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Androgen receptors and sociosexual behaviors in mammals: The limits of generalization

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ABSTRACT

Circulating testosterone is easily aromatized to estradiol and reduced to dihydrotestosterone in target tissues and elsewhere in the body. Thus, the actions of testosterone can be mediated either by the estrogen receptors, the androgen receptor or by simultaneous action at both receptors. To determine the role of androgens acting at the androgen receptor, we need to eliminate actions at the estrogen receptors. Alternatively, actions at the androgen receptor itself can be eliminated. In the present review, I will analyze the specific role of androgen receptors in male and female sexual behavior as well as in aggression. Some comments about androgen receptors and social recognition are also made. It will be shown that there are important differences between species, even between strains within a species, concerning the actions of the androgen receptor on the behaviors mentioned. This fact makes generalizations from one species to another or from one strain to another very risky. The existence of important species differences is often ignored, leading to many misunderstandings and much confusion.

1. Introduction

All mammals and most other vertebrates and invertebrates reproduce sexually. This means that gametes from one sex need to encounter gametes from the other. In most animals, be they invertebrates or vertebrates, a series of preprogrammed, stereotyped behavior patterns assure that this encounter occurs (Ågmo and Moralí, 2022; Dewsbury, 1972). In primates, the behaviors associated with gamete transfer are less stereotyped than in other animals (Dewsbury and Pierce Jr, 1989), and in humans there are no preprogrammed or innate patterns involved. Only the visceral sexual responses, basically erection in men and clitoral engorgement and vaginal lubrication in women, are automatic, or inborn, if that expression is preferred (Ågmo and Laan, 2023). There is an overwhelming amount of data showing that the behaviors required for gamete transfer is under the control of steroid hormones of gonadal or adrenal origin in both males and females (reviewed in Ågmo, in press; Le Moëne and Ågmo, 2018).

Mammals do not only interact with others when transferring gametes, but also in numerous contexts unrelated to reproduction. Prosocial and antisocial behaviors are commonly displayed by most mammals. Some of these behaviors, for example aggression or social recognition, are also modulated by steroid hormones. The earliest data relating these hormones to behavior stem from ablation studies, in which the consequences for sociosexual behaviors of removal of ovaries, testicles and adrenal glands were carefully described. See, for example, Allen and Doisy (1923), Hemmingsen (1933), Long and Evans (1922), Steinach (1894), and Stone (1932) for mating behavior after castration or ovariectomy, and Bloch and Davidson (1968), Dixson (1987), and Rissman and Bronson (1987) for the effects of adrenalectomy on mating behavior. When it became known that the testicles secrete testosterone and the ovaries estrogen and progesterone, castrated and ovariectomized animals were treated with these hormones, and it was found that such treatment restored behavior to the level of the intact animal (e.g. Beach and Holz-Tucker, 1949; Boling and Blandau, 1939). In the 1970ies it was discovered that testosterone is subjected to conversion to dihydrotestosterone before having effects in many target tissues, and it was also shown that testosterone is easily converted to estradiol. Of particular importance was the discovery of the enzyme responsible for this conversion in brain areas thought to be important for sociosexual behaviors. It was soon shown that many actions of testosterone depended on the conversion to estradiol (Naftolin and Ryan, 1975), blurring the distinction between androgen and estrogen, as well as between the notions of male and female sex hormones.

Since circulating testosterone can be either aromatized or 5α-reduced in target tissues (and elsewhere in the body) the effects can be mediated either by the androgen or the estrogen receptors, or both.

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Consequently, we are victims of an inevitable conundrum whenever we are interested in finding out whether the actions of testosterone depend on binding to the androgen or to the estrogen receptors. We cannot even label the actions of testosterone as androgenic before having excluded a role for the estrogen receptors. The purpose of the present review is to describe the behavioral effects of testosterone mediated by the androgen receptor, and to determine whether these effects are similar in all mammals or if they are specific to a certain order, family, species, or strain. Since only a small fraction of the mammalian species have been studied in sufficient detail to allow for a determination of the receptor mediating the effects of testosterone, this review will, by necessity, be extremely limited.

Even though the number of mammalian species studied with regard to behavioral actions of testosterone and other androgens is rather small, the number of publications addressing that issue is quite large. A search crossing the topics "testosterone" and "behavior" in the Clarivate database returns 11669 references on November 15, 2023, and 6333 references are obtained when crossing "androgen" and "behavior". An exhaustive review of all purported behavioral actions of androgens would, consequently, be unfeasible. Therefore, only effects relevant for sociosexual interactions, including social recognition, and aggression will be mentioned. These are the most well-studied of the androgen-dependent behavioral functions. Although potential anxiolytic or anxiogenic actions of testosterone (e.g. Domonkos et al., 2018) as well as actions on learning and memory (e.g. Zhang et al., 2020) indirectly may affect both sociosexual and aggressive interactions, neither such effects nor any of the other possible effects of androgen will be discussed. There are several specialized reviews covering various androgen actions, for example on antisocial behavior, empathy, and impulsivity (Yildirim and Derksen, 2012) as well as on economic risk-taking (Apicella et al., 2015) in humans. Summaries of androgen actions on behavior in non-human animals have been published at irregular intervals (e.g. Hart, 1974; McCall and Singer, 2012; Rubinow and Schmidt, 1996). However, these reviews are focused on the effects of androgens regardless of the receptor on which they are acting. In fact, there is only one prior review focusing on the role of the androgen receptor in sex and aggression (Cunningham et al., 2012). However, this review was limited to pharmacological studies, meaning that large amounts of data were omitted. Furthermore, there have been some important advances since that review was published. Thus, there is a great need for a review of the current status of the androgen receptor in sociosexual and aggressive behaviors.

Before entering into the behavioral consequences of androgen receptor activation, I will briefly discuss the origin and fate of endogenous testosterone and describe the enzymes responsible for its conversion to estradiol and dihydrotestosterone. Further transformation of the latter steroid will also be considered, and the concept of neurosteroid will be introduced. Then a short description of the androgen receptor will be provided. This background information is most helpful for understanding some of the arguments that will be presented. Furthermore, since the actions of most endogenous as well as exogenous androgens may be mediated either by 5α-reduced metabolites binding to the androgen receptor or by aromatized metabolites binding to one or several of the estrogen receptors, I will describe the methods that can be used to distinguish these actions from each other. Likewise, I will provide a summary of the sequence of events constituting sexual interactions and how and where in that sequence the androgen receptor may be involved.

Following this rather extensive preamble, the effects of androgen receptor agonists and antagonists on male sexual behavior will be summarized. I will also point out that the brain is not the only site where androgen receptors important for sexual behavior are localized. Androgen receptor-mediated functions in the spinal cord and in the periphery are crucial for some aspects of male sexual behavior. After describing the effects of aromatase or 5α-reductase inhibition, studies of reduced or absent estrogen receptor expression will be summarized. Behavioral effects of androgens must be mediated by the androgen receptor if they are unaltered after aromatase inhibition or in animals lacking estrogen receptors. The consequences of suppressing androgen receptor expression throughout the body or in the nervous system will be discussed, and the behavior of male mice overexpressing this receptor will also be described before arriving at a conclusion.

Throughout this review, species and even strain differences will be pointed out whenever they have been reported. The purpose of this is to caution against excessive generalization of androgen effects, and the involvement of specific receptors, between species and particularly against unwarranted use of non-human data for predicting effects in humans.

2. Androgens

Androgens are a group of 19 carbons (C_{19}) steroid hormones, in males mainly produced in the Leydig cells of the testis. The main testicular androgen is testosterone, but small amounts of androstenedione and dihydrotestosterone are also secreted. The adrenal cortex produces several androgens, including dehydroepiandrosterone, androstenedione, androstenediol, and 11β-hydroxyandrostenedione. These additional androgens have low affinity for the androgen receptor, but they are converted to more active androgens, mainly testosterone, in peripheral tissues. Nevertheless, about 95% of circulating testosterone in young men are produced in the testis. In cycling women, about 25% of circulating testosterone originate in the adrenals. The remaining 75% stem from the ovaries and from peripheral conversion of weaker androgens (Rosato et al., 2022). The contribution of the different production sites to each of the main androgens found in the blood stream of women is illustrated in Fig. 1.

3. Conversion to estradiol

Circulating testosterone can be aromatized to estradiol in peripheral tissues and in the brain through the action of aromatase, an enzyme causing oxidation and elimination of the methyl group on carbon 19 and hydroxylation of carbon 3, leading to aromatization of ring A in the steroid nucleus. The gene coding for aromatase is *CYP19A1*, a member of the cytochrome P450 family 19, subfamily A, localized on chromosome 15. Aromatase has been found in all vertebrates (Castro et al., 2005) whereas its presence in invertebrates has been a matter of debate. Its nucleotide sequence seems to be well conserved, with only minor variations reported so far (Goldstone et al., 2016). It is widely distributed in the body, and is found in the lungs, skin, blood vessels, bone, and adipose tissue as well as in several areas of the brain. In humans, there is no consistent sex difference in the central nervous distribution of the enzyme (Takahashi et al., 2018). In rodents, it has been reported that the expression of aromatase is higher in the amygdala, bed nucleus of the stria terminalis and the medial preoptic area in males than in females (Roselli et al., 1997), reviewed in (Shay et al., 2018). It was believed that the enzyme was localized to the cytoplasm of neurons and glia, attached to the endoplasmic reticulum (Simpson et al., 1994), but recent data suggest that aromatase can be found in the nucleus, at least in astrocytes (Kata et al., 2022). The wide distribution of aromatase in the rodent brain is illustrated in Fig. 2.

4. Conversion to dihydrotestosterone and the neurosteroids

Testosterone is also the substrate of another enzyme, 5α-reductase. The double bond between carbons 4 and 5 in the steroid nucleus is reduced by the enzyme, and the resulting product, 5α-dihydrotestosterone, is a very active androgen. In fact, the affinity of dihydrotestosterone for the androgen receptor is between 5 and 10 times higher than that of testosterone (Wilson, 2002). 5α-reductase is found in typical target tissues for androgens, as well as in skin, liver, muscles and bone. Two variants of the enzyme have been described, with one variant mainly localized to the brain. It has a wide intracerebral distribution

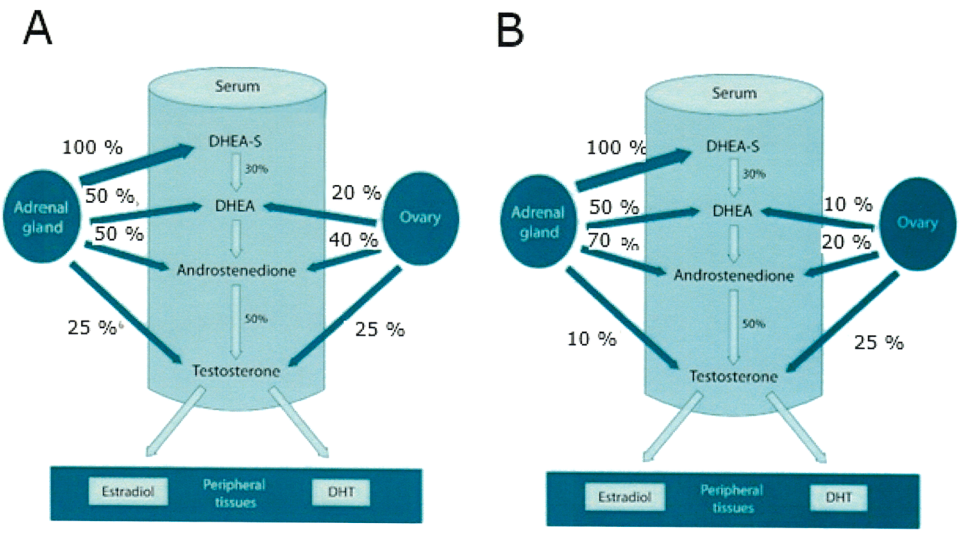

Fig. 1. DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; DHT = dihydroteststerone.
Sources of circulating androgens in premenopausal (A) and menopausal (B) women. Modified from Vigneswaran and Hamoda (2022) with permission from Wiley.

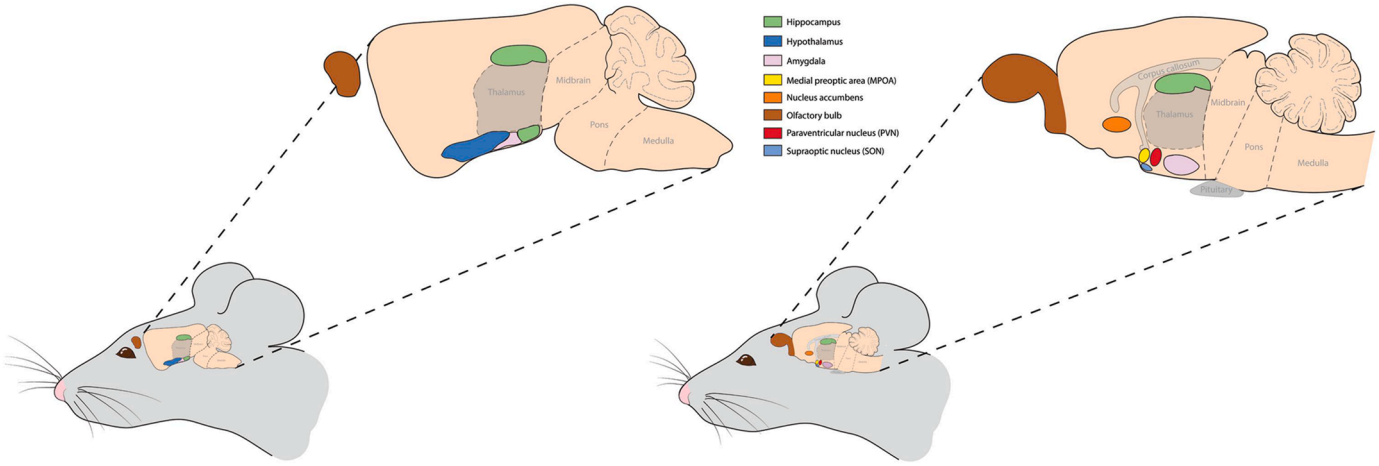

Fig. 2. Predominant brain regions expressing aromatase or the *Cyp19* gene in rats and likely in other animals. Two sagittal brain sections are illustrated to show the various brain regions, including the olfactory bulbs, hippocampus, hypothalamus, amygdala and nucleus accumbens. Within the hypothalamus, the medial preoptic area, paraventricular nucleus and supraoptic nucleus express high amounts of the enzyme. Reprinted from Shay et al. (2018) under license CC BY.

