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Review

Estrogenic encounters: How interactions between aromatase and the environment modulate aggression

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Abstract

Initial investigations into the mechanistic basis of aggression focused on the role of testosterone (T) and a variety of studies on non-human animals found that elevated T levels promote aggression. However, many correlational studies have not detected a significant association between aggression and peripheral T levels. One reason for this inconsistency may be due to differential metabolism of T within the brain, in particular, the conversion of T to estrogen by aromatase. Thus, differences in aromatase enzyme activity, estrogen receptor expression, and related cofactors may have important effects on how steroids affect aggressive behavior. Hormone manipulation studies conducted in a wide variety of species indicate that estrogens modulate aggression. There is also growing evidence that social experience has important effects on the production of estrogen within the brain, and some cases can not be explained by androgenic regulation of aromatase. Such changes in central aromatase activity may play an important role in determining how social experiences affect the probability of whether an individual engages in aggressive behavior. Although studies have been conducted in many taxa, there has been relatively little integration between literatures examining aggression in different species. In this review, we compare and contrast studies examining aggression in birds, mammals, and humans. By taking an integrative approach to our review, we consider mechanisms that could explain species differences in how estrogen modulates aggression.

Keywords: Aggression; Androgen; Hostility; Estrogen receptor; Progesterone; Social environment; Bird; Parental behavior; Peromyscus; Estrogen

1. Introduction

Aggressive behavior is extremely complex, and is influenced by a variety of genetic, physiological, social, and environmental factors. Although aggressive behavior has been described in a wide variety of species, there has been relatively little communication between clinical and basic researchers, and also among basic researchers studying different species. This may stem, in part, from diversity in how species handle aggressive interactions. In many species vocal, visual, or chemical displays are used to resolve conflicts, frequently without resorting to fighting. When aggressive displays do not settle disputes, the specific patterns of fighting can include various combinations of biting, wrestling, and chasing. Undoubtedly there are many important species differences in the mechanisms that underlie aggressive behavior. However, studies in fish, amphibians, birds, and mammals indicate that a common set of the hypothalamic and limbic brain regions is activated during aggressive behavior (reviewed in [36]). These data suggest that there are homologies in the neuroendocrine mechanisms regulating aggression. Neuronal activity in the so-called "social behavior circuit" [79] may regulate the probability that an individual will behave aggressively. Mechanisms regulating the decision to engage in aggression may be more likely to be phylogenetically wide-spread, as opposed to mechanisms controlling species-specific aggressive behaviors [105].

In support of this hypothesis, testosterone is known to affect aggression in a wide variety of species and was one of the first physiological mechanisms discovered to regu-

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late aggression. Over time, many studies have demonstrated that testosterone (T) promotes aggression in a wide variety of species [109,128]. However, it has also become apparent that the simple hypothesis that high T levels result in elevated aggression has limited explanatory power, as aggressive behavior can be expressed in conjunction with low circulating T [16,27,52,65,88,121,127]. Efforts to relate aggressive behavior with plasma T levels in humans have yielded inconsistent results [2,3,68]. However, the lack of a correlation between plasma T levels and a behavioral outcome does not rule out T as a contributor to behavioral variation. For example, there is a growing literature indicating that dynamic changes in testosterone (i.e., in response to social interactions which cannot be reliably assessed by a baseline blood sample) may have important effects on aggressive behavior [87,92,120,128]. Additionally, testosterone can have important effects on behavior after it is converted to dihydrotestosterone or estradiol within the brain.

Testosterone is converted to estradiol by the aromatase enzyme. In birds and amphibians aromatase is distributed throughout the brain [6,107] whereas in mammals, the distribution of aromatase is limited to hypothalamic and limbic brain areas [77]. Interestingly, many of these brain areas are known to regulate sexual and aggressive behaviors [78]. The most detailed studies of the effects of aromatase on behavior examine sexual behavior. Studies in birds [5], rodents [8], and primates [132,133] indicate that estrogen formed within the brain can affect various aspects of male sexual behavior (although the evidence is less clear in humans [94]). There is growing evidence that estrogen produced in the brain regulates aggression as well. Thus if aromatization of T has important effects on behavior, individuals with similar T levels could behave very differently if they differed in central aromatase activity or estrogen sensitivity (e.g., estrogen receptors).

