diarylpropionitrile (DPN) in combination with fadrozole treatment. Both PPT and DPN ameliorated the effects of fadrozole on aggression, increasing offensive attacks in short days and decreasing offensive attacks in long days. This was an unanticipated result, as previous studies on knockout mice had demonstrated that deletion of ERα reduced aggression [42], whereas deletion of ERβ knockout mice increased aggression [41]. These results showed that the effects of estrogens on aggression are determined by more than a simple balance between classical estrogen receptor subtypes.

To generate a new hypotheses to explain how photoperiod regulates the effects of estrogens on aggressive behavior, we used microarrays to examine gene expression in the BNST. Previous studies in *Peromyscus* and other rodents have demonstrated that the BNST is an important nucleus that regulates aggressive behavior. Analyses focused on genes that were controlled by estrogen response elements (ERE) in the promoter region [49, 50]. After controlling for the false discovery rate, a total of 11 these ERE controlled genes were differentially expressed in the BNST. Of these 11 genes nine were upregulated in long day mice, suggesting that short days may inhibit the expression of genes regulated by EREs. A follow up qPCR study on one of these genes (*XRCC1*) demonstrated that this upregulation was estrogen dependent. These data provide evidence for weaker gene transcription in the BNST under short days. If short day photoperiods inhibit estrogen-dependent transcription in neural networks controlling aggression, we hypothesized that nongenomic mechanisms may become more important. Unlike genomic pathways, nongenomic effects of estrogens can occur within minutes or seconds [51, 52]. To test this hypothesis, we then examined whether estradiol could act rapidly to control aggression in short days but not long days.

Old-field mice housed under short and long days were castrated and then implanted with a minipump containing fadrozole. After recovery, each mouse received an injection of water soluble estradiol or saline [48]. Fifteen minutes later each mouse was tested in a resident-intruder test. Short day mice receiving estradiol showed an increase in aggressive behavior as compared to short day mice receiving saline. No effect of estradiol was seen in long day mice. This same pattern of results was replicated in California mice [45]. Because gonadal hormones and nuclear estrogen receptor expression are unaffected by short days in California mice, these results suggest that photoperiod modulation of estrogen action is not dependent on these processes. Although rapid action of estrogens on behavior is consistent with a nongenomic mechanism of action, we further tested this hypothesis by testing whether rapid action could be blocked with the use of a protein synthesis inhibitor.

Genomic action of steroids relies on changes in protein expression mediated by steroid receptor binding to promoter regions. If this process is required for the effects of estrogens on aggressive behavior, it should be possible to block the effects of estrogens with a protein synthesis inhibitor such as cycloheximide (CX). California mice were housed under short days or long days and then castrated and treated with fadrozole. After recovery each mouse was injected with either saline or CX 1 hour before resident-intruder tests [53]. Thirty minutes before testing, mice were given an oral dose of cyclodextrin-encapsulated estradiol, cyclodextrin alone, or saline vehicle. In this study estradiol was administered orally to reduce the stress of handling before behavior testing. Estradiol is frequently administered

orally in avian studies [54], and we demonstrated that increasing the dose could produce the same blood levels of estradiol achieved by subcutaneous injection. Estradiol treatment reduced aggression when mice were housed under short days, but not long days (Fig 3). The rapid effects of estradiol on aggression were not blocked by CX treatment, even though it was demonstrated that CX blocked increases in c-fos immunoreactivity. On the one hand these results were consistent with our hypothesis that estradiol acts on aggression via nongenomic pathways under short days. Rapid effects of estradiol were observed under short days but not long days and pretreatment with a protein synthesis inhibitor did not block this rapid effect. On the other hand, the results were surprising because estradiol *decreased* aggression under short days whereas previous studies utilizing *Peromyscus* observed that estradiol administration *increased* aggressive behavior under short days [45, 48]. These conflicting results prompted an anxiety-filled review of all of the differences between the CX study and the initial studies documenting rapid effects of estradiol on aggression.

Eventually it was determined that cage bedding could be a crucial factor impacting the results. In the first two studies [45, 48], corncob was used as cage bedding, whereas the CX study [53] used a cardboard-based bedding (Carefresh). Corncob bedding is attractive for animal facility managers because it is absorbent and has lower dust levels. Corncob bedding, however, is a significant source of phytoestrogens [55]. When the two bedding types were directly compared using California mice housed under short days, we observed that fadrozole increased aggression when Carefresh bedding was used and decreased aggression when corncob was used [56]. These results have important implications because they illustrate that a simple change in cage bedding can have a dramatic impact on experimental results. The estrogenic effects of corncob bedding are discussed further below. Despite these important effects of bedding, a key finding across all of these studies is that photoperiodic modulation of nongenomic estrogen action is a robust phenomenon, and that no matter what type of bedding was used, rapid estrogen action was only observed under winter-like short day photoperiods.

Given that previous microarray data indicated a decrease in estrogen dependent gene expression under short days, we hypothesized that increased levels of melatonin during short days would inhibit estrogen dependent gene expression. Melatonin can affect estrogen signaling via melatonin receptor (MT) dependent and independent mechanisms. When melatonin binds to the MT_1 receptor, cyclic adenosine monophosphate (cAMP) expression is reduced [57], which can lead to a decrease in ERα expression [58]. Melatonin can also bind directly to calmodulin, which acts as a steroid receptor cofactor [59]. By interacting with calmodulin melatonin can inhibit the binding of estrogen receptor dimers to promoter regions. As an initial test of whether melatonin interferes with estrogen-dependent gene expression, California mice housed under long days were administered exogenous melatonin injections or injections with the MT_1/MT_2 antagonist luzindole [60]. Mice receiving melatonin showed increased aggression as compared to mice receiving vehicle injections, however luzindole didn't completely ameliorate the effect of melatonin. This suggests that some of the effects of melatonin on aggression may occur independently of MT receptors. The effects of melatonin and luzindole on estrogen dependent gene expression were also examined to determine whether melatonin might affect downstream gene transcription of