(Lephart, 1993), not limited to the areas traditionally believed to be important for sociosexual and neuroendocrine functions. Among the unexpected areas showing a high level of expression of 5α-reductase is the cerebellar cortex. It seems that the enzyme is mainly localized to glial cells, including Bergmann cells (Kiyokage et al., 2014; Pelletier et al., 1994), but there is also much evidence for localization to neurons in many brain regions (Castelli et al., 2013). Presence in GABAergic subcortical output neurons as well as in cerebellar Purkinje neurons has been reported (Agis-Balboa et al., 2006). There is no obvious sex difference in the expression of this enzyme in humans (Steckelbroeck et al., 2001), whereas data from rats are contradictory. No sex difference was found in one study (Pelletier et al., 1994), whereas males showed higher expression than females in the cerebellum but not in cerebral cortex in another (Giatti et al., 2019). Even though the main androgen, testosterone, binds to the androgen receptor, most of its androgenic activity is mediated by dihydrotestosterone.

Before finishing this brief description of 5α-reductase it must be mentioned that testosterone is not its only substrate. Progesterone is reduced to dihydroprogesterone and deoxycorticosterone to dihydrodeoxycorticosterone by this enzyme. The latter compound is further converted into allopregnanolone, the most potent of all neurosteroids (Pinna, 2020). Neurosteroids are a group of steroids synthesized both in the central and peripheral nervous system, either de novo or from circulating steroids. They mainly act on neuronal membrane receptors. Interaction with $GABA_A$ and NMDA receptors has been studied in some detail (Lloyd-Evans and Waller-Evans, 2020). None of the many neurosteroids described so far has been found to interact with androgen receptors in any significant way, and their actions are consequently outside the scope of this review. Despite this, it may be worth mentioning that some of the behavioral actions of androgens are not necessarily mediated by nuclear or membrane bound steroid receptors, but by allosteric modulation of ion channels and other membrane events (Raciti et al., 2023). It is also noteworthy that the local concentration of neurosteroids vary between brain regions and between the sexes. The sex difference is region specific, and it varies according to the estrous cycle, at least in rodents. Furthermore, gonadectomy and hormone replacement affect the levels of the neurosteroids (Giatti et al., 2019; Giatti et al., 2020) as well as direct androgen actions at the androgen receptor. Such indirect effects are not relevant in the present context, but it should be kept in mind that androgen metabolites may affect nervous function independently of androgen receptors.

As was made evident in the preceding paragraph, not all

consequences of the activity of 5α-reductase can be attributed to dihydrotestosterone. In fact, dihydrotestosterone itself is rapidly converted into 5α-androstane-3α,17β-diol (3α-diol) by 3α-hydroxysteroid dehydrogenase. The product is a weak agonist at androgen and estrogen receptors, but a potent neurosteroid and a positive allosteric modulator of $GABA_A$ receptors. In that capacity, it has been reported to facilitate female rat sex behavior (Montoya et al., 2010), whereas its effects in males are unclear (Moralí et al., 1994; Södersten et al., 1988). Nevertheless, these actions of 3α-diol are independent of the androgen receptor and will not be further discussed. Another metabolite of dihydrotestosterone is 5α-androstane-3β,17β-diol (3β-diol). The enzyme 3β-hydroxysteroid dehydrogenase is in charge of this conversion. This steroid binds neither to the $GABA_A$ receptor nor to the androgen receptor. However, it is a weak agonist at the estrogen β receptor and still weaker at the estrogen α receptor (Kuiper et al., 1997). None of these actions is relevant for the issue at hand, and none of the many proposed actions of the dihydrotestosterone metabolites will be considered in this review.

5. The androgen receptor

The androgen receptor gene is located on the X chromosome at the locus Xq11-Xq12. The gene encodes a 110 kDa protein consisting of 919 amino acids. This protein is found in the cytoplasm. When testosterone leaves the blood stream and enter target tissue it becomes converted to dihydrotestosterone by 5-α-reductase before binding to the ligand-binding pocket on the receptor protein. This leads to the dissociation of heat-shock proteins from the androgen receptor and subsequent translocation into the nucleus. There the receptor protein dimerizes before binding to the androgen response element in the promoter region of target genes. With the help of several coregulators, transcription is activated (Davey and Grossmann, 2016; Sutinen et al., 2017).

In addition to the well-characterized, nuclear androgen receptor, there are at least to putative receptors, called ZIP9 and GPRC6A, awaiting further description (Foradori et al., 2008; Thomas, 2019). Whereas the "nuclear" androgen receptor is localized to the cytoplasm when unliganded, the proposed receptors are membrane-bound. There are also several splice variants of the classical receptor (Guo and Qiu, 2011). Some of them appear to be important in some forms of prostate cancer, particularly in castration resistant prostate cancer (Konda and Viswanathan, 2022). The role of the membrane-bound receptors as well as of the splice variants is beginning to be explored in the context of prostate cancer. Their possible role in the control of behavioral functions remain unknown. Therefore, they will not be further mentioned. The ensuing discussion is strictly limited to actions at the nuclear androgen receptor.

6. Androgen receptor distribution in the brain

Before we can proceed with a meaningful discussion of the function of the androgen receptor, we must have some idea about its intracerebral localization. Early studies revealed that the androgen receptor is intensely expressed in the medial amygdala, lateral septum, the bed nucleus of the stria terminalis, preoptic area and the ventromedial nucleus of the hypothalamus (Simerly et al., 1990) of adult male rats. The androgen receptor is also found in the cerebellum, with high expression in superficial Purkinje neurons of the vermis (Perez-Pouchoulen et al., 2016). The receptor is also present in the female rodent brain with a distribution similar to that found in males (Simerly et al., 1990). However, several studies show that the expression generally is higher in males than in females (Feng et al., 2010; Roselli et al., 1989).

In humans, androgen receptor expression in the hypothalamus is weaker in women than in men (Fernández-Guasti et al., 2000). No sex difference was found in the hippocampus, though (Beyenburg et al., 2000). A study showing high expression of the androgen receptor in the temporal cortex failed to report data on sex differences although brains from both men and women were analyzed (Puy et al., 1995). It appears that potential sex differences in androgen receptor expression in humans is not an issue of major concern. Nevertheless, the human data show that the androgen receptor is widely distributed in the brain, including areas important for sociosexual behaviors.

7. How to distinguish androgen actions on the androgen receptor from actions at the estrogen receptor

A consequence of the wide distribution of both aromatase and 5α-reductase is that as soon as testosterone is present, dihydrotestosterone and estradiol can also be expected to be present. This means that actions of endogenous as well as of exogenous testosterone can be attributed either to the androgen or the estrogen receptors, or to the simultaneous actions at both receptors, as mentioned. Considering that 95% of circulating androgens are easily aromatizable as well as 5α-reducible, simultaneous actions on both androgen and estrogen receptors can be expected. Therefore, in case we want to elucidate the specific consequences of ligand binding to the androgen receptor, we would need to assure that estrogen receptors are not simultaneously activated.

In addition to the two nuclear estrogen receptors, α and β, there is a G protein coupled, membrane bound receptor, often labelled GPR30 or GPER 1. There is only one study suggesting a possible role of the GPR30 in male rat sexual behavior. The antagonist G15 ((3aS,4 R,9bR)− 4-(6-bromo-1,3-benzodioxol-5-yl)− 3a,4,5,9b-tetrahydro-3 H-cyclopenta[*c*] quinoline) reduced approach to a sexually receptive female in Long Evans males without sexual experience. The antagonist had no effect in sexually experienced males. Likewise, copulatory behavior was unaffected (Hawley et al., 2017). There is neither any replication nor data from any other species available. Therefore, in the following I will ignore the potential contribution of aromatized androgens acting at the GPR30.

The androgen receptor is found in many tissues throughout the body both in rodents and humans, and it is present in several brain sites relevant for sociosexual and other behaviors (see previous section). This is also the case for the estrogen receptors (Pelletier, 2000; Simerly et al., 1990). Estrogen and androgen receptors are often present in the same brain structures, and are frequently colocalized on the same neurons (Greco et al., 1998; Wood and Newman, 1995). This means that separating testosterone actions mediated by estrogen and androgen receptors may be difficult. However, the difficulty is not unsurmountable.

Indeed, in intact animals, i.e. animals with endogenous steroid production, there are several ways to eliminate testosterone actions on estrogen receptors as well as on the androgen receptor. Aromatase expression could be eliminated, thereby indirectly eliminating androgen action at estrogen receptors. There are several ways to silence the expression of each of these receptors or of aromatase. Whole body knockouts for the relevant receptors as well as for aromatase were created many years ago, and these mice have been extensively used in studies of sex behavior. More recently, Cre-driver strains have been bred with floxed mouse strain to create conditional knockout mice, for example mice lacking androgen or estrogen receptors in the nervous system. These strains have been used in some studies. It is also possible to inactivate receptor genes in specific brain structures with the help of interference RNA or with the use of antisense nucleotides. These procedures have been used in studies of sexual behavior both in rats and mice, but they were limited to silencing estrogen receptors. Specific genes at specific sites and at a specific time could also be inactivated by local injection of Cre-expressing virus into floxed mice. This can also be achieved by using inducible Cre-loxP systems (Kim et al., 2018). These newer techniques are beginning to be used in studies of male sexual behavior, but as will become evident in Sections 10.6 and 7, they have only been applied to the estrogen receptors.

Instead of manipulating gene expression, pharmacological tools can be used for blocking aromatase as well as the estrogen receptors. There are several drugs available for both approaches. The structural and temporal specificity of drug treatment can be varied from chronic,

systemic treatment to local injection into target structures at a specific time point. Whichever of these procedures should guarantee that the endogenous androgens only act at androgen receptors provided that the compound used has no action at other receptors and that no crosstalk between receptors occurs. As with all pharmacological studies, results need to be interpreted with caution.

Another approach to the issue of separating androgen actions on estrogen receptors from actions on androgen receptors is to use experimental subjects in which the endogenous production of testosterone and estradiol has been eliminated, for example by castration or ovariectomy. If androgen substitution is made with a non-aromatizable androgen, then all effects must be attributed to the androgen receptor. Dihydrotestosterone is one such androgen. Others are fluoxymesterone and oxandrolone, both in clinical use. All these compounds act exclusively on the androgen receptor and offer an efficient and simple way to study the behavioral effects of that receptor, uncontaminated by actions at estrogen receptors. Local administration into the brain increases anatomical specificity. In fact, intracerebral implantation of gonadal steroids has provided invaluable information as to central site of action of these molecules. For example, testosterone implanted into the preoptic area in castrated rats restored sex behavior (Davidson, 1966; Lisk, 1967), showing that androgen action in this area are sufficient for maintaining that behavior. Implants adjacent to, but outside of, the preoptic area were ineffective. Similar observations have been made in mice of a C57/BL6 x AKR/J hybrid strain (Matochik et al., 1994). In castrated guinea-pigs, implants of dihydrotestosterone into the preoptic area restored sexual behavior. There was no leakage of hormone to the general circulation, since the seminal vesicles were not larger than those of castrated controls (Butera and Czaja, 1989). Russell et al. (2012) showed that the estrogen receptor α agonist PPT administered to the preoptic area maintained sexual behavior in castrated male Sprague Dawley rats treated with dihydrotestosterone. The β agonist DPN was ineffective. These are only some examples of the valuable data obtained in studies employing administration of androgens either alone or combined with estrogens.

In principle, it would also be possible to install stimulatory or inhibitory opsins exclusively in neurons expressing androgen receptors. After transfection, these neurons could be either excited or inhibited, and the immediate behavioral consequences could be determined. Alternative, Designer Receptors Activated Only by Designer Drugs (DREADDs) could be used instead of opsins, although this would provide comparatively poor temporal resolution. Indeed, both chemogenetic and optogenetic procedures have been employed for altering activity in neurons expressing the estrogen receptor β (Takenawa et al., 2023). For some reason, androgen receptor expressing neurons do not seem to attract scientists' attention as much as neurons expressing the estrogen receptors do. Despite the somewhat limited range of procedures that have been employed in studies of androgen receptor effects on behavior, enough data are available for a preliminary description of these effects. In the following, I will review data relevant for male copulatory behavior in males and females as well as for female sexual behavior in females and males. In later sections, the role of the androgen receptor in aggression and social recognition will be analyzed.