In this review, we consider the evidence that aromatization within the brain may mask relationships between androgens and aggressive behavior. First, we review the effects of aromatase and its estrogenic products on aggressive behavior in a variety of species. Second, because many of these species have complex social systems, we consider the importance of social context on estrogenic mechanisms of aggression. Finally, we consider how studies of aromatase and aggression conducted with animal model systems may relate to human behavior. A limited number of clinical studies suggest that estrogens modulate aggression or its components (e.g., hostility). Animal studies clearly show that previous social experience (especially reproductive experience) regulates aromatase activity within the brain, and could therefore modulate the effects of aromatization on aggression. Humans and non-human animals exhibit similar steroid hormone responses to certain types of social stimuli, suggesting that there may be similar homologies in aromatase function.

2. Effects of aromatization on aggression in non-human vertebrates

Defense of territories is one of the most well studied contexts of aggressive behavior. In a wide variety of species, estrogen has been found to regulate aggressive defense of a territory. However, in some species estrogen facilitates aggression whereas in other species estrogen appears to dampen aggression. Thus, there is no simple rule that increased aromatase activity leads to increased aggression. This does not, however, mean that there are no general patterns. Factors such as the source of androgen, expression of different estrogen receptor types, and social experience can play an important role in how aromatization affects aggressive behavior. Understanding how these factors work together should reveal the bases for species differences in the estrogenic control of behavior.

2.1. Birds

Estrogens increase aggression in several species of birds, although the methodology used to measure aggression differs among studies. In Japanese quail, aromatase activity in the preoptic area (POA) of males is positively correlated with aggressive pecking responses towards a stimulus male in an adjacent cage [100], and males that are treated with an aromatase inhibitor exhibit reduced aggressive pecking responses [101]. While these results were collected in a laboratory environment, several field studies have found comparable results by measuring aggressive behavior in response to a caged "intruder" next to a speaker playing taped bird songs. Territorial males usually respond vigorously by producing aggressive song and by darting at the intruder. A study on pied flycatchers (*Ficedula hypoleuca*) found that aromatase activity in the diencephalon (including the POA) was positively correlated with aggression levels, even though plasma T levels were not correlated with aggression [108]. Studies on the Pacific Northwest song sparrow (*Melospiza melodia morphna*) found that in the non-breeding season, male song sparrow plasma T levels were low [127] and castration did not reduce aggressive song production [126]. However, treatment with an aromatase inhibitor decreased aggressive song and chasing behavior in males [112]. The substrate for aromatase during the non-breeding season appears not to be T, but dehydroepiandrosterone (DHEA), an androgen precursor. In the non-breeding season male song sparrows treated with exogenous DHEA increased aggressive song in response to intruders [113]. Experiments in zebra finches showed high levels of 3β-hydroxysteroid dehydrogenase activity (which converts DHEA into the aromatizable androgen, androstenedione) in the brain [111], which indicates that songbirds can produce estrogen in the brain from plasma DHEA. In birds, increased aromatase activity in the brain is associated with increased aggression and hormone manipulations indicate that aromatization increases aggression. Thus, individual differences in aromatase activity in the brain can be an

important factor in determining individual differences in aggressive behavior.

2.2. Mammals

The majority of experiments examining the effects of estrogenic metabolites of T on aggressive behavior in mammals have used rodents, primarily domestic house mice (*Mus musculus*). Similar to studies in birds, these studies generally find that estrogens increase aggression. One of the most common laboratory tests used to measure aggression in rodents is the resident-intruder aggression test. A male (resident) is individually housed for 2–6 days, and then an unfamiliar male (intruder) is introduced into the resident's cage. Experimenters have measured a variety of behavioral variables including bites, bouts of wrestling, and attack latency. Residents that attack intruders more quickly (short attack latency) and/or attack intruders more are considered to be more aggressive because these individuals initiate aggression faster and more frequently.