ER's. Although melatonin did not affect estrogen dependent gene expression in the BNST, an interesting effect was observed in the MPOA. Melatonin reduced oxytocin receptor expression and this effect was reversed by luzindole. Although the MPOA is generally not considered to be important for inter-male aggression in rodents [35], recent data suggest that the MPOA may be important under certain contexts. In the MPOA, c-fos expression is elevated following a resident-intruder aggression test in California mice if males are tested under short days [45] or after the birth of pups [61]. Interestingly the MPOA is very important for maternal aggression [62], which raises the question of whether the neural circuitry of aggressive behavior in short days may overlap with mechanism of maternal aggression. Overall, these data do not support the hypothesis that increased aggression under short day photoperiods is strictly mediated by a decrease in estrogen dependent gene expression. An alternative hypothesis is that melatonin may modulate aggression by regulating ERKs (see section on Effects of photoperiod on extracellular regulated kinase below).

The overwhelming majority of laboratory studies are conducted under a standard light cycle of 12L:12D. Based on results in *Peromyscus*, it is unclear how results under a 12L:12D light cycle would generalize to longer or shorter day photoperiods. Some species and strains may be unaffected. For example, photoperiod had no effect on aggressive behavior or estrogen receptor expression in outbred CD-1 mice [63]. On the other hand, some common laboratory strains could be strongly affected. Wistar rats housed under short days showed increased anxiety-like behavior and anhedonia, indicating that behavior in this strain is photoperiod sensitive [64]. Although biomedical science is increasingly seeking standardized conditions to obtain repeatable results, it is important to consider whether results obtained under one set of conditions will generalize to a different environmental context.

2.2 Sexual Behavior

A major goal of aggressive encounters is to obtain mating opportunities, so it is not surprising that estrogens have rapid effects on mating behaviors as well. Cross and Roselli [65] conducted one of the first studies investigating rapid actions of estrogens on copulatory behavior in Sprague-Dawley rats. The authors demonstrated that estradiol rapidly (within 15 – 35 minutes) induced chemoinvestigation and mounting behaviors, and reduced the latency to mount in sexually experienced male rats that had been castrated. Injections of testosterone alone did not change these behaviors, indicating that rapid mediation of copulatory behavior may rely on local estradiol synthesis, and/or conversion of testosterone to estradiol via aromatase activity. Indeed, inhibition of aromatase activity in Japanese quail (*Coturnix japonica*) reduced consummatory and appetitive sexual behaviors [66], with aromatase acting rapidly (within 30 – 45 minutes) to affect these behaviors [67]. Calcium dependent phosphorylation may play a role in the rapid action of aromatase, particularly in the quail preoptic-hypothalamic region [68]. Further study is needed, however, to investigate the role of locally synthesized estrogens in facilitating copulatory behaviors in vertebrates.

Work in male comet goldfish (*Carassius auratus*) has shown similar roles for estradiol in mediating sexual behavior. When male goldfish were injected with estradiol, they spent more time in proximity to a female (higher proximity score) – a behavior that was induced

10 – 25 minutes following estradiol administration, indicating rapid action of estradiol on sexual behavior [69]. The authors also showed that an injection of testosterone induced higher proximity scores to females, but over a slower time period (30 – 45 minutes). Blocking aromatase activity via fadrozole blocked the effect of testosterone, supporting the hypothesis that rapid conversion of testosterone to estradiol is one pathway through which sexual behavior is mediated.

Sexual behavior is coupled to aggression through mate guarding, which is typically when males defend a female mate from rival males. Not surprisingly, males who are mate guarding initiate and participate in more agonistic interactions with conspecific males than do males who are solitary [70, 71], indicating that sexual behavior and aggression are indeed two highly associated behaviors. Two important aspects of mate guarding are territory and resource defense, which are essential components of attracting and maintaining a mate [72, 73]. Such defense strategies are frequently maintained via aggressive conspecific interactions. These aggressive signals may not always escalate to physical combat, but can be communicated via visual, auditory, or olfactory cues in order to delineate territorial and resource boundaries [74-76]. As such, we next review the importance of rapid estrogens in communicatory signals since these signals play such a large role in mediating aggressive interactions (see below).

2.3 Communication

There has been recent interest surrounding the role of rapid estradiol signaling and auditory processing in several songbird species. The auditory caudo-medial nidopallium (NCM), which is analogous to the mammalian auditory cortex, has been a major focus of auditory processing in songbirds since it is an area that is highly associated with the processing of conspecific and heterospecific song [77, 78]. When male zebra finches (*Taeniopygia guttata*) heard male conspecific song, there was a rapid increase in locally synthesized estradiol in the NCM, but not when the finches were exposed to white noise [78], indicating that estradiol synthesis in the brain is affected by auditory perception. Furthermore, the synthesis of neuroestrogens in the NCM is dependent on local aromatase concentrations, since local infusion of fadrozole decreased estradiol levels [79, 80]. Local administration of estradiol to the NCM caused rapid increases in NCM firing rate, whereas local administration of an estrogen receptor antagonist suppressed NCM firing rates [80, 81], suggesting that local estradiol may nongenomically mediate auditory perception. In support of this hypothesis, retrodialysis of estradiol conjugated to E6biotin (which is membrane impermeable) to the NCM increased HVC activity for the bird's own song, but not for conspecific song or white noise [82, 83]. This indicates that estradiol is most likely acting via membrane-bound, as opposed to nuclear, ER receptors in the avian brain to affect song perception.