8. Organizational and activational effects

In male fetuses androgens are secreted quite early during gestation in primates. In the human, the fetal testis begins to secrete androgens around gestational week 10, with a peak around week 16 (reviewed in Braun et al., 2021). In guinea-pigs, there is a peak between days 33 and 36 of gestation (Vreeburg et al., 1981), i.e. in the middle of pregnancy. In rats and mice, the peak is close to the end of gestation, with a surge a few hours after birth (Konkle and McCarthy, 2011). The early secretion of androgens determines the sexual differentiation of future behavior in the way that female behavior patterns are permanently suppressed and male behavior pattern are established. This is called "the organizational effects" of androgens (Arnold and Breedlove, 1985). From the end of the early androgen surge until puberty, the gonads produce insignificant amounts of sex hormones. When hormone production is reinitiated, males will display their sex-typical mating behavior whereas females will display theirs. It should not be forgotten, though, that males occasionally display behavior patterns typical of females, and that females may display male-typical behaviors. The effects of the gonadal hormones in adults are called "activational". This review will not consider organizational effects at all. Thus, the following analysis will be strictly limited to the activational effects of androgens.

9. A note on the nature and quantification of sexual behavior

One definition of sexual behavior is "any action leading to sexual reward. Sexual reward is a state of positive affect activated by physical stimulation of the genitalia or mental representations of such stimulation" (Ågmo, 2007, p. 3). Except for masturbation and sexual fantasies, stimulation of the genitals requires a partner. Therefore, before sexual behavior per se can be initiated, physical contact with a partner must be established. This is normally achieved by displaying behaviors leading to reduced physical distance to a potential partner, eventually ending in physical contact and copulation. In fact, behaviors displayed during sexual encounters are organized in an ordered sequence. This sequence was first described in humans (Byrne, 1977). Somewhat later it was formalized and integrated in an incentive motivation framework (Ågmo, 1999; Ågmo and Laan, 2023). Fig. 3 illustrates this ordered sequence of events, including the motivational process underlying it.

It is most convenient to distinguish the sexual approach behaviors from copulatory acts. The former are extremely variable, determined by the context and the experiences of the approacher whereas the copulatory acts are highly stereotyped in all non-primate animals. They can, in fact, be understood as a series of viscerosomatic reflexes (Contreras and Ågmo, 1993; Le Moëne and Ågmo, 2019).

Male copulatory behavior is characterized by a small number of motor patterns. In the male rat these are: Mounts, the male poses his forelegs over the female's back, and makes rapid (17–22 Hz) anteroposterior pelvic thrusts for about 300 ms. He then dismounts rather slowly; intromission (vaginal penetration). This behavior starts with a mount, but suddenly the male makes a deep thrust forward and stops pelvic thrusting. The vaginal penetration lasts for about 400 ms. He then vigorously withdraws and always licks his genitals; ejaculation begins like an intromission, but after vaginal penetration the male remains on the female for 1–3 s. Rhythmic contractions of the posterior abdomen are clearly visible. He then slowly raises with his forelegs held open, and the female runs away (Moralí et al., 2003). In mice, intromission duration is far longer than in rats, and low-frequency (about 2 Hz) intravaginal thrusting is always present. Among lagomorphs, the male rabbit displays a mount lasting for about 3 s. If intromission is achieved, he ejaculates immediately (Contreras and Beyer, 1979). An extensive review of copulatory behavior patterns covering most mammals was published many years ago (Dewsbury, 1972). In primates, some species show a single, long intromission with vaginal thrusting, whereas others show a series of short intromissions before ejaculation (Dewsbury and Pierce Jr, 1989).

Regardless of the specifics of copulatory behavior, there are some common parameters that are used to characterize it. The simplest is to report the proportion of animals in a treatment group displaying a particular behavioral item. The number of occurrences of a behavior pattern (either absolute or per unit time) is also frequently reported. In addition, the temporal aspects of the sexual interaction can be recorded. The time from the moment a member of the other sex becomes available until the first copulatory act is often used, as is the time between the initial vaginal penetration and ejaculation. All or some of these standard parameters are used to determine if a certain treatment affects copulatory behavior, and this allows for comparisons not only between studies within a species but also for comparisons between species. Several

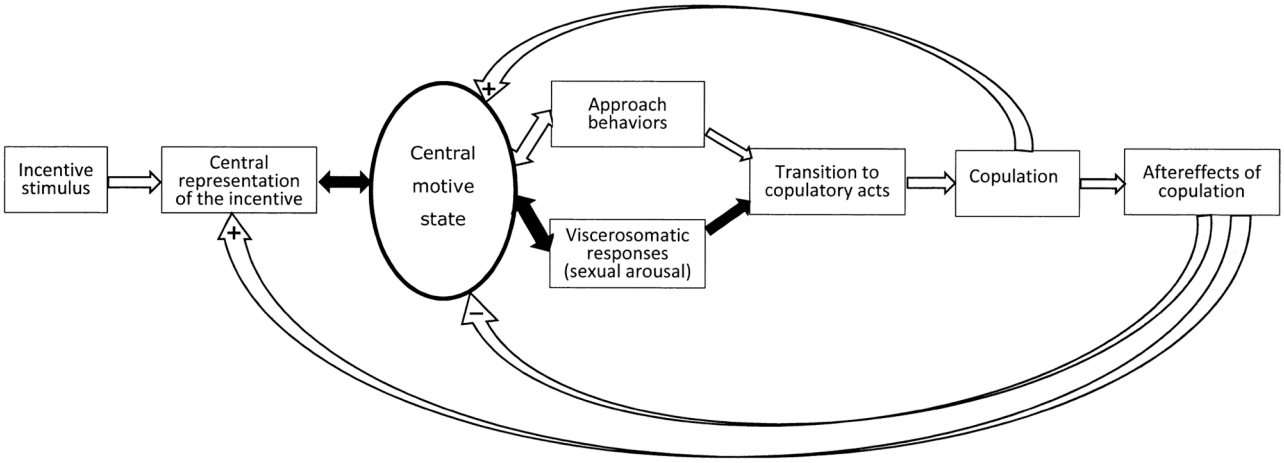

Fig. 3. Schematic description of the sequence of events constituting a sexual encounter and the underlying mechanisms. It is reasonable to suppose that the gonadal hormones act on the entity labelled "central motive state" when determining the intensity of sexual approach behaviors. Most likely, peripheral hormone actions are important for copulatory performance, but less so for motivational mechanisms.
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additional parameters may be used for detailed descriptions of copulatory behavior, but most of these are not appropriate for interspecies comparisons. For a detailed discussion of this issue, see Ågmo (1997) and Ågmo and Moralí (2022). In men, copulatory behavior *sensu strictu* is rarely quantified. Instead, questionnaires are used to evaluate the frequency of sexual acts.

In female rodents, copulatory behavior is limited to the lordosis posture, a concave arching of the back, raised hind quarters, and the tail moved to one side. Usually, the proportion of male mounts leading to a lordosis response is the indicator of the intensity of copulatory behavior (Kuehn and Beach, 1963). This proportion is usually expressed as a quotient, the lordosis quotient, defined as the number of lordoses displayed divided by the number of mounts received. The result is often multiplied by 100 to avoid the use of decimals. Sometimes the proportion of females displaying lordosis is reported. These measures are generalizable between studies and between rodent species. In other mammals, including primates, the frequency of sexual acts or the proportion of subjects displaying such acts are often used to determine the intensity of copulatory behavior (Young, 1941a; b). In women, self-report questionnaires are used instead of direct observation. It is believed that this kind of data adequately reflect the effects of experimental or clinical manipulations on copulatory behavior.

Measures of copulatory behavior are inappropriate for estimations of the intensity of sexual motivation both in humans and non-human animals (Ventura-Aquino and Ågmo, 2023). In non-human animals, sexual motivation in the form of approach behaviors can easily be quantified and used to compare the effects of different treatments within a study or the effects of similar treatments in different studies or different species. In humans, the genital responses (enhanced blood flow) to sexually relevant stimuli are exquisite measures of sexual motivation (see Ventura-Aquino and Ågmo, 2023 for a review). Both sexual approach behaviors and genital responses can be recorded in both males and females.

There is no obligatory relationship between the sexual approach behaviors and the copulatory behaviors with the exception of temporal order, approach always preceding copulation. The intensity of approach and the intensity of copulatory activities vary independently as soon as approach intensity surpasses a threshold (Ågmo and Laan, 2023; Le Moëne and Ågmo, 2019). This is similar to the independent variation of serum testosterone concentration and the intensity of copulation as soon as the serum level is above a threshold (see, for example Damassa et al., 1977 for data from rats and Brown et al., 1978 for data from men).

The overwhelming majority of studies of sexual behavior focus on copulation while completely ignoring sexual approach. This is unfortunate, since the intensity of approach is an exquisite measure of sexual motivation, whereas copulatory behaviors are not (Ventura-Aquino and Ågmo, 2023). In the same way as the copulatory behaviors depend on gonadal hormones, sexual approach is strictly hormone dependent.

10. The androgen receptor and male sexual behavior

10.1. A comment on peripheral androgen receptors

Copulatory behavior in males is heavily dependent on spinal and peripheral mechanisms, notably those related to erection, seminal emission and ejaculation. All these events depend on activity in both branches of the autonomous nervous system as well as in the somatic nervous system. Sensory input from the penis and the preputial area is crucial for the coordination between behavioral elements and the autonomous as well as somatic responses. Anesthesia of the glans penis or section of the dorsal penile nerve leads to an inability to achieve intromission in rats, (Larsson and Södersten, 1973), rabbits (Ågmo, 1976), dairy goats of the Saanen breed (Metzler et al., 1988), cats (Aronson and Cooper, 1968), bulls (Beckett et al., 1978) and marmosets (Dixson, 1988). In rhesus monkeys, the effects of penile desensitization are less dramatic. Section of the dorsal penile nerve almost abolishes ejaculation, but intromission accompanied by intravaginal thrusting occurred in some males (Herbert, 1973). Despite these minor species differences it may be concluded that sensory stimulation is essential for the execution and timing of the entire copulatory pattern.

Androgen receptors are widely distributed among the sensory as well as autonomic neurons innervation the accessory sexual glands and the corpora cavernosa (Keast, 1999; Keast and Gleeson, 1998; Lewis and Mills, 2004). Likewise, such receptors are found on neurons in the spinal ejaculation generator and in preganglionic efferent neurons as well as on somatic neurons innervating the bulbocavernosus and ischiocavernosus muscles (Jordan, 1997; Sar and Stumpf, 1977). The size of the soma and the length of the dendrites in the latter neurons depend on ligand activity at the androgen receptor since mice lacking this receptor in the nervous system show reduced soma size (Raskin et al., 2012). The muscles themselves express abundant androgen receptors, and the administration of compounds exclusively acting at these receptors are sufficient for preventing the effects of castration on the penile muscles in Fisher F344/Brown Norway rats (Ye et al., 2014).

In castrated rats, dihydrotestosterone and testosterone are equipotent for stimulating the erectile response to nerve stimulation (Lugg

et al., 1995). The response to testosterone was significantly reduced by concurrent administration of finasteride, suggesting that testosterone acted on the androgen receptor after 5α-reduction. The capacity of testosterone to prevent the deleterious effects of castration on the corpora cavernosa response to electrical stimulation of the cavernous nerve has been confirmed in another study (Baba et al., 2000). Likewise, the reduction in pelvic ganglion soma size following castration can be prevented by administration of testosterone or dihydrotestosterone. Estradiol is ineffective (Purves-Tyson et al., 2007). Moreover, the thrusting displayed during mount, intromission and ejaculation in rats is under the control of androgens. Testosterone and dihydrotestosterone synchronize spinal motoneuron discharge, thereby enhancing thrusting vigor, whereas estradiol has no such effect (Beyer and González-Mariscal, 1994). These observations strongly suggest that the androgen rather than the estrogen receptor is the target of testosterone actions.

This short overview of spinal and peripheral actions mediated by the androgen receptor should be sufficient for proposing that many of the effects of testosterone indeed depend on this receptor. However, both cytosolic estrogen receptors are expressed in most of the structures mentioned here (see e.g. Purves-Tyson et al., 2007; Sun et al., 2013), meaning that a role for aromatization of testosterone cannot be completely excluded until more data have become available.

10.2. Evidence from studies employing hormone replacement in castrated animals or receptor antagonists in intact animals

10.2.1. A note on hormone replacement procedures

Castration of male rodents leads to a gradual reduction of copulatory behavior. Within a couple of days, ejaculation will no longer be achieved. After some additional days, the castrated male ceases to display intromission. About three weeks postcastration, mounts will also disappear in most males. The effect of androgen replacement will appear in the opposite order. First, mounting will be reinitiated. This occurs often during the first week of treatment. Intromissions will be displayed a few days later, and after about three weeks of treatment, copulatory behaviors, including ejaculation, will return to precastrational level (reviewed in (Hart, 1974).

The slow, genomic actions of androgens, mean that experimental studies almost always employ chronic treatment, either by daily injections of the steroid dissolved in oil (olive, corn, arachis, etc.) or by implanting s subcutaneous Silastic® capsule filled with crystalline androgen. Since the steroid penetrate the capsule wall at a constant rate, depending on the surface area, such capsules can maintain serum concentration at a stable level for several months (Damassa et al., 1977). Instead of a Silastic® capsule, a pellet consisting of compressed, crystalline steroid can be implanted subcutaneously. It will provide constant release for weeks.

Intracerebral administration is usually made by filling the distal end of a guide cannula with crystalline steroid and leave it in place for the duration of the experiment, usually a few weeks. Sometimes a steroid solution is infused intracerebrally via a cannula connected to an osmotic minipump. Such infusions may last from a couple of days up to 28 days. Androgen receptor antagonists are usually administered in a way similar to that of the agonists, i.e. chronically via daily injections or via capsule or cannula implantation.

I usually indicate treatment route and duration. When pertinent, additional details of treatment are provided. Since the androgen agonists or antagonists mentioned here almost always are administered chronically and often by a constant release system, possible differences in pharmacokinetics are not of major concern. This also applies to the estrogens that sometimes have been used. Furthermore, there is no evidence for U shaped, inverted or not, dose – effect relation with regard to androgen effects on sexual behavior. There is a linear dose – effect relationship up to maximum response, which is at the same level as in the intact animal (e.g. Beach and Fowler, 1959; Damassa et al., 1977). Most studies employ supramaximal androgen doses.