While many studies have investigated the effects of castration or exogenous T administration on aggression, fewer studies have considered the behavioral effects of the estrogenic metabolites in mammals. Similar to studies of sexual behavior [28], variability in the sensitivity of aggression to estradiol has been described among different strains of domestic mice. Castrated CFW mice treated with estradiol were more likely to fight than males treated with DHT or oil, whereas castrated CF-1 mice treated with the non-aromatizable androgen R1881 or estradiol showed an increased probability of fighting compared to mice treated with oil [110]. It is unclear from these studies whether different hormone treatments led to subtle differences in the intensity of aggression, as aggression was scored as either present or absent (as opposed to number of bites, attack latency, etc.). Male mouse plasma estradiol levels are usually extremely low, which suggests that behaviorally active estrogen is produced in the brain.

Studies of aromatase "knock-out" mice (ArKO), in which the aromatase gene was selectively inactivated, have found similar results. An initial study reported that the duration of aggression in resident-intruder tests was extremely low for ArKO mice compared to wild-type mice [118]. Interestingly, estradiol injections restored aggression to wild-type levels, but only if treatment started within the first two weeks post-partum, and was maintained until the day of testing [118]. These data suggest that estrogen may modulate the formation of neuronal circuitry involved in male–male aggression. ArKO mice treated with estrogen only during development showed reduced aggression, suggesting that estrogen acts in adulthood as well. A second study also found that ArKO mice showed less intense aggression than wild-type mice, but only in the second of two aggression tests [67]. This was mainly because wild-type mice became more aggressive in the second test whereas ArKO mice exhibited no change in aggression. One possible reason why no effect of genotype was detected in initial aggression tests is that some of the mice used in this study were from the 129/Sv background, which may be more aggressive than C57BL/6 mice that are typically used in transgenic mouse studies [59]. These studies suggest that aromatization has important effects on aggression in mice, but do not address where in the brain aromatization takes place.

The relationship between aggression and aromatase activity in the brain was examined in male California mice (*Peromyscus californicus*), which are highly territorial [93] and more aggressive in resident-intruder tests than closely related white-footed mice (*Peromyscus leucopus*) [13]. Aromatase activity was measured in males that had been tested in three resident-intruder aggression tests [120]. Aromatase activity was measured in the medial preoptic area, ventromedial hypothalamus, medial amygdala, and bed nucleus of the stria terminalis (BNST). In all brain areas examined, aromatase activity did not differ from control males that were not tested in aggression tests. Only aromatase activity in the BNST was correlated with attack latencies measured in each of the three aggression tests. Thus, individuals with more aromatase activity in the BNST were less aggressive. Previous studies suggest that the BNST is an important brain area regulating aggression in rodents [12,50,53]. These results in California mice were unexpected because estrogen increased the probability of aggression in domestic mice. However, when the production of estrogen in male California mice was blocked an aromatase inhibitor (fadrozole), males were more aggressive compared to control males [120]. Thus correlational and experimental data indicate that production of estrogen is associated with reduced aggression in California mice. Currently, it is not yet clear why estrogen increases aggression in domestic mice but decreases aggression in California mice. A study on interfemale aggression in California mice found that plasma estradiol levels were positively correlated with attack latency [25], suggesting that estradiol may inhibit aggression in female California mice as well. The California mouse is not the only species in which aromatization in the brain is negatively associated with aggression. The onset of aggressive territorial behavior in the bluebanded goby fish (*Lythrypnus dalli*) is associated with a rapid decrease in aromatase activity in the brain [14]. These reports in California mice and gobies raise the question of how aromatase can be positively associated with aggression in some species but negatively associated with aggression in other species.

One important factor in determining the directional effects of estrogen on aggression may be the expression of estrogen receptor subtypes. There are at least two subtypes of the estrogen receptor (ER): the classical or α estrogen receptor [125] and the β estrogen receptor [56,76]. Evidence for subtype specific effects of estrogen receptor on behavior are primarily limited to studies on knock-out mice, so it can be difficult to distinguish whether observed behavioral effects are due to effects during development, adulthood, or both. Unlike studies of aromatase activity in birds and California mice, there is very little correlational data linking

ER expression with individual differences in behavior. Despite these gaps in knowledge, knock-out mouse studies provide some interesting clues that may lead to a better understanding to variability in the estrogenic mechanisms of aggressive behavior.