The mitogen activated protein kinase (MAPK) cascade has been shown to be of importance in auditory memory, assisting in the process of learning tutor songs during development [84]. MAPK regulates several immediate early genes in the NCM that mediate synaptic plasticity [85]. Interestingly, local estradiol injections to the NCM of zebra finches increased MAPK dependent gene expression, including the immediate early genes zenk, c-fos, and arc

– an effect that was blocked by the ER antagonist tamoxifen and the estradiol synthesis inhibitor 1,4,6-androstatrien-3,17-dione (ATD) [81]. Furthermore, ERE binding sites were not present on the promoter sites of several MAPK dependent genes, suggesting that estradiol may be mediating MAPK cascades via nongenomic actions [86]. Indeed, it appears that when activated by local estradiol, ERß activates the MAPK pathway and induction of MAPK dependent gene expression within NCM neurons [86]. Tremere and colleagues point out that although it is unlikely that estradiol and ERß are working via ERE's to affect immediate early genes in the MAPK cascade, they could conceivably be working through AP-1 binding sites that are present on promoter sites of MAPK dependent genes [86].

Auditory perception can be very important for mediating aggressive conspecific encounters, especially in songbirds. When faced with a stimulated territorial intrusion, songbirds will increase their rate of song production, and alter the frequency parameters of their song in response to rivals [87]. This process of auditory perception requires an ability to discriminate between familiar versus novel conspecifics, as well as threatening versus neutral conspecific displays [88]. In the next section we discuss how rapid estrogens may affect social recognition, which can clearly be linked to the onset or repression of aggressive interactions.

2.4 Learning and memory

Social recognition clearly plays a large role in facilitating and/or repressing aggression towards a conspecific. An individual might be less likely to direct aggression towards a familiar conspecifc as compared to a novel conspecific, since a novel intruder may present a greater threat to territory maintenance and resources [76]. Similarly, object recognition could play a role in recognizing territory boundaries, and when to direct aggression against intruders. Phan and colleagues [89] recently investigated the effects of rapidly acting 17ß-estradiol on a suite of learning behaviors spanning social (social recognition), non-social (object recognition), and spatial learning (object placement). In this series of studies, the authors demonstrated that 40 minutes following injection with 17ß-estradiol, female CD-1 mice demonstrated improvement in tests of social and object recognition, but not object placement, as compared to mice injected with vehicle. Interestingly, the ERα agonist, 1,3,5-Tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole (PPT), but not the ERß agonist 2,3-bis(4-hydroxyphenyl)-propionitrile (DPN), was shown to rapidly facilitate social recognition behavior in CD-1 mice, suggesting a role for ERα in mediating the rapid effects of estrogens on learning behavior [90].

In addition to being localized at nuclear sites, ERα and ERß have been found at extranuclear sites within the hippocampal formation [12, 14]. This suggests that once bound by estradiol, ER's at extranuclear sites may be mediating non-genomic actions associated with learning behavior. Mice receiving intracerebroventricular (ICV) injections of BSA-E_2 spent more time investigating a novel object compared to a familiar object, indicating memory of the familiar object [91]. Since BSA-E_2 is unable to cross the cell membrane [92], it can be inferred that the rapid effects of estradiol on object recognition depends on the activation of membrane-bound receptors, such as GPR30 [23, 93, 94]. These behavioral effects were not

blocked by the nuclear ER agonist ICI 182,780, further supporting the hypothesized role of membrane-bound ERs in social [90] and non-social learning [91].

Long-term potentiation (LTP) and long-term depression (LTD) are important mechanisms for regulating learning and memory by modulating synaptic plasticity in the hippocampus [95]. When estradiol was administered to *ex vivo* hippocampal slices, there was a rapid enhancement of LTD in the CA1, CA3 and dentate gyrus [96]. Furthermore, spine density was rapidly increased by estradiol in the stratum radiatum in the CA1 [89, 96, 97], but mossy fiber synapses are rapidly inhibited in the CA3 [98]. Interestingly, PPT, but not DPN, created the same enhancing effects on LTD and spinal density in the CA1 as administration of estradiol [96], suggesting a role for ERα in mediating the rapid effects of estrogens on hippocampal morphology. The highest density of ERα -labeled terminals is in the stratum radiatum of the CA1 [12], suggesting that ERα may be working at extranuclear sites to rapidly affect LTD.

The extracellular signal regulated kinase (ERK) pathway has also been implicated in estradiol regulation of learning and hippocampal spinogenesis. When mice were administered BSA-E_2, an increase in dorsal hippocampal ERK activation was observed [91]. Similarly, when mitogen-activated protein kinase kinase (MEK) (the kinase that activates ERK) was inhibited by the antagonist SL327, estradiol enhancement of object recognition was blocked [91]. Inhibiting MEK also blocked estradiol-facilitated increases in CA1 spinal density [99] and estradiol-facilitated decreases in CA3 mossy fiber synapses [98], indicating that the ERK pathway interacts with estradiol to mediate learning and hippocampal morphology [100]. Blocking Ca^{2+} influx via AMPA receptor inhibition also suppresses estradiol facilitation of CA1 spinal density [99] and estradiol inhibition of CA3 mossy fiber synapses [98], demonstrating that glutamate receptors may mediate the effects of estradiol on both hippocampal morphology and learning [101].

Estrogen signaling affects aggressive interactions, as well as several behaviors that are closely linked with aggression, including sexual behavior, communication, and learning and memory. Sarah Newman proposed that a social behavior network consisting of several hypothalamic and limbic nuclei works in concert to modulate a variety of social behaviors [35]. Both estrogen receptors and aromatase are expressed in this network across a wide range of species. This may explain how estradiol functions as a central mediator of behaviors that are crucial components of social interactions. Given the importance of photoperiod in mediating estrogen-sensitive networks of behavior, it is not surprising that these networks are sensitive to other signals from the environment. As mentioned previously, estrogen-like components of corncob can have a dramatic impact on how estrogens regulate behavior. In the next section we consider how phytoestrogens and other endocrine disruptors impact estrogen-sensitive social behavior.