10.2.2. A note on the determinants of individual differences in the intensity of sexual behaviors

Since the serum concentration of androgens is unrelated to the intensity of sexual behavior (see above), other factors must underly the interindividual differences in the intensity of this behavior. The earliest evidence for this stems from a study in guinea pigs (Grunt and Young, 1952, 1953). The performance of intact males was determined in 10 tests for copulatory behavior. Based on average performance, the males were classified as having either high, medium, or low sex drive. They were than castrated, and when postcastrational sex behavior had reach a very low level, all males were treated with the same dose of testosterone propionate (injected daily) for several weeks. It turned out that the precastrational classification was reestablished during testosterone replacement. The authors concluded that the individual differences were "strongly influenced by the reactivity of the tissues" (Grunt and Young, 1953, p. 144).

Individual differences between the sex behavior of intact animals are preserved after castration and constant dose androgen replacement also in rats (Beach and Fowler, 1959; Larsson, 1966), rabbits (Ågmo, 1976), and rhesus monkeys (Phoenix and Chambers, 1988), showing that the sensitivity to androgens is a stable characteristic also in these species. The exact nature of the individual differences in sensitivity to androgens remain obscure, although some scientists propose that differences in receptor expression might be of importance (Fernández-Guasti et al., 2010; Portillo et al., 2006). Against this proposal speaks the observation that androgen receptor overexpression throughout the nervous system fails to alter male sexual behavior (see Section 10.7). The intricate relationship between androgen receptor expression during the organizational as well as activational phases of androgen actions has been pointed out in an exhaustive review (Swift-Gallant and Monks, 2017). There might also be many factors influencing the coupling between ligand binding to the androgen receptor and transcription of target genes. The actions of most of these factors are only partly understood. A discussion of this issue goes far beyond the purpose of the present review. Nevertheless, it is important to realize that androgen action beyond receptor binding may be crucial for the behavioral actions of this steroid.

10.2.3. Androgen receptor agonists and antagonists and sex behavior

Shortly after it was discovered that testosterone is metabolized to dihydrotestosterone in peripheral target tissues before exerting its androgenic actions (Bruchovsky and Wilson, 1968) it was hypothesized that dihydrotestosterone might also be responsible for the central actions of testosterone. This hypothesis was tested in an experiment in which castrated male rats were treated with dihydrotestosterone. This steroid failed to restore copulatory behavior (McDonald et al., 1970). Shortly after McDonald's observation, Naftolin and collaborators showed that aromatase was present in the brain (Naftolin et al., 1971, 1972). This made it reasonable to suppose that part of the testosterone present in the brain needed to be aromatized to estradiol to stimulate male copulatory behavior. To test this supposition, castrated male rats were treated with a combination of dihydrotestosterone and estradiol. Copulatory behavior was rapidly restored to precastrational levels (Baum and Vreeburg, 1973; Larsson et al., 1973). It may be interesting to note that the importance of testosterone conversion into estradiol for male sexual behavior had been suggested long ago by Steinach et al. (1936). In the 1970ies this suggestion had been forgotten, and neither Baum and collaborators nor Larsson and colleagues referred to Steinach. A kind of excuse for this omission was published many years later (Södersten et al., 2014).

Studies of the effects of androgen receptor blockade with antagonists suggest that this receptor is not indispensable. Cyproterone acetate was without effect in one study (Whalen and Edwards, 1969), and so was flutamide in another (Södersten et al., 1975). To the contrary, a

metabolite of flutamide, 2-hydroxyflutamide (also known as SCH-16423), has been found to inhibit the *restoration* of copulatory behavior in castrated males treated with testosterone (McGinnis and Mirth, 1986). *Maintenance* of that behavior was also impaired by this androgen antagonist. Similar effects have been found after intracerebral administration of hydroxyflutamide. Restoration of copulatory behavior was impaired when the antagonist was implanted into the medial preoptic area together with testosterone in castrated Long-Evans rats (McGinnis et al., 1996). A slightly different approach was employed in a subsequent study. Now testosterone was administered systemically to castrated Long-Evans rats through a subcutaneous Silastic® capsule. At the same time as the capsule was implanted, an hydroxyflutamide containing cannula was inserted either into the anterior or posterior part of the medial preoptic area. The anterior cannula efficiently blocked the restoration of copulatory behavior. Similar results were reported in a later study also using Long-Evans males (Harding and McGinnis, 2004). In that study, it was also found that hydroxyflutamide efficiently blocked restoration of copulatory behavior after implantation into the ventromedial nucleus of the hypothalamus. In addition to blocking restoration of copulatory behavior, implants into this area reduced sexual approach behaviors. The males did not approach an ovariectomized female (a nonsexual stimulus) less than they approached a sexually receptive female.

Similar results were obtained in a study of intact Long Evans rats. When flutamide was implanted into the posterodorsal medial amygdala, preference for approaching a sexually receptive female over another male was eliminated. Odor discrimination was unaffected (Hosokawa and Chiba, 2010). These observations show that androgen receptors outside the preoptic area and ventromedial nucleus are needed for maintaining some aspects of male rat sexual behavior.

The series of studies from the McGinnis lab mentioned above convincingly shows that androgen receptors within the brain are needed for the expression of copulatory behavior. Some of these receptors are also involved in sexual approach behaviors. These results appear to contradict the older studies reporting that androgen receptor antagonists do not affect male rat sexual behavior. It is difficult to provide an explanation, but a contributing factor to the conclusions presented in the older studies may be the enthusiasm surrounding the discovery of aromatization.

A detailed study of the role of aromatization for sexual approach behaviors in castrated male Wistar rats revealed that dihydrotestosterone by itself indeed stimulates approach to a sexually receptive female, whereas estradiol by itself was ineffective. Testosterone, however, was significantly more effective than dihydrotestosterone for stimulating approach behavior (Attila et al., 2010). Incidentally, the stimulating effect of testosterone was much reduced when combined with the aromatase inhibitor fadrozole. In fact, the combined treatment was no more effective than dihydrotestosterone by itself was. These observations show that sexual motivation, manifested as approach to a sexually relevant stimulus, requires simultaneous stimulation of androgen and estrogen receptors to be at the level of intact males. Nevertheless, stimulation of androgen receptors with dihydrotestosterone increases sexual motivation above the level found in castrated animals even in the absence of estrogens. It is noteworthy that these animals did not display any copulatory behavior whereas the proportion of animals displaying mounts and intromissions was increased by estradiol, albeit to a level far below intact animals or castrated animals treated with testosterone. Thus, dihydrotestosterone alone stimulates sexual approach to some degree but not copulatory behavior while estradiol has the opposite action, to some degree stimulating copulatory behavior but not

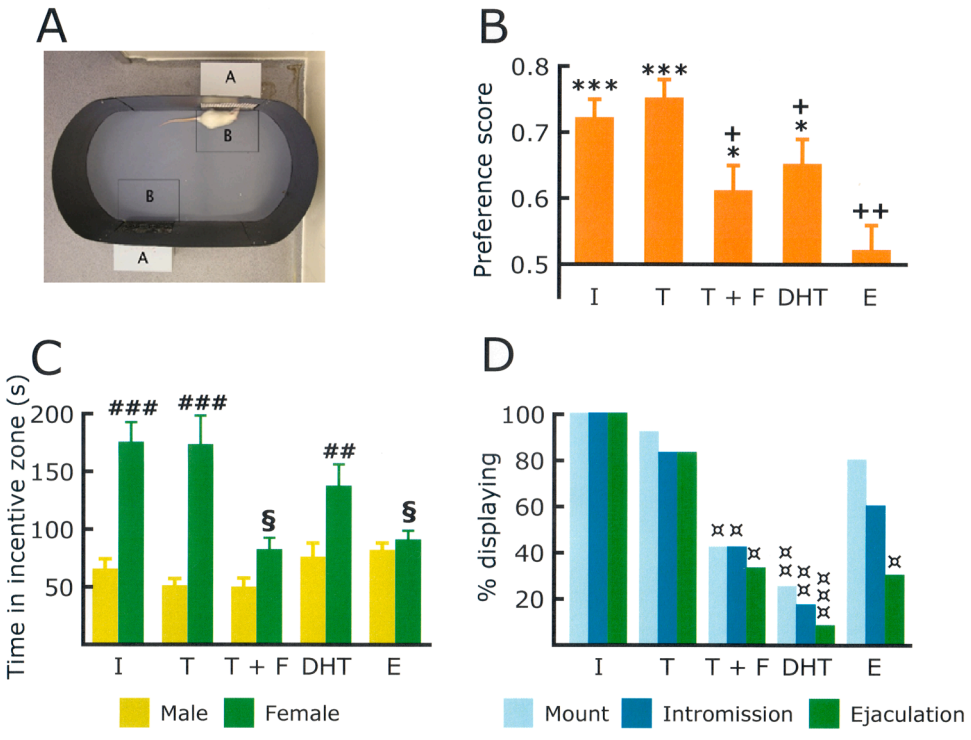

Fig. 4. A. The setup used for studying sexual approach behaviors. **B.** Preference score (time spent in the sexually receptive female zone / (time spent in that zone + the time spent in the intact male zone)) in intact male rats (I) and in castrated males treated with testosterone (T), testosterone + fadrozole (T + F), dihydrotestosterone (DHT), or estradiol (E). Data are from a test performed 20 days after beginning treatment. **C.** Time (in s) in the incentive zones during the test at 20 days of treatment. **D.** Copulatory behavior in these groups displayed at a test 21 days after the beginning of hormone treatment. Data are mean + SEM. * , different from no preference (i.e. a score different from 0.5), $p < 0.05$; * ** , $p < 0.001$. + , different from I and from T, $p < 0.05$, + +, $p < 0.01$. ##, different from male incentive in the same treatment group, $p < 0.01$, ###, $p < 0.001$. §, different from female in groups I and T. ¤, different from I and T, $p < 0.05$; ¤¤, $p < 0.01$, ¤¤¤, $p < 0.001$.
For further details, see Attila et al. (2010), from which the figure has been modified. It is reproduced with permission from Elsevier.

approach. The data from the Attila et al. (2010) study mentioned here are illustrated in Fig. 4.

In addition to rodents, aromatization of testosterone seems to be necessary for the activation and maintenance of sexual behavior in pigs (Levis and Ford, 1989). This is also the case for other domestic animals, including rams (D'Occhio et al., 1985) and steers (Dykeman et al., 1982). Even if it is not within the scope of this review, it can be mentioned that the importance of aromatization of testosterone is not limited to mammals. For example, dihydrotestosterone is inactive if not combined with estradiol in quails (Balthazart and Surlemont, 1990; Harada et al., 1993).

There are also reports showing that dihydrotestosterone is capable of activating sexual behavior in castrated King-Holtzman rats, even though the intensity of behavior did not return to precastrational levels (Olsen and Whalen, 1984). Likewise, the 5α-reduced steroid maintained sex behavior for a period after castration, but did not prevent the long-term decline. Strain differences with regard to the effectiveness of dihydrotestosterone have also been reported in mice. Whereas the Swiss-Webster strain responds to dihydrotestosterone, CD-1 mice do not (Luttge and Hall, 1973b). However, later data from the same lab show that dihydrotestosterone indeed can maintain copulatory behavior in CD-1 mice, albeit at a lower level than when combined with estradiol (Wallis and Luttge, 1975). As a curiosity it may be mentioned that when dihydrotestosterone was administered in a propylene glycol vehicle it failed to stimulate sex behavior in Swiss-Webster mice, whereas it was almost equipotent to testosterone when dissolved in oil (Luttge et al., 1974). The authors do not propose any explanation for this difference between solvents, but mention that it applies to other steroids as well.

Studies in guinea-pigs have established that aromatization is not necessary (Alsum and Goy, 1974; Butera and Czaja, 1985), and that local administration of dihydrotestosterone into the preoptic area efficiently reestablishes copulation in castrated males (Butera and Czaja, 1989). Also in castrated hamsters, dihydrotestosterone efficiently activates sex behavior (Payne and Bennett, 1976; Romeo et al., 2001), but testosterone has been reported to be more effective (Whalen and Debold, 1974). In castrated rabbits neither dihydrotestosterone nor estradiol stimulates sexual behavior whereas testosterone does (Ågmo and Södersten, 1975). Moreover, the non-aromatizable androgen fluoxymesterone is equipotent to testosterone for reestablishing sex behavior in castrated males (Ågmo, 1977) confirming that aromatization is not necessary. It has also been shown that an androgen receptor antagonist, cyproterone acetate, reduces sexual behavior in intact rabbits (Ågmo, 1975). Furthermore, in a reptile of the order squamata, the green anole (*Anolis carolinensis*), dihydrotestosterone facilitates male copulatory behavior after peripheral administration (Adkins and Schlesinger, 1979). However, another study reports that this steroid was unable to activate copulation in this species (Crews et al., 1978). It is difficult to reconcile this kind of contradictory data, and I will not speculate about possible reasons for the inconsistency. Nevertheless, it is interesting to find opposing observations also in non-mammalian species.

