Neuroendocrinology of sexual behavior

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Abstract

One of the consequences of sexual behavior is reproduction. Thus, this behavior is essential for the survival of the species. However, the individual engaged in sexual behavior is rarely aware of its reproductive consequences. In fact, the human is probably the only species in which sexual acts may be performed with the explicit purpose of reproduction. Most human sexual activities as well as sex in other animals is performed with the aim of obtaining a state of positive affect. This makes sexual behavior important for wellbeing as well as for reproduction. It is not surprising, then, that sexual health has become an increasingly important issue, and that knowledge of the basic mechanisms controlling that behavior are urgently needed. The endocrine control of sexual behavior has been extensively studied, and although it is established that gonadal hormones are necessary, some controversy still exists concerning which hormone does what in which species. The brain areas necessary for sexual behavior have been determined in almost all vertebrates except the human. The media preoptic area is crucial in males of all non-human vertebrates, whereas the ventromedial nucleus of the hypothalamus is important in females. Modulatory functions have been ascribed to several other brain areas.

INTRODUCTION

One obvious result of sexual behavior is reproduction. It could even be stated that this behavior has evolved to assure the union of male and female gametes. Notwithstanding this biological function of the sexual behaviors, individuals executing them are almost always unaware of their reproductive consequences. Humans are probably unique in the way that they are aware of the relationship between sex behavior and reproduction. This means that humans, at difference to other animals, may copulate with the conscious aim to reproduce. Humans may also take actions to reduce or eliminate the probability that copulation leads to reproduction. Rather than being impelled to have sex because of mysterious urges to reproduce, humans and other animals are attracted to and interact with individuals emitting stimuli predicting a positive affective state following genital stimulation [1]. Both the attraction to sexually relevant stimuli and the motor patterns needed to obtain genital stimulation are dependent on gonadal hormones.

Among mammalian behavior patterns, female rat sexual behavior is unique in the way that it is under immediate control of ovarian hormones. In fact, the main motor pattern of this behavior, lordosis, is only displayed when the brain is exposed to appropriate amounts of these hormones, i.e. during the late proestrus and early estrus phases of the vaginal cycle. This absolute hormone dependency of female rat lordosis has made it possible to discover not only the endocrine events determining the occurrence of this behavior, but also the central nervous structures involved. Even the peripheral sensory and motor nerves participating in the display of this behavior have been carefully described.

The neuroendocrine control of the affective response to genital stimulation is poorly understood. Positive affect produced by vagino-cervical stimulation in female rodents has been experimentally studied mainly with the conditioned place preference procedure [2]. That procedure has been extensively used for studying affective consequences of drugs and natural

rewards. Despite considerable progress in this area, it would be premature to present any specific proposal as to the mechanisms involved.

In male rodents, the endocrine control of sexual behaviors is on a longer time scale. Although plasma androgens are undetectable around 6 h after castration, the sexual motor pattern of mounting as well as approach to sexually receptive females may persist for a few weeks in the absence of testicular hormones. Nevertheless, male rats will sooner or later stop to display sexual behaviors when deprived of these hormones. Hormone replacement will need a few weeks to reinstate behavior to the level of intact animals. Thus, hormone actions in males are slow, but sexual behavior is absolutely dependent on testicular hormones, in the same way as female sexual behavior is dependent on ovarian hormones. The copulatory postures in rats are illustrated in Fig. 1.

The affective response to penile stimulation has been evaluated with conditioned place preference. Vaginal penetration, even without ejaculation, is enough for producing positive affect, at least in rodents. The underlying neural mechanisms are as obscure in males as they are in females.

Whereas the endocrine and nervous control of the sexual motor patterns have been carefully studied in many species, data concerning the determinants of sexual attraction are far less abundant. Nevertheless, there are no data contradicting the proposal that gonadal hormones are as crucial for attraction as they are for copulation. I will first review the evidence for all the above assertions concerning female and male rats and other rodents, and also analyze the brain sites of action of the gonadal hormones. I will also analyze the role of hormones in primates, including the human. Some speculations concerning the neural structures important for primate, especially human, sexual behavior will be presented.