3. Environmental estrogens as behavioral disruptors

While photoperiod is a very important cue, individuals can detect seasonal changes through dietary changes such as the availability of green food [102]. Intriguingly, many plants produce estrogen-like compounds that have significant effects on estrogen signaling in the

brain. In addition, many industrial chemicals have estrogen-like properties. These exogenous sources of estrogens are important regulators of estrogen-dependent behaviors. For rodent researchers, two of the most significant sources of estrogen-like compounds come from food and bedding. Corncob bedding in particular is becoming one of the most wide-spread sources of phytoestrogens. The presence of estrogen-like compounds in corncob bedding, especially tetrahydrofuran diols (THF-diols), has been known for some time [55, 103]. Still, the impact of these compounds is generally under appreciated. As discussed above estrogens were found to increase aggression in *Peromyscus* when corncob bedding was used [45, 48], whereas estrogens decreased aggression when Carefresh was used [53, 56] (Fig 4). Previous work had determined that corncob bedding disrupts male and female sexual behavior in rats, and that this effect was mediated by THF-diols. Presumably the route of administration of THF-diols is via ingestion of corncob bedding, and we confirmed that California mice indeed ingest corncob bedding. This resulted in a significant increase in THF-diols in plasma as measured by liquid chromatography tandem mass spectrometry analysis. Increased plasma levels of THF-diols also coincided with a decrease in the number of ERα-ir cells in the BNST and VMH of mice housed on corncob bedding. Interestingly the BNST and VMH also control reproductive behaviors, suggesting a possible mechanism for previous inhibitory effects of corncob on sexual behavior. More recent observations have demonstrated that the effects of corncob use extend beyond sexual and aggressive behavior. Male rats housed on corncob bedding have reduced anxiety-like behavior and decreased slow-wave sleep compared to rats raised on wood pulp based bedding [104, 105]. In addition, corncob bedding also reduced sex differences in social withdrawal behavior following social defeat stress [106]. These results suggest that corncob may have widespread effects on brain function. Consistent with this hypothesis, California mice housed on corncob bedding had greatly reduced pERK immunoreactivity in the BNST, MPOA, MEA, and VMH [56]. As reviewed above, ERK signaling is an important mediator of many behaviors. These findings highlight the impact that seemingly mundane choices in cage bedding can have on brain function and behavior.

Phytoestrogens such as isoflavone are abundant in soy products and can affect behaviors mediated by the rapid action of estrogens. Sexual behavior is particularly susceptible to dietary increases in phytoestrogen compounds [107]. Female rats that received supplemental isoflavone (13 parts/million (ppm) genistein and 33 ppm daidzein) in their diet demonstrated reduced lordosis (receptive behaviors) and hops and darts (proceptive behaviors) in response to a male rat [108, 109]. The ER antagonist tamoxifen also reduced both receptive and proceptive behaviors [109], indicating that phytoestrogens may be acting as an ER antagonist to affect sexual behavior in rodents. It was similarly found that in gonadectomized aromatase knock-out mice raised on a high phytoestrogen diet, lordosis behavior was suppressed in adulthood [110]. The authors suggest that exposure to phytoestrogens during development may defeminize sexual behavior.

Bisphenol A (BPA) is a major component of many plastics that has been studied for its interactions on steroid signaling pathways. Research on BPA has focused primarily on exposure during development, when sexual differentiation of many social behaviors occurs. It has been hypothesized that behaviors under strong sexual selection will be especially

sensitive to developmental exposure to BPA [113]. Consistent with this hypothesis, BPA exposure was found to increase male aggression in mice and rats [111, 112]. Similarly, male but not female deer mice (*Peromyscus maniculatus*) exposed to BPA during development showed impairments in a spatial learning task [113]. Spatial learning is thought to be under sexual selection in this species because males defend large territories whereas females do not. Exposure to BPA following sexual differentiation also appears to affect cognitive processes. Miyagawa and colleagues [114] showed that BPA exposure impaired learning in a passive avoidance test and was associated with a decrease in markers of acetylcholine activity in the hippocampus.

Phytoestrogens and endocrine disruptors differ from other environmental signals such as photoperiod in that they directly engage estrogen signaling networks. The effects of endocrine disruptors such as BPA can be especially long lasting, because these compounds can induce long lasting changes in DNA methylation in the brain [115]. Although it is currently unclear how these estrogenic compounds impact human behavior, it would appear likely that estrogen-sensitive social behavior networks could be affected.

4. Rapid Effects of Estrogens on Brain Function

Across many rodent species, males are more aggressive under short day photoperiods as compared to long day photoperiods, yet two studies using c-fos immunohistochemistry as an indirect marker of brain activity found no effects of photoperiod on aggression induced c-fos staining in brain networks known to modulate male aggression such as the anterior hypothalamus, BNST, and medial amygdala (MEA) [43, 45]. Although c-fos is a widely used marker of brain activity, important changes in neuronal activity can occur without altering c-fos signatures [116]. An alternative approach to assessing brain activity is via analysis of the activation of intracellular signaling cascades such as calcium, protein kinase C, and extracellular signal regulated kinase (ERK).

4.1 Effects of photoperiod on extracellular signal regulated kinase

Examination of phosphorylated ERK has revealed photoperiod modulates the activity of several nuclei that modulate aggressive behavior. In male California mice, engaging in resident-intruder aggression tests significantly increased the number of pERK–ir cells in the BNST and MEA under short days but not long days [44]. In addition, pERK cell counts in the BNST and MEA were positively correlated with aggressive behaviors. When these experiments were repeated using western blots to measure pERK in BNST punch samples, increased aggression-induced pERK expression was again observed in short days but not long days. In the MEA, pERK expression was elevated in short days even in animals that were not tested in resident-intruder tests. These were the first data to show an effect of photoperiod on cellular activity within the brain that might be connected to the short day high aggression phenotype. Previous studies in knockout mice suggested that phosphorylation of ERK could be a mechanism of rapid estrogen action. An acute injection of estradiol increased the number of pERK positive cells in the medial preoptic nucleus within 15 min, and the effect was not observed in ER and ER knockout mice [30]. Once activated, ERK can modulate neuronal activity and neurotransmitter release.