Turning to primates, it has been reported that male copulatory behavior is efficiently activated by dihydrotestosterone in the rhesus monkey (Cochran and Perachio, 1977; Phoenix, 1974) showing that aromatization is not necessary for the display of male sex behavior. To the contrary, in the cynomolgus monkey (*Macaca fascicularis*), testosterone is much superior to dihydrotestosterone for the activation of copulatory behaviors (Michael et al., 1986). In men, transdermal treatment with dihydrotestosterone for 24 months, in a dose sufficient to completely suppress serum testosterone and estradiol, had no deleterious effect on sexual functions (Sartorius et al., 2014). It was concluded that aromatization of testosterone is not necessary. This observation confirmed an older study in which it was found that an estrogen receptor antagonist, tamoxifen, did not affect sexual function in healthy young men. Moreover, replacing the habitual treatment with testosterone with dihydrotestosterone did not reduce sexual functions in agonadal men (Gooren, 1985).

The effects of compounds binding to the androgen receptor in several mammalian species and strains are summarized in Table 1. It can be seen that selective stimulation or blockade of this receptor have varying effects on sexual behaviors according to the species or strain that was used. This variability precludes inter-species generalization of effects and often also generalizations between strains within a species. However, the fact that different hormones, and consequently different receptors, are involved in different species and strains in no way contradicts the notion that gonadal hormones are needed for the display of sexual behaviors.

10.3. Studies with aromatase inhibitors

The importance of aromatization for activating sexual behavior by testosterone in some strains of castrated male rats was confirmed in studies with aromatase inhibitors (Beyer et al., 1976; Moralí et al., 1977). Also in intact male Sprague-Dawley rats, treatment with the aromatase inhibitor fadrozole strongly reduced copulatory behavior (Roselli et al., 2003). It was restored to pretreatment level about a week after implantation of an estradiol containing Silastic® capsule. Moreover, local administration of testosterone to the medial preoptic area of castrated male Long Evans rats failed to activate copulatory behavior when combined with an aromatase inhibitor whereas this behavior was stimulated by testosterone alone (Christensen and Clemens, 1975). However, there are important species differences within mammals with regard to the effects of aromatase inhibition. For example, fadrozole failed to reduce male hamster sexual behavior even though aromatase was efficiently blocked (Cooper et al., 2000). Furthermore, another aromatase inhibitor, ATD, failed to reduce the effects of testosterone in castrated guinea-pigs (Roy and Goy, 1988). These observations coincide with data showing that dihydrotestosterone efficiently activated copulatory behavior in hamsters and guinea pigs, as mentioned in the previous section.

The first indication that testosterone does not need to be aromatized for maintaining sexual behavior in the human male was obtained in a study in which healthy young men were treated with an aromatase inhibitor for several weeks (Bagatell et al., 1994). Serum estradiol concentration was much reduced, but no deleterious effect on sexual functions was found. In another study, the aromatase inhibitor letrozole was found to improve sexual function in men who have sex with men and who complained of low sexual desire (Richardson et al., 2007). Since serum estradiol concentration was reduced while testosterone concentration remained unchanged during letrozole treatment it was suggested that estradiol in fact has an inhibitory action on sexual behavior in men. A similar proposal was presented in another study of impaired sexual function in HIV-infected men on antiretroviral therapy (Lamba et al., 2004). The ensemble of these data strengthens the conclusion based on studies of the effects of receptor agonists and antagonists mentioned in the previous section, namely that actions on estrogen receptors are not a requisite for maintaining sexual activity at a normal level in the human male.

10.4. Studies based on manipulations of the aromatase gene

Studies in mice lacking the aromatase gene further support the notion of a role for estrogen receptors in male mouse sexual behavior. Knockout males derived from the C57BL/6 strain showed a highly deficient copulatory behavior, basically limited to an occasional mount (Honda et al., 1998). Furthermore, these males did not approach a sexually receptive female (Bakker et al., 2002), suggesting that all aspects of sexual behavior were severely deficient in mice lacking the aromatase gene. The deficient sexual behavior of these mice was improved by administration of estradiol to adult males (Bakker et al., 2004), further strengthening the evidence for a crucial role of estrogens, hence estrogen receptors, in sexual behaviors in the C57/BL6 strain. A summary of the evidence for the role of estrogen receptors in mouse

Table 1
Effects of stimulation or inhibition of androgen receptors on copulatory behavior in males. DHT, dihydrotestosterone. ↑, stimulation of behavior; ↓, inhibition of behavior; 0, no effect.

Hormone/Drug	Species	Strain	Effect	Reference
DHT	Rat	Wistar/Sprague Dawley[a]	0	McDonald et al. (1970)
DHT	Rat	Wistar	0	Larsson et al. (1973)
DHT	Rat	Wistar	0	Attila et al. (2010)
Cyproterone	Rat	Long Evans	0	Whalen and Edwards (1969)
Flutamide	Rat	Long Evans	0	Södersten et al. (1975)
2-hydroxyflutamide	Rat	Long Evans	↓	Harding and McGinnis (2004); McGinnis and Kahn, 1997;McGinnis and Mirth (1986)
DHT	Pig	Unspecified	0	Levis and Ford (1989)
DHT	Ram	Merino	0	D'Occhio et al. (1985)
DHT	Bull	Mixed beef breeding	0	Dykeman et al. (1982)
DHT	*Capra aegagrus hircus*	Alpine goat	0[b]	Fritz et al., 2019
DHT	*Mustela furo*	Fitch ferret	0	Baum et al., 1983
DHT	Rat	King Holtzman	↑	Olsen and Whalen (1984)
DHT	Mouse	Swiss-Webster	↑	Luttge and Hall, 1973
DHT	Mouse	Mixed C57/BL6 and 129	↑	Ogawa et al. (1998)
DHT	Mouse	CD-1	0	Luttge and Hall, 1973;Luttge et al. (1974)
DHT	Guinea pig	Unspecified	↑	Alsum and Goy (1974)
DHT	Guinea pig	English short hair, Topeka	↑	Butera and Czaja (1989);Butera and Czaja (1985)
DHT	*Mesocricetus auratus*	–	↑	Payne and Bennett (1976);Romeo et al. (2001)
DHT	Rabbit	Mixed strains	0	Ågmo and Södersten (1975)
Fluoxymesterone	Rabbit	Mixed strains	↑	Ågmo (1977)
Cyproterone	Rabbit	Mixed strains	↓	Ågmo (1975)
DHT	Rhesus monkey	–	↑	Cochran and Perachio (1977);Phoenix (1974)
DHT	*Macaca fascicularis*	–	0	Michael et al. (1986)
DHT	Human male	–	↑	Gooren (1985);Sartorius et al. (2014)

[a] No further specification provided; [b]Testosterone and DHT stimulated mounting to a similar degree, but only testosterone and DHT + E enhanced ejaculation.

sexual behavior has recently been published (Yu et al., 2023). That review is limited, however, by insufficient attention to strain and species differences and an assumption that the model produced applies to all mammals. Instead, I would present a more modest conclusion: It may be established that aromatization of testosterone to estradiol, acting at some of the estrogen receptors, contributes to maintain sexual behavior in some mouse strains. However, there may also be strains in which aromatization is not necessary, and in which estrogen receptors are not involved in the maintenance of male sexual behavior.

10.5. Studies with 5α-reductase inhibitors

In castrated male Wistar rats, sexual behavior can be restored to a level equal to that of intact rats with an androgen, 7α-methyl-19-nor-testosterone, that is not a substrate for 5α-reductase (Moralí et al., 1993). This compound can also restore copulatory behavior in castrated C57BL/6 as well as DBA/2 J mice to the same level as testosterone (Ogawa et al., 1996b). These data suggest that reduction of the steroid A ring is not necessary for androgenic actions on sexual behavior in rodents, at least not rodents belonging to the species and strains employed in the studies mentioned in this paragraph.

Results from studies of the effects of 5α-reductase inhibitors suggest that testosterone needs to be reduced to dihydrotestosterone rather than aromatized to estradiol in order to maintain sexual functions in men. Both finasteride and dutasteride are known to reduce sexual function in men with benign prostatic hyperplasia (e.g. Kaplan et al., 2012). It appears that sexual motivation is more affected than erection and ejaculation (Corona et al., 2012). Treatment with dutasteride leads to much reduced brain concentrations (as determined by analysis of cerebrospinal fluid) of testosterone and dihydrotestosterone while estradiol concentration is increased. In serum, the concentration of both estradiol and total testosterone is increased by dutasteride (Favilla et al., 2021). The authors proposed that the reduced availability of androgens in the brain may be the mechanism whereby dutasteride causes sexual dysfunctions. The rather extensive clinical literature discussing the effects of 5α-reductase inhibition on sexual functions in men has been reviewed several times (e.g. Gur et al., 2013).

The data from the studies showing lack of effect of aromatase inhibition on sexual functions in men combined with the deleterious effects of inhibition of 5α-reductase strongly suggest that stimulation of androgen receptors without concomitant activity at estrogen receptors is sufficient for the display of sexual behavior in the human male. This makes men more similar to the rhesus than to the cynomolgus monkey.

10.6. Studies based on manipulations of estrogen receptor expression

A different approach for evaluating the role of androgens and estrogens in male sexual behavior has been used ever since mice strains lacking the androgen receptor or one or both of the nuclear estrogen receptors became available. Whole body knock out of the estrogen receptor β (Ogawa et al., 1999) or conditional knockout in the nervous system (Naulé et al., 2016) did not affect male copulatory behavior. However, site specific knockdown of the estrogen β receptor in the medial amygdala of Jcl:ICR mice abolished the capacity to distinguish between a sexually receptive and a non-receptive female (Nakata et al., 2016). The experimental males approach both stimuli equally. Approach towards the sexually receptive female remained far superior to approach to another male in the experimental subjects. Since castration abolishes preferential approach to the receptive female in both cases, it may be proposed that aromatized testosterone acts on the estrogen β receptor for making the male able to distinguish between females in different reproductive states, whereas such actions are not involved in the preferential approach to a female when the alternative is a male. These findings have been replicated and extended in a subsequent study (Takenawa et al., 2023). The involvement of the androgen receptor in these effects was not evaluated in these experiments. Copulatory behavior is not altered in animals with few estrogen β receptors in the medial amygdala.

Mice lacking the estrogen receptor α show strongly impaired copulatory behavior (Ogawa et al., 1996a; Rissman et al., 1997; Wersinger et al., 1997). It has also been shown that sexual approach towards a living, sexually receptive female is reduced in these males (Rissman et al., 1997) whereas approach to urine from such females is unaffected (Ogawa et al., 1996a). Moreover, knock down of this receptor either in the medial preoptic area or in the ventromedial nucleus of the hypothalamus reduced copulatory behavior in intact male Jcl:ICR mice (Sano et al., 2013). Furthermore, chronic infusion of an antisense oligonucleotide to estrogen receptor α mRNA into the medial preoptic area of male

Sprague-Dawley rats reduced all aspects of copulatory behavior (Paisley et al., 2012). All these data suggest that estrogen action at the α receptor is necessary for the expression of copulatory behavior, at least in the mouse and rat strains employed in the studies mentioned here.

Specific knock down of the estrogen receptor α in the nervous system has only moderate effects on male sex behavior in a mouse line derived from a mixture of C57BL/6 and CD1 (Trouillet et al., 2022). In fact, combined knockdown of the estrogen α and androgen receptors were needed for producing severe deficit.

In castrated mice of a mixed C57BL/6 and 129 background, dihydrotestosterone activated copulatory behavior to the level of intact males (Ogawa et al., 1998). In males lacking the estrogen receptor α, dihydrotestosterone was less effective. It is not easy to explain how lack of this receptor could affect the actions of a compound not binding to it. Despite this, the strain used in this experiment must be added to the list of mouse strains in which aromatization is not needed for the expression of copulatory behavior. More recent data have established that optogenetic activation of neurons within the medial preoptic area expressing the estrogen receptor α as well as the vesicular GABA transporter robustly induces stimulation-bound mounting (Karigo et al., 2021). Still more recent data show that optogenetic stimulation of a subset of neurons in the bed nucleus of the stria terminalis expressing the estrogen receptor α receptor as well as aromatase enhanced mounting when applied at the start of an encounter with a female. Inhibiting these same neurons inhibited mounting (Bayless et al., 2023). In addition, it was shown that projections to the medial preoptic area was crucial for this effect, and that the innervated preoptic neurons then projected to the ventral tegmental area as well as to the periaqueductal gray. A circuit starting in the vomeronasal organ and ending in hypothetical motor programs was proposed by these authors. It coincides with earlier data showing that optogenetic stimulation of mitral or tufted cells in the accessory olfactory bulb during males' anogenital investigation of females enhances the likelihood of a stimulation-bound intromission (Kunkhyen et al., 2017).

Although the Bayless et al. (2023) study is extremely elegant, employing sophisticated techniques from molecular biology, the role of the estrogen receptor is completely ignored. Even though the experimental manipulations were concentrated on neurons expressing both the estrogen receptor α and aromatase, no administration of testosterone or estradiol was attempted in these experiments. Thus, whether the receptor needs to be active or not was of no concern to the authors. Likewise, the possible role of aromatase was not evaluated. The purpose of choosing neurons expressing both aromatase and the estrogen α receptor is not immediately evident. Furthermore, depending on the genetic manipulations required for each part of the experiment, several mouse strains were used, most of them from the Jackson Laboratory. They were either of the C57BL/6 J strain or that strain mixed with another. For example, the Tac1cre mouse used in several experiments originated in a mixed 129S6/SvEvTac x C57BL/6 strain. Considering the important strain differences in sexual behavior found in many studies (e.g. David et al., 2022; McGill and Tucker, 1964), see also Bonthuis et al., 2010) for a review) the use of multiple strains in the same study is quite confusing. In any case, the circuit the authors of the Bayless et al. (2023) paper propose is illustrated in Fig. 5. Despite the fact that this circuit does not directly contribute to our understanding of the role of estrogen or androgen receptors in male sexual behavior, it illustrates how modern genetic techniques can be used to dissect components of the neural circuitry involved in that behavior. It also illustrates how the techniques themselves overshadow the basic question of how hormones control sexual behavior. Nevertheless, with some modifications and additional controls, a similar procedure could be used to elucidate the functions of neurons expressing the androgen receptor.