As expected from previous estrogen manipulation studies on domestic mice, estrogen receptor α knock-out mice (ERαKO) mice display *less* aggression towards intruders in resident-intruder tests compared to wild-type males [83]. Artificially increased T levels do not restore wild-type aggression levels in ERαKO males [104], suggesting that this effect is not due to deficient androgen levels. In contrast, sexually experienced estrogen receptor β knock-out (ERβKO) adult males were more aggressive than sexually experienced wild-type mice in resident-intruder aggression tests [81]. In a subsequent study, sexually inexperienced male ERβKO mice were more aggressive than wild-type mice when tested before puberty but not when tested as fully mature adults [80]. These results also suggest that the effect of sexual experience could modulate the behavioral effects of ERβ, especially since some sexually inexperienced ERβKO mice were observed to direct sexual behavior towards intruders [80]. In general, relatively little is known about how the social environment affects estrogen receptor expression or function.

How estrogen receptors modulate aggressive behavior is still unclear. Knock-out studies suggest that ERβ may have inhibitory effects on the transcriptional effects of ERα, [62,122]. The relative ratio of the two subtypes could also influence the behavioral action of estrogens by affecting dimerization processes. When an estrogenic ligand binds to ERα, these receptors can either homodimerize with bound ERα receptors or heterodimerize with bound ERβ receptors. These processes can affect the downstream transcriptional activity of each receptor type [41]. Recent studies have also demonstrated that a variety of nuclear coactivators can have important behavioral effects both during development [4] and in mature adults [18,73]. These studies have focused on sexual behavior, and it is still unclear whether species differences in coactivator function could contribute to observed species differences in the effects of estrogen on aggression. Finally there is growing evidence that the two ER subtypes may affect different motivational systems. For example, selective deletion of ERα has been found to reduce male sexual motivation [123], and several lines of evidence suggest that ERβ modulates anxiety-like behavior [20,49,64]. Because reproductive experience [129] and affective state [55] are known to influence aggression, species differences in these motivational systems could translate into differences in how estrogen acts on aggressive behavior.

In summary, estrogen has been shown to modulate aggression in a variety of species. Although in most cases estrogen increases the probability and intensity that males will engage in aggressive behavior, there are exceptions in which estrogen decreases the intensity of aggression. Studies of the molecular mechanisms of estrogen signaling in mice indicate that there are multiple pathways that could influence how estrogen regulates aggression including: differences in the distributions of estrogen receptor subtypes, differences in aromatase activity, effects of receptor dimerization, and species differences in affective behavior. Species differences in these factors may underlie the observed species differences in estrogen-dependent aggression. Further study is needed to characterize how these systems operate in the context of aggressive behavior.

3. Environmental effects on aromatase in the brain

As hinted at earlier, aspects of the social environment may also have critical effects on aromatase function. Aggressive behavior occurs in the context of a physical and social environment, and previous studies demonstrate that aspects of the physical and social environment regulate aggressive behavior. Given the evidence that aromatase can affect aggressive behavior, it might be expected that central aromatase could be modulated by the physical and social environmental. There is evidence in several species that aromatase activity changes seasonally, often increasing during the breeding season (see below). There is growing evidence that social interactions can modulate aromatase activity. Although some cases can be explained by androgen-dependent regulation of aromatase, other cases cannot be explained by changes in androgens. Thus, non-androgen based pathways may be important for explaining effects of social interactions on aromatase activity [5].

3.1. Aggressive experience

One study has examined the effect of experience in aggressive encounters on aromatase activity in California mice. Neither residents exposed to a winning experience nor intruders exposed to a losing experience differed from control animals in aromatase activity in several brain areas including the preoptic area, BNST, and medial amygdala [120]. This finding was consistent with the result that aromatase inhibition did not block increased aggression caused by winning experiences. Increased aggression caused by winning experiences is mediated by a transient increase in T shortly following attacks on an intruder, apparently via activation of androgen receptors [66,87,120]. Thus, in California mice, aromatase may regulate baseline aggression levels while transient changes in T may be more important for integrating the effect of winning experiences on aggression.