FEMALE RODENTS: HORMONES

To make the following discussion meaningful, I will begin with a short description of female sexual behavior. The basic motor pattern is the lordosis, a concave flexion of the back accompanied by stretched hind legs and the tail turned to one side. In this way, the vaginal opening is exposed, allowing a mounting male to penetrate the vagina with his erect penis. This motor pattern is activated by mechanical stimulation of the skin on the flanks and rump. The sensory pathways bringing this stimulation to the spinal cord and then to the brain has been described in detail. Likewise, the motor pathways from the spinal cord to the muscles causing the lordosis posture as well as the supraspinal control of these pathways were elucidated many years ago [3]. In addition to lordosis, females display a few other behavior patterns associated with sexual interactions. Prominent among these is solicitation, an approach towards the male followed by a rapid turn and run-away. The female often hops and darts during the run-away, and she may also rapidly shake the head up and down and laterally, giving the impression that she is wiggling the ears. Run-away is ended by a sudden stop, usually with raised hind quarters. This latter posture is often called a presentation. All these behaviors, lumped together under the label paracopulatory behavior, have been carefully studied [4]. It has been found that stimuli provided by the male are crucial for these behaviors, since they are rarely or never displayed in the absence of males.

Whereas humans can have solitary sex, rat sexual behavior always requires an interaction between at least two individuals. Thus, before a female displays any of the behaviors mentioned in the preceding paragraph, she needs to attract a male. The sequence of events constituting sexual behavior is shown in Fig. 2. All sexually receptive females induce males to approach them, even when no direct physical contact is possible. Olfactory stimuli are necessary, but not sufficient, for making males approach a receptive female more than non-receptive females [5]. The odorant responsible for this effect has not been identified,

probably because the search has been concentrated on excreta left outside the female body rather than on relevant body odors [6].

Intact females are approached by and respond to males only during a short period of the estrous cycle. This period, behavioral estrus, corresponds in time to late proestrus – early estrus in the vaginal cycle. Serum estradiol concentration is declining during this period, whereas progesterone concentration first increases and then remains stable. The duration of full receptivity, i.e. the period during which the female responds with lordosis to every male mount, has been found to vary between 6 – 9 h [7]. The onset of receptivity is characterized by a sudden increase in paracopulatory behaviors, and the end is associated with a rapid decline in these behaviors [8]. A simplified scheme of the mechanisms controlling lordosis is found in Fig. 3.

Estrogens act on the estrogen receptor α when activating sexual behavior, whereas the estrogen receptor β is not necessary [9]. Both these receptors are known to be transcription factors, i.e. they have rather slow, genomic actions. In addition, estrogens may act at a membrane receptor, GPR30 or GPER1, which has fast, non-genomic actions, some of which are mediated by the proteinkinase A or phosphoinositide-3-kinase pathways (e.g. [10]). It should be noted, however, that the physiological relevance of the GPER1 receptor has been questioned. Among the reasons for this is the low affinity of this receptor for estradiol. In fact, it has only about a tenth of the affinity of the nuclear α and β receptors, and it is not evident that endogenous concentrations of estradiol are high enough for any action at the membrane receptor [11].

FEMALE RODENTS: BRAIN SITES

Ever since Geoffrey Harris' and Richard Michael's classical study in cats, it has been known that estrogens act in the hypothalamus to make the expression of lordosis possible [12]. Later

studies revealed that a small area, the ventrolateral part of the ventromedial nucleus of the hypothalamus, is crucial for female sexual behavior. Lesion of this area strongly reduces or eliminates estrogen-induced lordosis whereas electrical stimulation of that area has a facilitatory effect in estrogen primed animals. Furthermore, implantation of a minute amount of estradiol into the ventromedial nucleus reinstates lordosis responses in ovariectomized females. Knock-down of the estrogen receptor α in that area strongly reduces estradiol-induced lordosis responding in female rats [13] and mice [14]. The molecular events underlying estrogen actions in the hypothalamic neurons are beginning to be elucidated [15].