Returning to the estrogen receptors and their importance for the expression of male copulatory behavior, it would appear that the estrogen receptor α indeed contributes to maintain that behavior at a normal level, i.e. the level found in unmanipulated mice. However, this

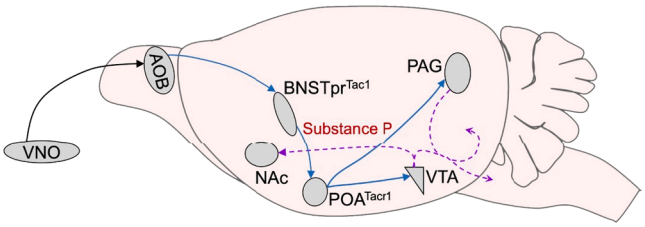

Fig. 5. Neural circuit for sexual behavior proposed in Bayless et al. (2023). VNO, vomeronasal organ; AOB, accessory olfactory bulb; BNSTpr^{Tac1}, Tac1-expressing neurons in the principal nucleus of the bed nucleus of the stria terminalis. These neurons belong to a subgroup of neurons expressing the estrogen receptor α and aromatase; POA^{Tacr1}, Tacr1-expressing neurons in the preoptic area (Tacr1 is the gene coding for the tachykinin receptor 1); VTA, ventral tegmental area; PAG, periaqueductal gray; NAc. Nucleus accumbens. All the areas shown in the figure are rich in androgen as well as in all estrogen receptors. However, the circuit is incomplete, since the tactile input from the perineal and preputial areas needed for activation of mount, intromission and ejaculation (Contreras and Ågmo, 1993) is missing. Although the authors make the typical mistake of considering olfactory stimulation as sufficient for activating copulatory behavior, their proposal is interesting.
Modified from Bayless et al. (2023) under CC BY-NC-ND license.

receptor is not indispensable, since sex behavior is still displayed in males lacking this receptor in the nervous system while having functioning estrogen receptors in the periphery. This conclusion applies to mice of the strains used in the studies mentioned here. It is unknown how silencing estrogen receptors would affect sex behavior in other mouse strains. Furthermore, although some studies suggest that the estrogen receptor α is *necessary* for the full expression of sexual behaviors, they do not show or even suggest that this receptor is *sufficient*. Perhaps that simultaneous actins at the androgen receptor are needed.

10.7. Studies based on manipulations of androgen receptor expression

Although nature provides a series of mutations of the androgen receptor gene disrupting the resulting protein's capacity to bind to specific androgen response elements, impeding dimerization, phosphorylation or interactions with accessory proteins (Brown, 1995), these mutations are useless for the purpose of this review. Due to the absence of peripheral effects of androgens during development, the external genitalia in individuals with non-functional androgen receptors are those of a female. In fact, most human infants carrying this kind of mutation are assigned the female sex and raised as girls. In male rodents, absent androgen action leads to altered development of the external genitalia, exactly as in humans. Because of the peripheral alterations, studies of male sexual behavior are rare both in humans and non-human animals carrying this mutation. Furthermore, since the mutation has been present from the moment of conception, the effects observed may be organizational as well as activational. Since this review is limited to activational effects, I will not further discuss the natural mutations to the androgen receptor.

A way to walk around the problems caused by the peripheral consequences of androgen-receptor inactivation is to leave the receptor intact outside the nervous system while silencing it within that system. Conditional knockout of the androgen receptor within the nervous system leads to severely deficient copulatory behavior in mice derived from mixed C57BL/6 and 129 Sv strains. None of the male subjects displayed any copulatory behavior in a 30 min test, whereas 33% of them ejaculated when test duration was extended to 10 h (Raskin et al., 2009). A subsequent experiment employing another genetic background found that 70% of males lacking central androgen receptors ejaculated. The intensity of copulatory behavior was somewhat reduced in the ejaculating mutants when compared to the wildtype. Fertility was also slightly reduced. During a long period of cohabitation with females, the mutants generated a mean ± SEM of pups of 31.7 ± 2 whereas the

corresponding values were 44 ± 5 for the wildtype (Raskin et al., 2012). These data show that in these mice, the androgen receptor is far from indispensable for the display of copulatory behavior or for fertility. Another study showed that the main effect of central deletion of the androgen receptor was to reduce the likelihood that the mice initiated copulation. Once initiated, mice with the receptor deletion copulated equally to the wild type (Juntti et al., 2010). The mice used in this study were also from a mixed background of C57BL/6 and 129/Sv strains. These knockout studies confirm that even though the androgen receptor contributes to sexual behavior in males derived from these strains, this receptor is not indispensable, since mice lacking it continue to display sexual behavior, albeit with lower intensity than control males. It is also noteworthy that all these males sired offspring after cohabitation with females. This means that the lack of androgen receptors in the nervous system does not impede fertility although it is slightly reduced. A substantial drawback of these studies is that organizational and activational effects are confounded.

Instead of silencing the androgen receptor gene, it is possible to make it overexpress itself. When this is done, it is found that male olfactory preference for a sexually receptive female over a male is eliminated. However, when overexpression was limited to the nervous system, there was no difference between mutants and the wildtype (Swift-Gallant et al., 2016). These data were interpreted as showing that androgen receptors outside the nervous system may alter the response to sexually relevant stimuli. When males were castrated, the wildtype lost its preference both for female odors and for living females. In males overexpressing the androgen receptor in the nervous system castration had no effect on preference for female odor whereas the males lost preference for a living female. Males overexpressing the androgen receptor throughout the body did not prefer female odors neither when intact nor when castrated. Testosterone treatment made them show such preference. Concerning their preference for a living female it turned out that there was none when the males were intact. Castration and testosterone treatment lead to a preference for the living female (Swift-Gallant et al., 2020). The authors concluded that the altered sexual preference is males globally overexpressing androgen receptors is mediated by inhibitory activational functions of the testis. Which these functions may be remain a mystery. The mice used in these studies were all from a C57BL/6 background.

Experimental manipulations of androgen receptor expression seem to be limited to mice and occasionally rats. Neither universal nor conditional knockout of androgen receptors have been attempted in any species besides the mouse. This also applies to overexpression. Interference RNA has not been used for silencing this receptor, and the use of antisense oligonucleotides targeting the androgen receptor has been limited to studies of the mechanisms and treatment of prostate cancer. In that field, oligos have been used quite extensively (e.g. De Velasco et al., 2019; Yamamoto et al., 2015), but data on effects on sexual behavior have never been reported. A review of the data obtained from the genetic models used to unravel the role of androgen receptors in sexual behaviors (and cognition) is available (Mhaouty-Kodja, 2018).

10.8. Conclusion concerning the role of the androgen receptor in male sexual behavior

Stimulation of the androgen receptor appears to be necessary for the display of sexual behavior in males. In some species and strains, concurrent stimulation of estrogen receptors is required for the full expression of that behavior. This, however, is not a general principle. In the human male, for example, estrogen receptors are not needed for normal sexual function.

10.9. The androgen receptor and mounting behavior in females

Females of many mammalian species readily display mounting. An influential survey established that female mounting of males has been described in 43 mammalian species, and that mounting coincided with estrus (Dagg, 1984). As is often the case, the female rat is far better known than any other mammal with regard to the hormonal control of female mounting. Females of that species not only mount other females and males, they also exhibit behavior patterns that are indistinguishable from male intromissions and ejaculation (Beach, 1942a; Emery and Sachs, 1975). Mounting of males is absent in ovariectomized females, but it is easily activated by the administration of estradiol, with or without the addition of progesterone (Afonso and Pfaus, 2006). Testosterone is as effective as estradiol for stimulating female mounting according to one study (Roselli and Chambers, 1999). It is most likely that the actions of testosterone are at least partly mediated by the androgen receptor, since dihydrotestosterone enhances mounting in ovariectomized Long Evans females (Gladue, 1984). In fact, many years ago it was reported that ovariectomized Wistar rats displayed high levels of mounting after treatment with testosterone or dihydrotestosterone combined with estradiol. Equal doses of estradiol alone or dihydrotestosterone alone were less effective (Baum et al., 1974). These data make it possible to propose that the control of mounting in female rats is similar to that in males in the way that concurrent stimulation of androgen and estrogen receptors are needed under physiological conditions. However, the selective stimulation of one of these receptors can activate mounting to some degree.

In guinea pigs of the Topeka stock, dihydrotestosterone does not activate mounting even after 50 days of treatment with a large dose (Goldfoot and Van Der Werff Ten Bosch, 1975). This was also the case when dihydrotestosterone was combined with estradiol (Goldfoot, 1979). The failure of the combined treatment to activate mounting is difficult to explain, since testosterone was highly effective. It is possible that the dose of either dihydrotestosterone or estradiol was insufficient, or that daily injections rather than implanting the usual Silastic® capsule can explain the lack of effect of the combined treatment with these steroids. Another study replicated the observation that testosterone activates female mounting in the Topeka guinea pig. The combination of testosterone and an aromatase inhibitor was ineffective (Roy and Goy, 1988). The blocking effect of aromatase inhibition could be reversed by the administration of diethylstilbestrol. These results strongly suggest that part of available testosterone needs to be aromatized, and that androgen and estrogen receptors must be simultaneously active in order to induce mounting behavior in females. Since dihydrotestosterone by itself consistently activates sexual behavior in male guinea pigs, there seems to be an important sex difference in the hormonal control of mounting. This is in sharp contrast to the rat. This is another species difference of some importance.

Hamsters seem to be similar to rats. Ovariectomized hamsters of an unspecified strain were subcutaneously implanted with Silastic® capsules containing either testosterone or dihydrotestosterone or a combination of dihydrotestosterone and estradiol. Testosterone and dihydrotestosterone + estradiol induced mounting while dihydrotestosterone and estradiol alone had no effect (Noble, 1977). Similar results have been obtained in a study in the golden hamster (DeBold and Clemens, 1978). Combined treatment with dihydrotestosterone and estradiol stimulated mounting in females, whereas these steroids were ineffective by themselves. Since male hamsters respond to dihydrotestosterone alone, we may here have another example of a sex difference in the hormonal control of mounting.

11. The androgen receptor and female sexual behavior

11.1. Rodents

Dihydrotestosterone is believed to inhibit estradiol-induced lordosis in female rats. For example, daily treatment with estradiol benzoate for about a week leads to a high lordosis quotient even in the absence of progesterone. If dihydrotestosterone is administered concurrently with estradiol, no lordosis will be displayed (Baum and Vreeburg, 1976).

Hooded Wistar rats were used in this experiment. Similar observations were made in a substantial number of studies employing several rat strains (e.g. Baum et al., 1974; Dohanich and Clemens, 1983; Erskine et al., 1992; Kirkpatrick and Clark, 2011). The androgen receptor antagonist flutamide blocked the inhibitory actions of dihydrotestosterone as well as those of the anabolic steroids stanozolol and nandrolone in estrogen primed rats. However, when the females were given progesterone in addition to estradiol, none of the androgen receptor ligands reduced the lordosis quotient (Blasberg et al., 1998). The lack of inhibitory effect of androgens on receptivity in rats sequentially treated with estradiol and progesterone had been observed several times before (Baum and Vreeburg, 1976; Blasberg and Clark, 1997; Erskine et al., 1985).

An inhibitory effect of dihydrotestosterone on estradiol-induced lordosis has been found in Swiss Webster and CD-1 mouse strains (Luttge and Hall, 1976; Luttge and Sheets, 1977). As in rats, the inhibitory effect is absent when the females receive progesterone in addition to estradiol (Luttge et al., 1977). To the contrary, there are observations showing that dihydrotestosterone inhibits lordosis in female hamsters treated with estradiol + progesterone (Noble and Alsum, 1975). This may indicate an important difference between rats and mice on one side and hamsters on the other. However, confirmation of the hamster data is needed.

None of the effects of dihydrotestosterone can have any physiological significance. Plasma concentration of this androgen varies in parallel with sexual receptivity, being at a maximum during proestrus (Dunlap and Sridaran, 1988), when receptivity is at its highest. Thus, it seems unlikely that dihydrotestosterone would have any meaningful inhibitory action on lordosis. Furthermore, the plasma concentration achieved after the doses employed in the studies reporting inhibition of lordosis, is at least one order of magnitude above that reported during the proestrus peak. It is difficult to understand why a hormone treatment producing an endocrine environment never found under physiological conditions have attracted so much attention. Perhaps it is believed that local 5α-reduction of circulating testosterone, or even local steroidogenesis, produce high concentrations of dihydrotestosterone at some neural sites. However, there is little evidence that de novo synthesis of dihydrotestosterone is of importance in any brain area (Giatti et al., 2020), in contrast to the robust evidence for rapid synthesis and actions of estradiol (Diotel et al., 2018). Any significant contribution of local 5α-reduction is unlikely because of the low concentration of circulating testosterone found in females. Thus, there is no convincing explanation for the effects observed after treating females with massive, unphysiological doses of dihydrotestosterone. The fact that dihydrotestosterone has very low affinity for the estrogen receptors (Kuiper et al., 1997) as well as for the progesterone receptor (e.g. Bauer et al., 2000) makes actions at any of those most unlikely. It may also be mentioned that in intact, female rats and mice sexual receptivity is associated with high serum concentrations of estradiol and progesterone (reviewed in Södersten and Eneroth, 1982), among many others). The fact that progesterone eliminates the inhibitory effect of dihydrotestosterone strengthens the proposal that this effect can have no physiological significance.