3.2. Sexual experience

There is much more evidence that reproductive experience modifies aromatase activity, especially within the preoptic area of the brain. Adult male ring doves (*Streptopelia risoria*) that were paired with females for five days exhibited elevated aromatase activity in the preoptic area [30]. Visual contact with females was sufficient to increase aromatase

activity in the preoptic area [47,48], which suggests that increased aromatase activity may be related to motivation to mate. Ring dove courtship and mating behavior occurs over a period of about one week, after which males begin to sit on the nest [32], which is when aromatase activity declines in the preoptic area [60]. Increases in preoptic aromatase activity have also been observed in courting male pied flycatchers, *F. hypoleuca* [108], and male newts, *Triturus carnifex* [34]. These changes in aromatase activity could be related to an increase in T because reproductive activity usually increases T levels and in almost every species examined so far, testosterone increases aromatase activity in the preoptic area via an androgen receptor based pathway [5,95–97].

There is some evidence that sexual experience influences the activity of ERβ neurons. In female rats, mating increases the number of c-fos immunoreactive (-ir) cells in ERβ-ir, but not ERα-ir cells in the medial amygdala [38]. The medial amygdala has been implicated in the control of aggression in rodents [40,53], which suggests that sexual experience may affect aggressive behavior via changes in ER expression in the medial amygdala. These findings may relate to studies on ERβKO mice. One study testing sexually experienced ERβKO mice found that there was an interaction between genotype and number of aggression tests on aggressive behavior [82] whereas a study on sexually inexperienced ERβKO mice found no such interaction [80]. It is currently unknown whether sexual activity modulates ERβ function in male rodents.

3.3. Parental experience

In some mammals, the male's investment in reproduction does not end with mating, but continues with paternal care of offspring. These behaviors may be associated with changes in aromatase. Male infanticide of unrelated offspring has been reported in several species of biparental mammals [39,71] and birds [74]. Thus, aggressive behavior in males could protect offspring from infanticide [117,130]. When biparental California mice become fathers they become more aggressive (Trainor and Marler unpublished) and exhibit a reduction of aromatase activity in the BNST compared to sexually inexperienced males [119]. Aromatase inhibition decreases attack latency in California mice, and males with less aromatase activity in the BNST exhibit shorter attack latencies [120]. Thus, reduced aromatase activity in the BNST could increase aggression in fathers which need to defend their pups from potentially infanticidal intruders [39].

The onset of paternal behavior is associated with a decrease in both T and DHT [119], so a reduction of aromatase activity in the BNST of California mouse fathers could be due to previously described androgenic regulation of central aromatase activity. Androgens are known to increase aromatase activity [96]. Aromatase activity in the MPOA, however, does not appear to follow the classical association between androgen and aromatase levels. California mouse fathers exhibit increased aromatase activity in the MPOA despite decreased androgens. This association suggests that androgens do not mediate this change in aromatase activity in the MPOA. One possible mechanism for this change is regulation by progesterone. California mouse fathers have reduced progesterone, and preoptic aromatase activity in sexually experienced California mice is negatively correlated with progesterone (but not T or DHT) [119]. A connection between aromatase and progesterone is supported by progesterone receptor knock-out mice which exhibit increased paternal behavior [102], an observation that is consistent with the hypothesis that preoptic aromatase activity is regulated by progesterone. Thus, progesterone may play an important role in mediating the effects of social experiences on aromatase in the brain, thereby affecting behavior.

Parental experience may also affect estrogen receptors. Male house mice exposed to pups exhibit an increase in ERα immunoreactivity in the MPOA [31]. Lactating female rats also exhibit increased ERα mRNA in the MPOA compared to non-lactating females [17].

4. Estrogen and aggression in humans

Mechanisms of aggressive behavior in humans are complex, and many environmental and neurochemical systems interact to modulate aggressive behavior [24]. There has been a high level of interest devoted to assessing the relationship between T levels and aggression in humans, but consistent correlational findings have been elusive. Authors of previous reviews of this topic hypothesized that T levels do not modulate aggressive behavior in humans [2], or that confounding variables such as age or time of day mask correlations between T and aggression [15]. After reviewing the evidence that aromatization of T in the brain modulates aggressive behavior in non-human animal systems, we now consider the evidence that aromatization modulates human aggressive behavior. Aggressive behavior in humans has been classified as either premeditated or impulsive, with impulsive aggression being more spontaneous and unprovoked [7,24]. Currently, it is not yet clear how measurements of non-human animal aggressive behavior map out onto this classification. An additional complication is that studies of sexual behavior in humans have found conflicting evidence relating to the importance of steroid dependent mechanisms identified in non-human animals. However, recent studies on estrogen function in humans suggest that some estrogen dependent behavioral mechanisms identified in non-human animals may also be present in humans.