Several other brain areas have been shown to modulate lordosis behavior. One is the periaqueductal gray, an important relay station for efferent neurons from the ventromedial nucleus. Others are the septum and the medial preoptic area, both with inhibitory actions.

WOMEN AND OTHER FEMALE PRIMATES: HORMONES

Whereas the role of hormones in female rodent sexual behavior is well-established, the endocrine control of sexual behavior in women is still a matter of debate. Like all female primates, women display sexual behavior during the entire cycle. This simple fact makes it evident that if ovarian hormones are involved in the control of this behavior, that control must be far less strict than it is in rodents. A minimum requirement for the credibility of any proposal concerning the role of ovarian hormones is that the intensity of sexual behavior in women somewhat covaries with the serum concentration of these hormones. This implies that there should be some variation coinciding with the drastic variations in hormone production in the different phases of the menstrual cycle and across the life span. This issue has been the subject of an overwhelming number of studies. Despite this, there is still no consensus, since the results are inconsistent [16,17]. The only possible conclusion is that any potential influence on sexual behavior of the ovarian hormones must be weak, at most. This conclusion is further

supported by the observation that menopause has a negligible effect on women's sexual behavior [18].

Many years ago, adrenalectomy was found to have deleterious effects on female sex behavior [19]. The adrenals produce about 25 % of circulating testosterone as well as substantial amounts of the testosterone precursors dehydroepiandrosterone sulfate and dehydroepiandrosterone [20]. This might suggest that androgens synthetized by the adrenal cortex could be of some importance for maintaining sexual motivation in women. Indeed, clinical studies have found that premenopausal women as well as women in menopause complaining of low sexual desire have lower serum concentration of total and free testosterone than women not complaining about their level of desire [21]. Several other studies have found support for the notion that testosterone is important for female sexual functions [22]. Furthermore, androgen receptors are abundant in the vulvovaginal area [23], and it has been suggested that they may be important for regulating genital arousal [24]. Despite all this favorable evidence, there are many reports showing that sexual function and dysfunction are unrelated to serum concentrations of gonadal hormones [25]. A simple explanation for the contradictory data may be that while a certain level of testosterone is needed for adequate sexual functioning in women, further increases in testosterone availability has no consequence. Thus, only severe testosterone insufficiency should be associated with impaired sexual function. There is some direct support for this hypothesis [26,27].

It would be unfair to ignore that some endocrinologists still maintain that the ovarian hormones are important determinants of sexual activity in primates, including women (e.g. [28]). A strict association between ovarian hormone secretion and sexual function has also been embraced by sociobiologists and evolutionary psychologists (e.g. [29]). There is no need to dwell on this.

WOMEN AND OTHER FEMALE PRIMATES: BRAIN SITES

In non-human primates, experimental studies have found that brain areas corresponding to the ventromedial nucleus are important for sexual behavior. Brain areas supposed to be involved in the control of sexual behavior in women have been identified in imaging studies. Typically, women are asked to produce sexual fantasies, view pictures or watch movie fragments with sexual content or to masturbate to orgasm while in the magnetic resonance scanner. Sometimes the partner is recruited for performing the genital stimulation. Results are similar regardless of the method used to induce sexual excitation. Activation of amygdala, cingulate cortex, ventral striatum, thalamus and hypothalamus, among others, is usually observed (see, e.g. [30]). At orgasm produced by mechanical stimulation of the clitoris, enhanced activity is found in many brain regions, for example the nucleus accumbens, insula, anterior cingulate cortex, orbitofrontal cortex, amygdala, hypothalamus and the cerebellum [31]. The imaging studies of brain activity during sexual excitation and orgasm are still in their infancy, and many issues remains to be resolved before they can provide a coherent picture of the neurobiology of female sexual arousal [32].