Even though actions of dihydrotestosterone on female sexual behavior are unlikely under physiological conditions, they may become relevant in some pathologies. The polycystic ovary syndrome, for example, is characterized by abnormally high production of androgens. It is possible that local brain concentrations of dihydrotestosterone could reach high levels in women suffering from this syndrome. No data confirming this possibility are available, though. Nevertheless, the effects of dihydrotestosterone on female sexual behavior described in the preceding paragraph could have some relevance for these women. At least they are known to have alterations in sexual behavior related to elevated levels of androgens (Daescu et al., 2023; Tzalazidis and Oinonen, 2020). It is not necessarily the hyperandrogenism itself that leads to sexual dysfunctions. There are data suggesting that common manifestations of the polycystic ovary syndrome such as acne, hirsutism and obesity may underlie the enhanced incidence of sexual dysfunctions (Castelo-Branco and Naumova, 2020; Naumova et al., 2021). It may be of some interest to note that effects of stimulation of the androgen receptor completely unrelated to sexual functions per se nevertheless may affect these functions.

Rather than searching for actions of dihydrotestosterone limited to some pathologies, many scientists have pursued more common actions of this steroid. Since testosterone was known to be able to activate lordosis in ovariectomized female rats (Beach, 1942b; Beyer and Komisaruk, 1971), cats (Whalen and Hardy, 1970) and rabbits (Palka and Sawyer, 1966), it appeared reasonable to find out whether this action was mediated by androgen receptors. However, in non-human female animals, there are data firmly establishing that dihydrotestosterone cannot activate female copulatory behavior. This is the case in rats (Gladue, 1984), rabbits (Beyer et al., 1970), and hamsters (Noble, 1977) at least. It can be concluded that selective stimulation of the androgen receptor cannot activate lordosis. It would appear that testosterone needs to be aromatized in order to do so. The fact that both an aromatase inhibitor and an estrogen receptor antagonist blocks testosterone-induced lordosis in ovariectomized hamsters (Hsu, 1990) supports this notion. Similar data exist from female rats, where an aromatase inhibitor (Gladue et al., 1978) as well as an estrogen receptor antagonist (Whalen et al., 1972) prevented testosterone from stimulating lordosis.

In the female rat, both estradiol (Meyerson and Lindström, 1973) and testosterone (Meyerson et al., 1973) activate sexual approach behaviors. Dihydrotestosterone is ineffective, and the effects of testosterone are blocked by an estrogen receptor antagonist, showing that testosterone is active only after conversion to estradiol (McDonald and Meyerson, 1973). More recent data have shown that non-aromatizable specific androgen receptor modulators (SARMs) may stimulate sexual approach behaviors in ovariectomized Sprague-Dawley rats when combined with progesterone (Jones et al., 2010). Whether this effect is due to the weak estrogenic actions of the SARMs or to actions of progesterone is difficult to determine, but this observation clearly contradicts the (McDonald and Meyerson, 1973) study. This is also the case with another study of SARMs (Kudwa et al., 2010). In ovariectomized Sprague-Dawley females, sexual approach behavior was stimulated not only by a SARM but also by dihydrotestosterone, administered via a subcutaneous Silastic® capsule. The female subjects approached an intact male (sexual stimulus) far more than another female (a non-sexual stimulus). In a second experiment, ovariectomized females were again treated with dihydrotestosterone, this time via a subcutaneous injection. Now the females showed withdrawal from a sexual stimulus (an intact male) and enhanced approach to a non-sexual stimulus (a sexually receptive female) after acute treatment. After 7 days of treatment, sexual and non-sexual stimuli were equally approached, showing that dihydrotestosterone no longer altered sexual motivation. Furthermore, the effects as well as the absence of such, depended on the sexual experience of the females. The results of this study probably show that the androgen receptor is not systematically involved in female rat sexual behavior.

Data regarding the effects of intracerebral steroid administration may clarify the complex results obtained in studies using systemic administration of dihydrotestosterone. Estrogen-primed, ovariectomized female rats prefer male odor over female odor. This preference disappeared when a cannula containing crystalline dihydrotestosterone was implanted into the posterodorsal medial amygdala two hours before estrogen injection in Long Evans rats (Fujiwara et al., 2016). It also disappeared when the estrogen receptor agonist tamoxifen was implanted at this site. Thus, estrogen receptors are needed for the estrogen-induced preference for male odor. Since the obligatory estrogen priming cannot involve the androgen receptors, the inhibitory action of dihydrotestosterone suggests that the androgen receptor somehow interferes with estrogen activation of estrogen receptors. Here we have an example of the poorly known interactions between steroid

receptors.

In an experiment in female rats (Maseroli et al., 2020), estradiol was combined with dihydrotestosterone in the same way as it normally is combined with progesterone, i.e. dihydrotestosterone was given 48 h after estradiol benzoate and 4 h before testing. Dihydrotestosterone was ineffective in the absence of estradiol, confirming many older observations. However, it was about equipotent with progesterone for stimulating sexual behaviors in females pretreated with estradiol. The meaning of this observation is difficult to determine. In any case, the effects of dihydrotestosterone are probably not due to binding to the progesterone receptor, since affinity for that receptor is quite low, as mentioned. These effects of dihydrotestosterone may be another example of interaction between steroid receptors.

11.2. Women

Because androgens are believed to be important for sexual motivation and behavior in women (e.g. Davis et al., 2016; Maseroli and Vignozzi, 2022) it seems logical to suppose that they act at the androgen receptor. Estrogens are readily available in cycling women assuring that the estrogen receptors are already stimulated by endogenous estradiol. Thus, any effects of administration of testosterone to premenopausal women can be supposed to be mediated by the androgen receptor. In menopause, however, women have lower concentrations of estradiol than of testosterone (Simpson, 2003). Consequently, in menopausal women estrogen receptors are poorly stimulated by endogenous estradiol, potentially making aromatization of testosterone important. Indeed, most of menopausal estrogens are produced peripherally through aromatization of adrenal androgens (Nelson and Bulun, 2001). In premenopausal women, then, extraovarian aromatization of testosterone is of negligible importance whereas it is the principal source of estrogens for women in menopause.

When clinicians consider androgen administration appropriate, they prescribe testosterone in one form or another rather than dihydrotestosterone, making it impossible to know if the hormone actions are mediated by estrogen or androgen receptors. Had they prescribed dihydrotestosterone instead, they would have provided science with invaluable data. Nevertheless, a study in which testosterone treatment of women in menopause included a group of women given the aromatase inhibitor letrozole in addition to testosterone revealed that the beneficial effects of testosterone on sexual functions were not reduced by the aromatase inhibitor (Davis et al., 2006). This observation suggests that testosterone conversion to estradiol does not contribute to the effects on sexual functions, hence testosterone is acting on androgen receptors either directly or after 5α-reduction. Likewise, intravaginal testosterone has repeatedly been reported to enhance sexual desire, arousal and satisfaction in menopausal women given aromatase inhibitors for the treatment of breast cancer (Dahir and Travers-Gustafson, 2014; Davis et al., 2018; Melisko et al., 2017).

There are no published reports concerning the effects of dihydrotestosterone administration on sexual functions in women. This is also the case for the effects of synthetic androgen receptor agonists. Thus, the importance of the androgen receptor for sexual behavior has not been evaluated with a sufficient variety of methods for proposing a definitive conclusion. However, the rather abundant evidence against a role for the estrogen receptors makes it possible to suggest that sexual behavior in women depends on activity at the androgen receptor. This is in sharp contrast to other mammals, in which much data show that the androgen receptor is not involved in female sexual behavior.

11.3. Female sexual behavior in males

Lordosis in response to tactile stimulation of the rump and flanks is not only typical for sexually receptive female rodents, but it also occurs in males of several species, including rats (Södersten et al., 1974), guinea pigs (Thornton et al., 1987), and hamsters (Kow et al., 1976). Very little data is available from the latter two species. From rats, however, enough data exist for making some informed speculations. Male Wistar rats castrated around puberty and tested in adulthood did not display any lordosis when stimulated manually, whereas they readily did so after treatment with estradiol or testosterone. An estrogen receptor antagonist blocked the effects of both (Södersten and Larsson, 1974). A later study showed that treatment with testosterone enhanced lordosis in a dose-dependent way whereas dihydrotestosterone was ineffective (Södersten, 1975). These two studies strongly suggest that male lordosis depends on the estrogen receptors and that the actions of testosterone are a result of aromatization.

When Long Evans males were castrated when adult, treated with estradiol for three days and tested for lordosis, the response depended on the post-castration endocrine environment. Males wearing an empty Silastic® capsule displayed lordosis. This was also the case for males that had been implanted with a testosterone-containing capsule. However, those implanted with a capsule containing dihydrotestosterone showed a strongly reduced lordosis response (Butler et al., 2001). It was suggested that the inhibitory effect of dihydrotestosterone could be due to its conversion to 3α-diol, a neurosteroid known to inhibit lordosis (Frye et al., 1996). This could be an example of how androgen administration may affect behavior via neurosteroids.

Lordosis in males has never been an attractive subject, and very little experimental work relevant for the issue of androgen receptor involvement has been done. Despite the scarcity of data, it may be suggested that the androgen receptor is not directly involved. Androgens may affect male lordosis responses via indirect mechanisms, such as aromatization or 5-α reduction and further conversion to neurosteroids.

12. The role of the androgen receptor in aggression

12.1. Rodents

A classical ethology textbook described aggression as “a word with many meanings and a source of much confusion” (Barnett, 1981, p. 631). This description is as valid today as it was 40 years ago. Despite all the ambiguities involved, and the varied expressions of what is labelled aggression, the many behaviors falling under this label remain attractive for scientists. A summary of current definitions and procedures commonly used in the field is available (Takahashi and Miczek, 2014). I will not venture into a discussion of the many subtleties involved in the study of this kind of social interaction. Only a short outline of the possible role of androgen receptors is presented here.

In rodents, there is solid evidence showing that males are far more aggressive than females (Seward, 1945). Since this sex difference coincide with a sex difference in the level of circulating androgens, it seems logical to suppose that androgens promote aggression. This has indeed been shown to be the case (Simpson, 2001). A very interesting observation is that the intensity of aggression in male rats depends on the serum concentration of testosterone (e.g. Barfield et al., 1972; Beatty, 1979). To the contrary, the intensity of sexual behavior is unrelated to this concentration in gonadally intact males (e.g. Albert et al., 1990).

As was the case with sexual behavior, it became popular to suppose that testosterone needs to be aromatized for enhancing aggression. This notion was supported by several kinds of observations. One was that an androgen receptor antagonist failed to block testosterone-induced aggressive behaviors in mice of the Swiss - Webster strain (Edwards, 1970) and in the albino TO strain (Clark and Nowell, 1980). Another observation supporting the hypothesis of testosterone being aromatized when stimulating aggressive behavior comes from a study showing that silencing of the estrogen receptor α in the ventromedial nucleus of the hypothalamus in intact male ICR/JCL mice reduce aggressive interactions (Sano et al., 2013). A third observation implicating estrogen receptors in androgen-induced aggression comes from a study in which an estrogen receptor antagonist blocked the stimulating effect of testosterone administration on aggression in castrated mice of the TO

strain (Clark and Nowell, 1979). In fact, the mice given the estrogen antagonist together with testosterone did not differ from castrated controls and displayed very little aggressive behavior with long latency.

Observations in other mouse strains suggest that the need for aromatization and estrogen receptors does not apply to all mice strains. The estrogen receptor antagonist tamoxifen did not reduce aggression in CF-1 mice (Simon and Perry, 1988) while cyproterone reduced aggressive behavior in intact, wild males (*Mus musculus domesticus*) (Matte and Fabian, 1978). Whether the contrasting results are due to procedural or to strain differences is unknown at present.

In castrated CD-1 mice, dihydrotestosterone failed to increase aggressive behaviors in isolated males above the level shown by untreated control mice (Finney and Erpino, 1976), repeating an earlier observation (Luttge, 1972). When dihydrotestosterone was combined with estradiol, aggression was stimulated to the level of intact mice. Estradiol alone had some effect, but it was smaller than the effect of the combined treatment. It was concluded that estradiol and dihydrotestosterone act in synergy to stimulate aggression, in the same way as they do when stimulating sexual behavior (Finney and Erpino, 1976). However, in castrated TO mice, dihydrotestosterone was about equipotent to testosterone for activating aggression (Brain and Poole, 1976). Dihydrotestosterone also enhanced aggression in castrated Swiss – Webster mice, although somewhat less than testosterone did (Luttge and Hall, 1973a). Since all the studies mentioned in this paragraph employed the same test of aggression (isolation-induced fighting), it is likely that there is a strain difference between CD-1 mice on one side and TO and Swiss – Webster mice on the other with regard to the endocrine control of aggression.

Differential effects of dihydrotestosterone on different kinds of aggression have been reported. In castrated Swiss – Webster mice, this androgen restored social aggression (stimulated by individual housing) and electroshock-induced attacks to precastrational levels whereas locust-killing and tube restraint-induced attack were unaffected by dihydrotestosterone (Brain and Kamis, 1985). The heterogeneity of the many procedures employed for quantifying aggression was pointed out many years ago (Brain and Haug, 1992). It does not only confirm the statement made in the beginning of this section, but it can also provide an explanation for the contrasting effects, or lack of effect, of dihydrotestosterone reported in the literature. For example, the study in which cyproterone failed to reduce aggression in intact Swiss – Webster mice (Edwards, 1970), thereby suggesting that the androgen receptor is not involved, used a very simple test for aggression: Two males from the same experimental group placed in a neutral cage. The proportion of pairs fighting was the dependent variable. In the studies where dihydrotestosterone was found to enhance aggression in this same strain, a single housed experimental male was put together with a group-housed, castrated and untreated male, or with another isolated male from the same treatment group (Luttge and Hall, 1973a). It seems, then, that we here have another example of how minor procedural differences may give rise to opposing results and the correspondingly opposing conclusions.