4.1. Correlational evidence

The majority of correlational evidence regarding whether aromatization in the brain affects aggressive behavior in humans comes from studies investigating T. A comprehensive analysis of the relationship between T and

aggressive behavior is beyond the scope of this paper, especially since this question has already been reviewed [2,3,15]. While some correlational studies have found significant correlations between T and aggressive behavior, others have not. A recent meta-analysis of 106 correlational studies determined that there was a weak positive relationship between T levels and aggression [15]. Multiple factors likely contribute to the inconsistency of the reported relationship between T and aggression in humans. The time of day that samples are collected affects T levels, and individuals that self-report their behavior may not accurately describe past events or how they would behave in a certain situation. Also important is that most studies do not obtain hormone samples when individuals are interacting socially. Recent studies have documented the effects of sexual [42,44], parental [10,11,33,37], stressful [75,98], and competitive [35,103] experiences on plasma levels of gonadal steroids. These experiences are rarely accounted for in correlational studies. In addition to their possible effects on T levels, social experience may also affect aromatase and estrogen receptor expression within the brain.

Indirect evidence for effects of testosterone comes from studies on the effects of anabolic-androgenic steroids (AAS) on mood and aggressive behavior in humans. Anabolic-androgenic steroids are commonly used to increase strength and athletic performance and have been reported to have behavioral effects. However, similar to studies correlating T with behavior, the relationship between AAS abuse and increased aggressive behavior has been inconsistent [43]. Studies in rats indicate that the degree to which an AAS is aromatized influences its behavioral effects [21,70], although this question has not been directly addressed in human studies.

We suggest that individual differences in central aromatase activity and steroid receptor expression within the brain may be factors that may partially account for the inconsistent relationship between T and aggression in humans. The patterns of central aromatase activity and estrogen receptors in humans are similar to the distributions reported for other mammals. Studies in post-mortem tissue samples indicate that the distributions of aromatase mRNA [99] and aromatase activity [116] are very similar to other mammals (e.g., predominantly in hypothalamus and limbic regions). Similar to other mammals, human ERα expression is highest in the amygdala and hypothalamus, moderate in hippocampal regions, and relatively low in brainstem and cortex [29,86,90]. Expression of ERβ mRNA is highest in thalamus, hippocampus, amygdala, and some areas of temporal cortex and relatively low in hypothalamus and brainstem [46,51,85]. Thus, aromatase and estrogen receptors are present in human hypothalamus and amygdala, brain regions known to regulate aggressive behavior in non-human animals [54,63,69]. Whether these brain areas are related to aggression in humans is currently unclear. There are several reports that surgical amygdalotomy reduces severe violent outburst [45,61]. However, these effects may be due to ablation of important arousal systems and not to circuits specific to aggression. Imaging studies in humans indicate that the amygdala is a primary neural substrate for negative affect [24], although its precise role in mediating aggressive behavior is still unclear. Neural mechanisms of aggression in humans are likely to be more complex than rodents, as humans have important inhibitory circuits arising from the cortex.

Studies of the ERα gene in women have suggested a possible link between estrogen receptors and components of aggression. The ERα gene in humans has a polymorphic repetitive element (TA repeat) in its promoter sequence [26]. Recent studies in humans have illustrated that variability in non-protein coding regions of genes may be important in determining aspects of personality and temperament [22,91]. One study genotyped the length of the ERα TA repeat in women and correlated these data with measures of personality traits. Women that were homozygous for shorter TA repeats scored higher on scales designed to measure 'irritability' and 'indirect aggression' compared to women that were homozygous for longer TA repeats or heterozygous [124]. Shorter TA repeats in women were also associated with higher psychoticism (suspiciousness) scores, which was in contrast to a different study on men that reported that shorter TA repeats were associated with lower psychoticism scores [23]. These personality traits may influence or modify aggressive responses. Currently, it is unknown what effects, if any, TA repeats have on ERα transcription in the brain. Further research is needed to determine the effects of polymorphisms in promoter sequences on estrogen receptor expression, and whether these polymorphisms have different effects in different tissues.