MALE RODENTS: HORMONES

Castration has been used for centuries, perhaps even millennia, for reducing sexual and aggressive behaviors in many species of male mammals, including the human. Eunuchs were much appreciated for higher offices in the state, particularly during the Tsang dynasty (618 - 907) in China because of their dedication to work rather than to women, for example [33]. The elimination of sexual behavior following castration in rats was first described by Eugen Steinach in 1894 [34]. Some years later, it was shown that the testicular product responsible for activating sexual behavior was testosterone [35]. In peripheral, androgen-sensitive tissues, testosterone is reduced to 5α -dihydrotestosterone before binding to the androgen receptor. In

the early 1970ies, it was found that dihydrotestosterone was unable to activate sexual behavior in castrated male rats. At about that time, it had been found that testosterone is also aromatized to estradiol in some target tissues, including the brain [36] (see Fig. 4). It was soon shown that the combination of dihydrotestosterone and a small amount of estradiol restored male rat sexual behavior to levels indistinguishable from those found in intact male rats [37]. It was proposed that the simultaneous activation of estrogen and androgen receptors is needed for male sexual behavior. It is also needed for making males approach sexually receptive females (Fig. 5)

Studies in knockout mice have confirmed that males lacking the estrogen receptor α show no or strongly reduced sexual behavior. Knockout of the estrogen receptor β has no observable effect on that behavior. To the contrary, males lacking the androgen receptor show highly deficient sexual behavior. Thus, it is presently believed that sexual behavior in mice and rats requires the simultaneous activity in the estrogen receptor α and the androgen receptor (reviewed in [38]). However, when knockout of the estrogen receptor α is limited to neural tissue, the deleterious effects on sexual behavior in male mice are small, and fertility is unaltered [39]. Likewise, knockout of nervous aromatase reduces, but does not abolish, sexual behavior in male mice [40]. In fact, the importance of aromatization for sex behavior in mice has been a contentious issue for many years, because of several important strain differences and conflicting observations (discussed in [6]).

MEN AND OTHER PRIMATES

In the rhesus monkey, the non-aromatizable androgen dihydrotestosterone was shown to restore sexual behavior to the level found in intact controls [41], suggesting that stimulation of androgen receptors alone was enough. Observations in another macaque, *Macaca fascicularis*,

have shown that aromatization of testosterone may have some marginal effects on male sexual behavior [42,43], but it is uncertain whether these small effects have any functional significance.

An early study in men showed that an estrogen receptor antagonist or an aromatase inhibitor failed to affect sexual behavior, whereas dihydrotestosterone could replace testosterone for the treatment of hypogonadal men [44]. More recent data show that treatment with dihydrotestosterone maintains normal levels of sexual behavior despite non-detectable serum levels of estradiol and testosterone [45]. A considerable number of other observations suggest that sexual behavior in the human male is controlled by androgens acting at the androgen receptor. Activity at estrogen receptors are not needed (reviewed in [6]).

BRAIN SITES CONTROLLING MASCULINE SEXUAL BEHAVIOR

The medial preoptic area was proposed to be a crucial brain site in the control of male sexual behavior by Nils-Åke Hillarp already in 1954 [46]. This proposal was confirmed in lesion studies [47]. Massive destruction of this area led to a complete and irreversible elimination of male rat sexual behavior. To the contrary, electric stimulation of this area leads to immediate mounting activity. In castrated males, implants of minute amounts of testosterone into this area restores sexual behavior. There is no doubt that the medial preoptic area is necessary for male rat sexual behavior. For many years it was discussed whether this area controls sexual performance (the ability to execute mounts, vaginal penetrations and ejaculation) or motivation (the urge to engage in sexual interaction) or both. It appears that males lacking a functioning preoptic area lack motivation to perform sexual acts. Whether the lack of motivation is associated with incapacity to perform sexual acts cannot be determined [48]. Fig. 6 illustrates the preoptic area as a connector between sensory input and motor output.