Subsequent analyses indicate that any effects of pERK activity in the BNST and MEA on aggressive behavior are likely to be complex. Under short days, male California mice treated with fadrozole have elevated aggressive behavior but decreased numbers of pERK positive cells in both BNST and MEA [56]. In this study, mice were treated with aromatase inhibitor for 10 days. A study on song sparrows also examined the effect of estrogens on pERK immunoreactivity in the context of aggression [117]. Similar to rodents, male song sparrows are aggressive during the winter non-breeding season when day length is short [118]. Interestingly, estrogen levels in the BNST are rapidly reduced during aggressive interactions [119], and acute inhibition of aromatase activity reduces aggressive behavior [118]. To test the effects of rapid estrogen action on pERK immunoreactivity, birds in breeding and non-breeding condition were treated with fadrozole for 10 days and then injected with saline or estradiol (500 μg/kg) [117]. In BNST, estradiol had no effect on the number of pERK positive cells in both breeding and nonbreeding birds. Thus, there appears to be a disconnect between the effects of aggression on pERK expression in the BNST and effects of estrogen manipulations. One possible factor could be long term use of aromatase inhibitors as an experimental tool. The effects of ERK activation on cell function are very different depending on the time course of activation. Transient activation of ERK can modulate neuronal activity and neurotransmitter release [120]. In contrast, sustained but not transient activation of ERK induces translocation to the nucleus [121], which can induce long term changes in cell function [122]. Both the rodent and bird studies cited above used long term treatment with aromatase inhibitors. It is possible that this treatment has a long term effect of ERK activity that differs from the more rapid modulation of ERK by estrogens. Thus, it would be interesting to compare the effects of long term aromatase inhibition versus short term aromatase inhibition on both behavior and ERK activity.

4.2 Effects of photoperiod on CREB

The phosphorylation of cAMP response element binding protein (CREB) has also been assessed as an indirect marker of brain activity. Activation of CREB can occur via at least two pathways (Fig 1). Rapid activation of CREB is mediated by influx of calcium and activation of calmodulin kinase (CaMK) IV while ERK mediated activation of CREB occurs after about 60 min [123]. Thus, if samples are collected immediately after a behavioral test, the number of phosphorylated CREB cells could be independent from the number of the phosphorylated ERK cells. Studies that have compared the number phosphorylated CREB and ERK cells following aggression tests have indeed reported different patterns of immunoreactivity.

In song sparrows, estradiol injections increase aggression during the non-breeding season and reduce the number of phosphorylated CREB cells in several nuclei in song control circuits as well as social behavior network [117]. Although some studies have demonstrated that estradiol facilitates CREB phosphorylation in the brain [30, 124], most of these studies focused on females. When males have been studied, the effects of estradiol on CREB phosphorylation are generally weak [125] or absent [126]. Indeed, this sex difference appears to originate early in life. Female hippocampal neurons respond to estradiol with a rapid increase in phosphorylated CREB, but exposure estradiol during postnatal development blocks this response [127]. It should be noted, however, that these types of

studies tend to be conducted in domesticated rats and mice under relatively standard light cycles (e.g. 12L:12D).

In California mice, the effects of aggression testing on CREB phosphorylation are dependent on photoperiod. Intriguingly, regulation of CREB is strongest in mice tested under long day photoperiods and the predominant effect of aggression testing is a down-regulation of phosphorylated CREB cells. Resident-intruder testing reduced the number of phosphorylated CREB cells in the infralimbic cortex (IFL) and agranular insular cortex (AI) when mice were housed in long days but not short days [44]. The AI has strong connections with other frontal cortex regions such as IFL [128]. In rats, c-fos immunoreactivity in pyramidal cells in AI and IFL are negatively correlated with aggressive attacks [129], suggesting that activity in these brain regions modulate aggressive behavior. Photoperiod also had interesting effects on phosphorylated CREB in the lateral amygdala (LA). Males housed in short days had more pCREB positive cells than males housed in long days, regardless of whether mice were tested in aggression tests or control tests. However, in long day mice, aggression was positively correlated with the number of phosphorylated CREB cells in the LA whereas this correlation was absent in short day mice. Overall, these results are consistent with the hypothesis that photoperiod has important effects on the neural circuitry regulating aggressive behaviors. It is unclear whether the frontal cortex or LA are estrogen sensitive in California mice. Whereas nuclear estrogen receptors are not expressed in these regions [45], it is possible that membrane receptors could exist and escape detection without the use of electron microscopic methods. In general, the increased aggression phenotype in short days appears to be linked to a decrease in CREB activation, although the functional significance is not yet clear.

4.3 Effects of photoperiod on female aggressive behavior

Interestingly, a short day aggression phenotype has been described in female Siberian hamsters [130], Syrian hamsters [131], and California mice [132] (Fig 5). Similar to males, most evidence suggests photoperiod-induced aggression is not dependent on gonadal hormones in females. Ovariectomy did not reduce the high intensity bouts of aggression (bites and roll-fighting) of female Syrian hamsters housed in short day photoperiods [133]. In California mice estradiol levels were elevated during short days, but only during diestrus [132]. Increased aggressive behavior persists across the estrous cycle, suggesting that effects of photoperiod are not dependent on changes in estrogens. There also appear to be important sex differences in the neural circuits mediating increased aggression in short days. Although female California mice are more aggressive in short days, pERK expression was increased following a resident-intruder test in the posterior BNST and MEA regardless of photoperiod [132]. This result parallels results in female Syrian hamsters where an infusion of a V1a receptor antagonist into the anterior hypothalamus increases aggressive behavior under both long day and short day photoperiods [134]. At this point, it is clear that the basis for the elevated short-day aggression phenotype in females differs substantially from the mechanism in males.