While correlational data are suggestive, only studies in which estrogenic function is manipulated can provide direct evidence for effects of estrogen on behavior. We next consider data from clinical trials which either directly or indirectly address the hypothesis that aromatization mediates aggression in humans.

4.2. Clinical trial data

Several clinical trials have assessed the effects of T or estrogen treatment on aggressive behavior in humans. A major advantage of clinical trials is that patients are prospectively treated over time, which allows for assessments of cause and effect. Some studies have moved beyond self reports of aggression through the use of observers blind to treatment assignment to assess behavior, but the majority rely on self-reports via questionnaires which may be less accurate. A disadvantage of the clinical trials is that they are typically conducted in ill populations, such as those with endocrine or psychiatric disorders, so it is uncertain how the results will apply to healthy populations. Finally, it can be difficult to recruit qualified participants, so samples sizes are often low. This increases the risk for type II error, especially because there is evidence for large individual differences in behavioral responses to steroids. Despite

these problems, clinical studies are an essential tool to determine cause and effect.

Some clinical trials have assessed hostility as a component of aggression. Individuals that rate higher on hostility scales report experiencing anger more frequently and more intensely than individuals that rate lower on hostility scales [114]. Hostility can be manifested as verbal or physical aggression, or can be "held in." Although the construct of hostility is messy, individuals with higher hostility ratings have been consistently found to have higher blood pressure [131] and have a higher risk for coronary heart disease [72]. Assessments of hostility have been conducted in conjunction with hormone replacement therapy (HRT, Prempro), with two studies reporting that post-menopausal women using HRT scored lower on hostility scales than women that did not use HRT [84,115]. These studies suggest estrogens can modulate aspects of mood which may contribute to expression of aggressive behavior.

Several studies have examined the relationship between estrogen and aggression in elderly women and men diagnosed with dementia. Some of these patients exhibit physical violence and verbal aggression [1], and this behavior has been positively correlated with peripheral T and negatively correlated with peripheral estradiol [85]. Administration of estrogen compounds to patients with dementia resulted in reduced aggressive and sexually offending behavior [58]. Behavior was quantified by nurses trained to assess behavior but blind to treatment assignment. This negative effect of estrogen treatment on aggression was consistent with case reports in which aggressive behavior in patients diagnosed with dementia was reduced by estrogen treatment [57,106].

The continued development and use of objective assessments of hostility and aggressive behavior is essential for continued progress towards understanding the mechanistic bases of behavior. While extensive training of staff and long-term observations may not be practical outside of clinics, other objective criteria for measuring behavioral responses have been used. One method is the point subtraction task [19], in which individuals either press one button to receive points redeemable for money, or press a second button that subtracts points from an opponent (usually a computer). Using this task, investigators found that men treated with a supraphysiological dose of T were more likely to subtract points from their opponent, even though their self-report responses on a questionnaire did not differ from controls [89]. Another objective measure was used in a study in which participants were provoked by a confederate during a phone conversation [9]. When the conversation was finished, the force with which participants hung up the telephone was measured using a balance built in to the telephone. The magnitude of force was correlated with salivary T levels and predicted other behavioral responses. Although all tasks have potential drawbacks, the measurement of behavioral responses is an important complement to survey methods.

5. Conclusions

There is considerable evidence in a wide variety of species that estrogens play an important role in the regulation of aggressive behavior. Estrogen production is also influenced by the environment, in some cases by well described androgen based mechanisms, but in other cases by non-androgen based mechanisms that have yet to be fully characterized. Thus, estrogen signaling provides an important outlet for social interactions to feedback on behavior. Recent studies suggest that estrogens may influence components of aggression in humans, such as hostility. Although most evidence suggests that estrogen has a negative effect on hostility in humans, further investigation may reveal additional diversity, as has been observed in estrogenic modulation of aggression in other vertebrates. The continued development of objective measures of hostility and aggression in humans should aid in the collection of more consistent results. Studying how estrogen influences aggression in different species should lead to a greater appreciation of how the molecular machinery (androgenic substrate, aromatase activity, cofactors, and estrogen receptors) interact, and may lead to insights on how estrogen contributes to individual and species variation in aggression.

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