Data from gene deletion studies do not clarify the issue. Knockout of the aromatase gene in C57BL/6 mice leads to a complete suppression of aggression in a resident – intruder test in intact males (Toda et al., 2001). Estradiol administration to adult animals was ineffective, whereas neonatal administration followed by adult estradiol reinstated aggression in a dose-dependent manner. This show that estrogens have both an organizing and activating action on aggression in these mice. Strongly reduced aggressive behavior, again in the resident – intruder test, in mice lacking aromatase has been confirmed in another study (Matsumoto et al., 2003).

In mice of a mixed C57BL/6 and 129 background, knock out of the estrogen β receptor enhances aggressiveness relative to the wildtype (Ogawa et al., 1999; Ogawa et al., 2000). Knockout of the α receptor has the opposite effect (Ogawa et al., 1997; Ogawa et al., 1998). The opposing effects of the α and β receptors is quite interesting, since these receptors are frequently co-expressed in the same neuron (Campista Lana et al., 2023), and they have similar affinity for estradiol (Kuiper et al., 1997). This means that both receptors will be stimulated simultaneously by endogenous estradiol, making it difficult to predict whether stimulatory or inhibitory actions on aggression will dominate. Perhaps this fact can explain some of the many contradictory observations.

An intriguing study performed in ovariectomized females of the Tryon Maze Dull rats (also called the S3 strain) showed that aggressive behaviors were increased by long-term treatment with testosterone. What is more interesting is that estradiol was reported to reduce aggression below the level of oil-treated females whereas the synthetic, non-aromatizable androgen agonist, methyl-trienelone (R1881), was more efficient than testosterone for enhancing aggression (van de Poll et al., 1988). These data provide unequivocal evidence for a crucial role of the androgen receptor for testosterone-induced enhancement of aggressive behavior in female rats of the S3 strain.

12.2. *Primates, including the human*

It is widely believed that blood testosterone concentration and level of aggression are associated in male non-human primates (Muller, 2017) as they are in other mammals. However, a carefully conducted study in wild chimpanzees (*Pan troglodytes*) failed to confirm that relationship (Negrey et al., 2023). This study, however, does not directly address the role of the androgen receptor since circulating testosterone can be aromatized or 5α-reduced before binding to a receptor, as repeatedly mentioned throughout this paper. Fortunately, others have explicitly evaluated the role of the androgen receptor. In the Japanese snow monkey, *Macaca fuscata*, dihydrotestosterone and testosterone are equipotent for inducing aggressive behavior, and an aromatase inhibitor does not reduce the effect of testosterone. At difference, a 5α-reductase inhibitor reduced the effects of this androgen (Bethea et al., 2013). These observations suggest that aggressive behavior depends on stimulation of the androgen receptor, and that actions at estrogen receptors do not contribute to the observed effects in this monkey.

In the human, the relationship between circulating testosterone and aggression remains controversial. A classical review concluded that there is a relationship, albeit weak (Book et al., 2001). A mean correlation of 0.14 between aggression and plasma testosterone was found. i.e. about 2% of the interindividual variation in aggression can be attributed to testosterone. A reanalysis of the Book et al. (2001) data arrived at different conclusions regarding several moderator variables, and the correlation between aggression and plasma testosterone was reduced to 0.08 (Archer et al., 2005). More recent data show that the link between plasma testosterone and aggression is questionable in the human (Geniole et al., 2020).

Any possible relationship between testosterone availability and aggression is irrelevant with regard to the role of the androgen receptor. Therefore, a relationship between dihydrotestosterone availability and aggression might be more informative. Such a relationship has indeed been reported in men (Christiansen and Knussmann, 1987). Also in women, there is a correlation between plasma dihydrotestosterone and performance on a subscale on the Buss-Perry Aggression Questionnaire (Buss and Perry, 1992) evaluating anger (von der Pahlen et al., 2002). Even though significant correlations are far from proving a causal relationship, these observations are suggestive. To my knowledge, there are no published studies in which the effects of non-aromatizable androgens on aggression have been evaluated in women.

There are some reports relating consumption of anabolic steroids to aggression (Chegeni et al., 2021a; Chegeni et al., 2021b). Unfortunately for our purpose, many of the commercially (albeit often illegally) available steroids undergo aromatization (Kuhl and Wiegratz, 2007), thereby eliminating the possibility to ascribe their potential effects to the androgen receptor. Furthermore, poly-drug use is common among people consuming anabolic steroids (Sagoe et al., 2015), making it

difficult to unequivocally attribute the small increase in violent acts observed in the steroid users to steroid receptors. Indeed, a series of factors besides poly-drug use may contribute to acts of aggression among users of anabolic steroids. These include personality traits and lifestyle, among others (van de Ven et al., in press).

12.3. Conclusion

This short overview of a small proportion of the studies trying to relate aggressive behaviors to actions at the androgen receptor should have made clear that there is substantial evidence for such a relationship in some species. In others, the evidence is less convincing. Actions at the estrogen receptors may be important in some species. Nevertheless, a brave prediction would be that such actions are limited to specific experimental conditions in specific species and strains, being of limited importance. This state of affairs may be related to the confusing nature of the concept of aggression in itself, as repeatedly pointed out in this section.

13. A comment on social recognition and related behaviors

It is well known that rats, mice, and members of many other species distinguish between individuals from one sex and individuals from the other. In addition to distinguish between sexes, animals belonging to many species can identify the reproductive state of conspecifics. Male rats can clearly differentiate between a sexually receptive and a non-receptive female, for example. Furthermore, males with some sexual experience rarely try to mount a non-receptive female whereas they mount receptive females as soon as the opportunity arises (Chu and Ågmo, 2015). Likewise, female rats not only distinguish between males and females, but also between intact and castrated males (e.g. Ellingsen and Ågmo, 2004). The stimulus modalities providing this kind of information are partially known. In male rats, olfactory stimuli are necessary but not sufficient. Soiled bedding from a sexually receptive female is not able to attract a male more than another male behind a wire mesh screen is. To the contrary, a living, sexually receptive female is far more attractive than another male. It appears that the olfactory stimulus must be emitted by a living body to function as a sexual incentive (Ågmo and Snoeren, 2017). This kind of stimulus do not have any effect in a castrated male, but it is efficient in a castrated male treated with dihydrotestosterone, showing that activity at the androgen receptor is needed. Estradiol by itself has no effect, although it might reinforce the effect of dihydrotestosterone (Attila et al., 2010). In females, ovariectomy eliminates the capacity to distinguish between intact and castrated males, and treatment with estrogens reestablishes this capacity (Spiteri and Ågmo, 2006). Dihydrotestosterone is ineffective (McDonald and Meyerson, 1973). In rats, then, the androgen receptor in males and at least one of the estrogen receptors in females is needed for the capacity to distinguish between living members of the two sexes and between reproductive states. The endocrine control of the responses to excreta from conspecifics, like urine or feces, may be different, though, and it is not discussed here.

It is sometimes argued that it may be adaptive to be able to recognize specific individuals (Ferguson et al., 2002; Tumulty and Sheehan, 2020). Indeed, social recognition has become a large subject during the last couple of decades. Most of the abundant research performed in the area is irrelevant for the specific question of the role of androgen receptors. Instead, enthusiasm has been concentrated around the estrogen receptors. Nevertheless, there are some data showing that androgen receptors are of importance for the capacity of recognition of individuals. There are also data showing the opposite. The contradictions that will be described below may partially be explained by strain differences, known to be important for social recognition in mice (Mansk et al., 2023). Therefore, detailed descriptions of the strains used in each experiment will be provided.

In the ICR mouse, castration leads to impaired social recognition, and treatment with testosterone restores it. Since this was associated with an increased number of androgen receptors in the brain, the authors propose that the effects of testosterone depended on this receptor (Li et al., 2019). However, when male mice lacking the androgen receptor in the nervous system because of conditional knockout were tested for social recognition, it was found that the knockouts still recognized female conspecifics, but they had lost the capacity to recognize male conspecifics (Karlsson et al., 2016). The effects of androgen receptor deletion in females were unclear. The mice used in this study originated from male C57BL/6 expressing Cre driven by the Nestin promoter mated with females carrying LoxP sites. The offspring had been backcrossed into C57BL/6 for at least six generations. The stimulus mice used in the social recognition test were adult, intact males or ovariectomized females of the C57BL/6 strain. It is quite difficult to explain how the androgen receptor could be specifically involved in the recognition of males. Considering that the same authors previously had reported that castration does not impair social recognition in C57/BL6 males tested in the same procedure (Karlsson et al., 2015), it becomes still more difficult to understand how the androgen receptor could have a specific effect on the recognition of males. In any case, it appears that the C57BL/6 strain differs from the ICR strain with regard to the importance of androgens. This is another example of the strain differences mentioned above.

In male Wistar rats, castration does not reduce the capacity for social recognition (Bluthe et al., 1990). In this study, the traditional procedure of using juvenile rats as stimuli was followed. The conclusion must be that androgens are not involved in the capacity for social recognition in male rats.

In humans, testosterone has been ascribed innumerable effects besides its purported stimulatory effect on aggression mentioned above. Among the more exotic effects of testosterone administration to healthy young women is enhanced heart-rate responses to angry faces (van Honk et al., 2001). Exposure to a happy face had no effect. This fascinating observation was interpreted as showing that testosterone encourages dominance behavior and promotes an inclination toward aggression. The hormone has also been found to decrease interpersonal trust. Four h after receiving sublingual testosterone (mixed with cyclodextrine, ethanol and water), young women were presented a series of photographs of unfamiliar faces and asked to rate the trustworthiness of each face on a visual analog scale. Testosterone produced a significant reduction in rated trustworthiness (Bos et al., 2010). It was concluded that testosterone increases social vigilance. These two examples of the kind of studies and the kinds of effects attributed to testosterone should be enough for illustrating the diversity of actions that has been proposed. The issue of androgen effects on social recognition seems to have expanded in all directions, most of them entirely unrelated to any plausible effects of androgens. Among the more extravagant examples is the search for a failed association between serum testosterone concentration and optimism or pessimism (Kische et al., 2018). An extensive review of the older studies of unlikely testosterone effects is available (Eisenegger et al., 2011).

The many studies of the effects of testosterone administration published up to date do not offer any relevant information concerning the role of the androgen receptor. I have not been able to find a single study on the effects of dihydrotestosterone on social recognition in humans. Likewise, there is no single study in which testosterone was combined with an aromatase inhibitor. The explanation may be that the scientists involved in these studies are mainly concerned with the actions of testosterone without having any desire to describe the receptors mediating these actions.

To conclude this brief overview of social recognition and the androgen receptor it can be stated that the limited evidence available suggests that this receptor is of slight importance for social recognition. This is quite different from its essential role in sex discrimination, and discrimination between reproductive states, in male rodents. It does not seem to have any importance for this latter kind of discrimination in females. However, recent reviews suggest that androgen actions,

including those of the dihydrotestosterone metabolites 3α- and 3β-diol, in males and females must be elucidated before a full understanding of hormonal influences on social recognition can be attained (Aspesi et al., in press; Aspesi and Choleris, 2022).

14. General conclusion

The androgen receptor is necessary for male sexual behavior in all species studied so far. This assertion is valid both for sexual approach behaviors and for the execution of copulatory acts. In some species and strains, the androgen receptor acts in synergy with the estrogen receptor α, but this is far from a general principle. Furthermore, it seems that the androgen receptor is crucial for sexual behavior in women, and perhaps also in females of some other primate species. Similarly, aggression may be stimulated by an active androgen receptor. Whether this is the case in the human remains an open question. It is possible that androgens may act in conjunction with estrogens to enhance aggression in some species, but this should be regarded as an unproven hypothesis rather than as a fact.

The rather precarious state of knowledge concerning the role of the androgen receptor in non-sexual behaviors can be partially explained by the insistence of using testosterone rather than an non-aromatizable androgen in most studies. In addition to this, the general tendency to avoid considering species and strain differences with regard to the interactions between androgen and estrogen receptors has contributed to limited progress. In this review, I have emphasized the many differences found between strains and species. The habit of generalizing from one species to another and from one strain to another has undoubtedly been the source of many misunderstandings and the following confusion. One example is the proposal that estrogens could help improve sexual functions in men (Wibowo et al., 2011) . This proposal is based on rat data, while ignoring the overwhelming evidence against a role for estrogens in human males. Another is the already mentioned review by Yu et al. (2023) proposing a circuit for estrogen-dependent male sexual behavior without any consideration of strain or species differences with regard to the importance of estrogens. The use of a multitude of experimental procedures may be another factor contributing to confusion. It is not evident that we can generalize results from one procedure to any other procedure and from one context to any another. The vicissitudes of unwarranted generalizations have been discussed extensively elsewhere (Hernández-Arteaga and Ågmo, 2023) and these arguments will not be repeated here.

To simulate progress in the field it would be most helpful to apply existing molecular techniques for selective stimulation and inhibition of neurons expressing the androgen receptor. Since androgen receptors are widely distributed in the nervous system, including areas known to be unimportant for sexual behaviors, it can be expected that most of the neurons expressing this receptor are unrelated to sex. Thus, only neurons altering their firing frequency during the display of sexual activities should be selected for manipulation. Otherwise, too much noise would be created. This same reasoning applies to studies of aggression or social interaction or whichever behavior we find interesting. If this could be made in a substantial number of species, we could perhaps discover some general principles governing the behavioral functions of the androgen receptor.

Declaration of Competing Interest

The author declares no conflict of interest.

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