5. Conclusions

The effects of estrogens on behavior and cell function are typically studied under controlled conditions. This approach has led to major advances in our understanding of the neuroendocrine mechanisms controlling the brain and behavior. However, the world is not a static place and behavior that may be beneficial in one context may be detrimental in another context. In this review, we have highlighted evidence that a single hormone, estradiol, can have very different effects on behavior by activating different molecular pathways. Salient environmental cues such as photoperiod exert control over which pathways are activated. This provides flexibility in the behavioral response of a common hormonal signal. Similarly, the presence of estrogen-like compounds (both naturally occurring and man-made) in diet can have a dramatic impact on the behavioral effects of estrogen signaling. These findings illustrate that if we are to understand how estrogens regulate behavior, it will be important to be broad-minded in our approach. Considering how estrogens modulate behavior in different species and under different environmental conditions will provide novel insights to complement our growing knowledge of the molecular mechanisms.

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Highlights

Estrogens can regulate behavior through rapid nongenomic mechanisms or through slower genomic mechanisms

Environmental cues such as photoperiod can modulate whether estrogens activate nongenomic or genomic pathways

This flexibility allows a single hormone molecule, such as estradiol, to have diverse effects on a range of social behaviors

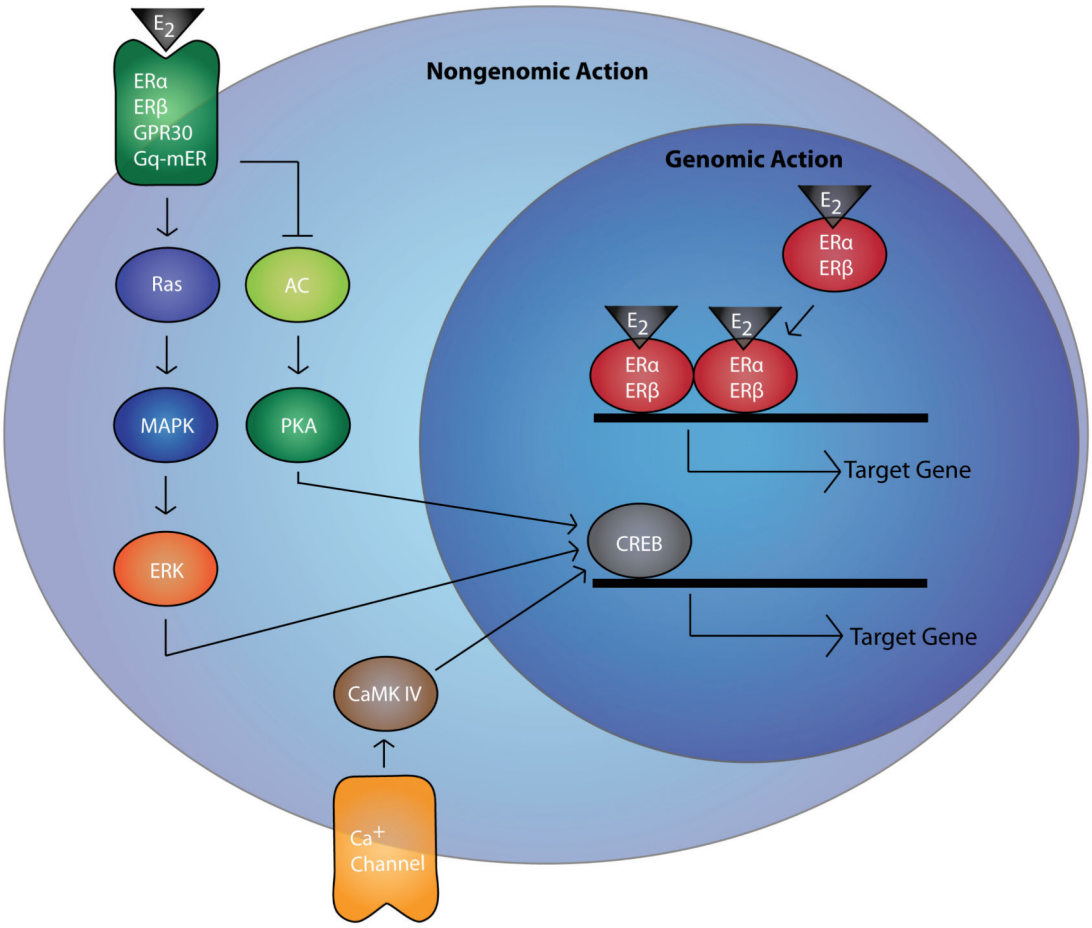

Fig 1.

Estrogens can act via genomic or nongenomic cascades. When estradiol (E_2) binds to nuclear estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ), the receptor complex dimerizes and binds to estrogen response elements (ERE's), which promotes downstream gene expression (genomic) [1-4]. E_2 can also activate a more rapid cascade via membrane-bound receptors, which initiates MAPK and downstream molecular targets, including ERK and CREB (nongenomic) [117].

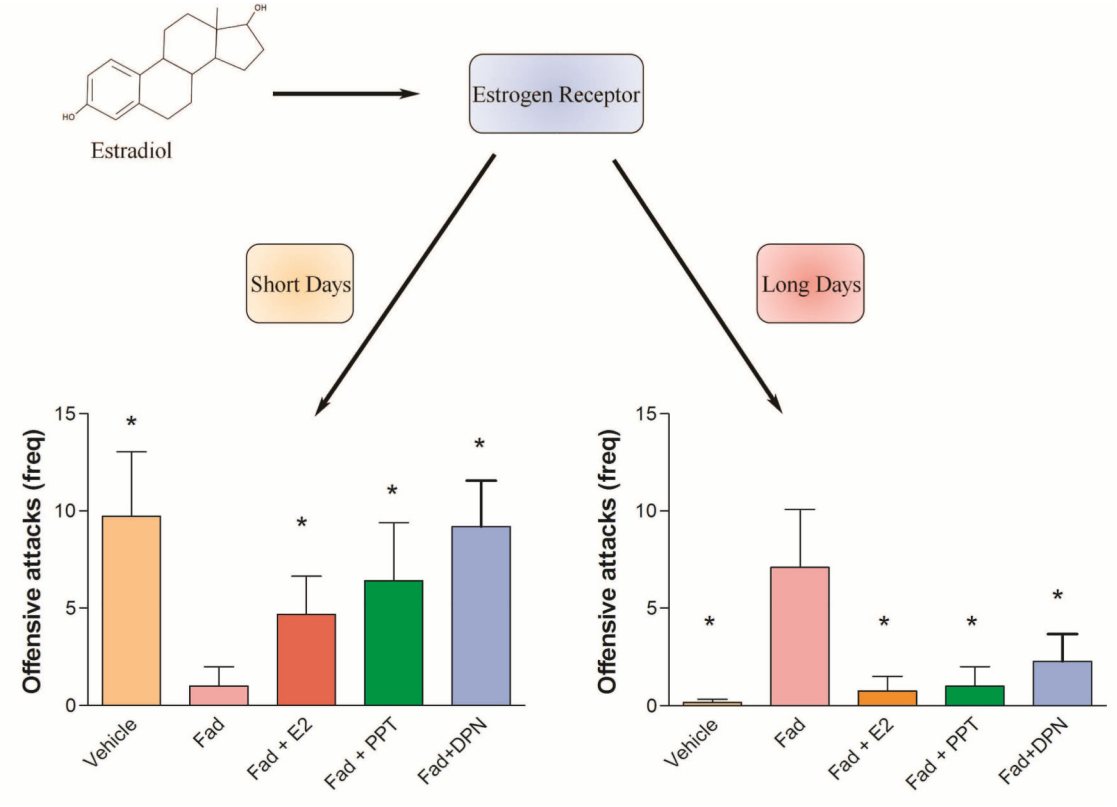

Fig 2.

Photoperiod determines the direction of the effects of estrogens on aggressive behavior in beach mice (*Peromyscus polionotus*). Beach mice are more aggressive when exposed to short days (shown in the left graph) than when exposed to long days (shown in the right graph). Treatment with the estrogen synthesis inhibitor fadrozole (fad) decreases aggression if beach mice are tested in short days, but increases aggression if tested in long days. The effects of fad are reversed with co-treatment with estradiol (E_2). The compounds PPT (propylpyrazole-triol, an estrogen receptor α (ERα agonist) and DPN (diarylpropionitrile, an ERβ agonist) both reversed the effects of fadrozole in the same way. Both PPT and DPN treatment increased aggression under short days and decreased aggression under long days. Photoperiod apparently regulates the molecular actions of estrogens, acting rapidly on short days (presumably nongenomically, via ERα and ERβ associated with the cell membrane) and more slowly on long days (presumably genomically). *$p < 0.05$. Adapted from [48, 135].

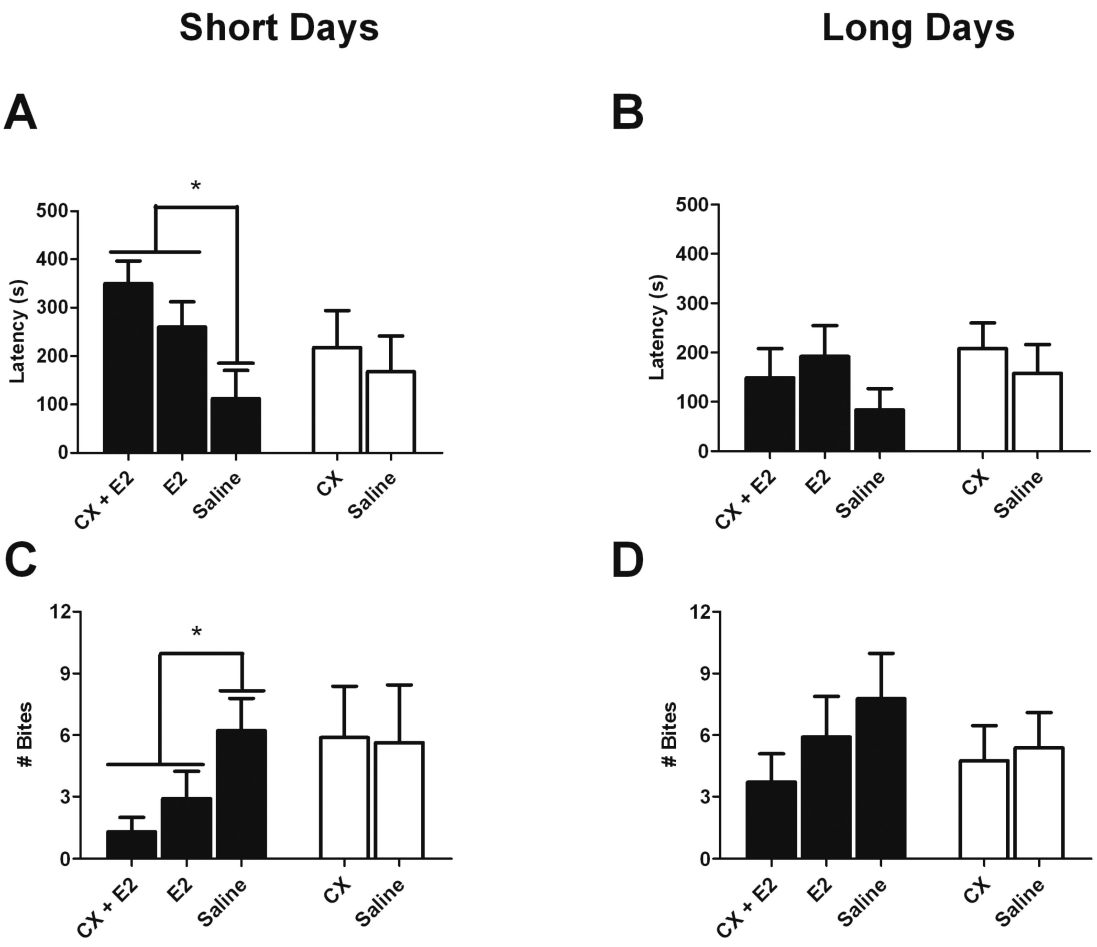

Fig. 3.

Estradiol regulates aggression via nongenomic mechanisms under short day photoperiods. All mice were housed under either short or long day photoperiods, and then castrated and implanted with a minipump containing fadrozole. Next, mice were randomly assigned to be treated with cycloheximide (CX) or saline 90 minutes before resident-intruder aggression tests. Mice were then treated orally with either estradiol (E_2, black bars) or saline (white bars) thirty minutes before behavior tests. Latency to attack a novel intruder and bites administered were recorded. Under short days, mice demonstrated a decrease in aggression following estradiol injections regardless of CX administration (A&C). This effect was not observed under long days (B&D). CX alone had no effect on aggression. *Planned comparison $p < 0.05$. Adapted from [53].

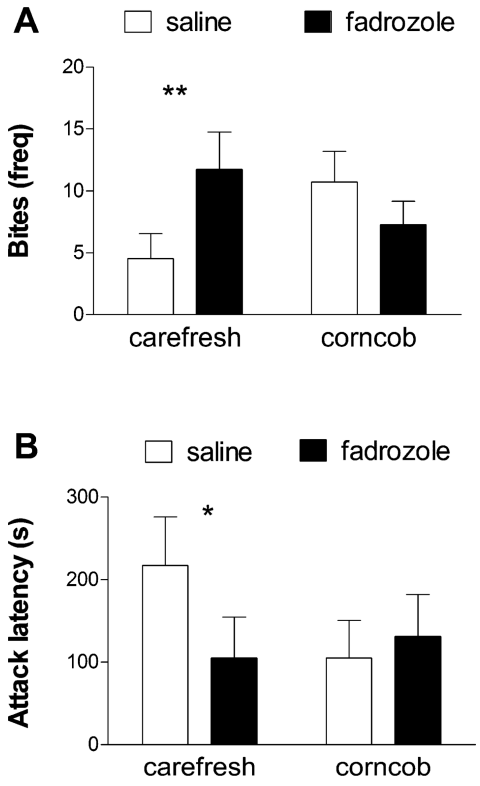

Fig 4.

The effects of bedding on aggression. Mice were housed on either a cardboard-based bedding (Carefresh) or a bedding containing phytoestrogens (corncob) and kept on a short day (8L:16D) photoperiod. Mice were castrated and administered either saline or the aromatase inhibitor fadrozole (fad) for 10 days, and then tested in resident-intruder tests. Number of bites and latency to attack a novel intruder were recorded. Those mice receiving fad on Carefresh bedding showed greater aggression as compared to mice receiving saline on Carefresh, whereas the opposite trend was seen in mice housed on corncob bedding. *$p < 0.05$. Adapted from [56].

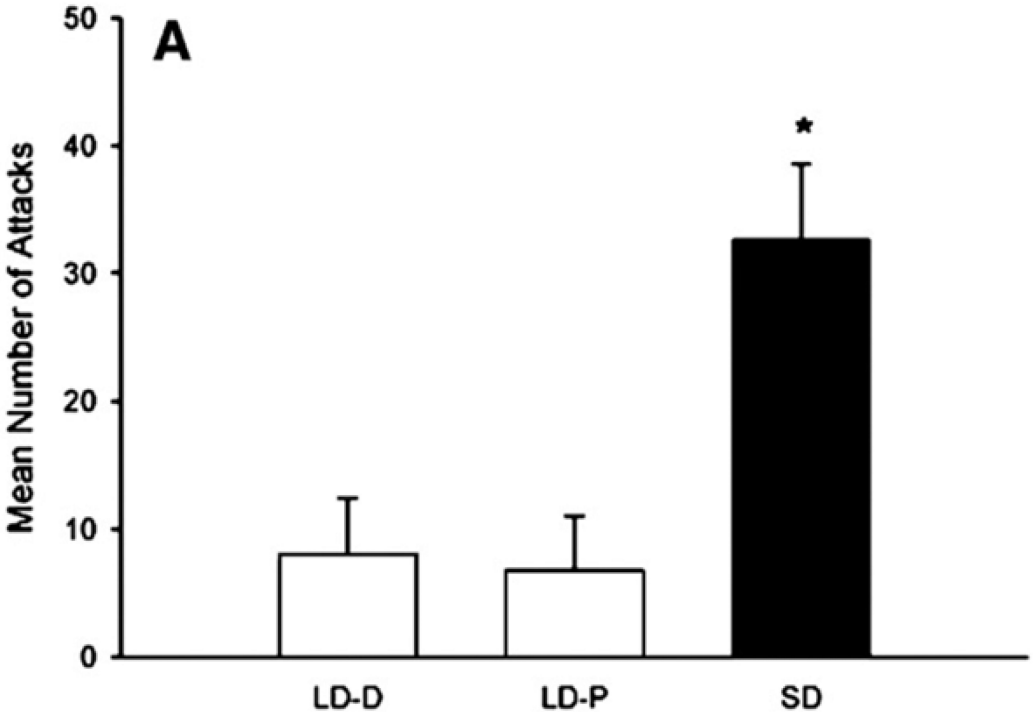

Fig. 5.

Female Siberian hamsters housed under short day photoperiods (black bar) show a significantly greater number of attacks in a resident-intruder paradigm as compared to diestrus (LD-D) and proestrus (LD-P) females housed under long day photoperiods (white bars). *$p < 0.05$. Adapted from [130].