Male sexual behavior is abolished after lesions of the preoptic area in all vertebrate species studied (fish, amphibians, reptiles, birds, and mammals, including primates). There

are no lesion or stimulation data from the human male preoptic area or its equivalent, but there is no reason to assume that the neural control of human sexual behavior would be exceptional among vertebrates. In fact, it appears that the neural control of sexual behavior has been conserved to a far higher degree than the endocrine control. This could be an interesting problem for evolutionary biologists.

Many other brain sites have been suggested to participate in the regulation of male sexual behavior. In rodents, these include structures involved in olfactory input (olfactory bulbs, amygdala, the bed nucleus of the stria terminalis). Effects on sexual behavior of manipulations of neural activity in these areas have been reported, but they are somewhat variable and often minor. Nevertheless, the many contradictions in the literature do not impede scientist from elaborating complex models including many structures and sophisticated networks (e.g. [49]). Imaging studies in humans have shown that viewing pornographic movies or masturbating in the scanner enhance blood flow in several cortical and subcortical areas, among those the lateral occipitotemporal, inferotemporal, parietal, orbitofrontal, medial prefrontal, insular, anterior cingulate, and frontal premotor cortices as well as, for subcortical regions, the amygdalas, claustrum, hypothalamus, caudate nucleus, thalami, cerebellum, and substantia nigra [50].

CONCLUSION

Sexual behavior is a two-factor process: First, physical contact needs to be established between at least two individuals, usually of opposite sex. Once the individuals are in close physical proximity, copulatory activities (behaviors involving genitals) may be initiated. The only exception to this two-stage process is masturbation, where genital stimulation does not require a partner. It appears that gonadal hormones are equally necessary for both stages. An important, but rarely mentioned, exception is masturbation in human infants and prepubertal

children. These behaviors occur at an age when the blood concentration of gonadal hormones is extremely low. Sine these behaviors are rarely studied, it is difficult to make any informed speculations as to the controlling mechanisms.

The particular gonadal hormones involved may vary between one species and another. The importance of androgens in women, and the lack thereof in female rodents, has already been mentioned. Likewise, whereas aromatization is crucial in male rats, it is not in men. Another example of species differences is the synergy between estrogen and progesterone. In rats, estrogen needs to precede progesterone whereas the opposite is the case in the ewe. In the latter species, progesterone priming facilitates estradiol-induced receptivity [51]. In rabbit does and female cats, progesterone following estrogen has an inhibitory effect, exactly the opposite to the effects in rats. These are just a few examples of the variable requirements for gonadal hormones. The need for them is, however, consistent.

In contrast to the many species variations in which gonadal hormone does what and when it needs to act, the neural control of sexual behavior has been conserved, as already pointed out. I will make no speculations about the causes for this difference. It should also be remembered that there are aspects of human sexual behavior where the need for gonadal hormones is unclear. Considering the rather short history of neuroendocrinology, the achievements are nevertheless impressive.

DATA AVAILABILITY STATEMENT

The data used for elaboration of Figure 5 are available from the author upon reasonable request.

COMPETING INTERESTS

There is no conflict of interest to disclose.

AUTHOR CONTRIBUTION

AÅ wrote the entire manuscript and was in charge of the production of the figures.

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Figure legends

Fig. 1. A. The female displays a lordosis while the male is mounting. B. The female remains in lordosis while the male achieves a vaginal penetration (intromission). C. The female is still in lordosis. The male has now performed several intromissions and ejaculated. He is slowly withdrawing from the female. Drawings by Olivia Le Moëne.

Fig. 2. The sequence of events in a sexual interaction. A sexually relevant stimulus activates the central motive state, a hypothetical brain function, which leads to approach to the emitter of the stimulus and viscerosomatic responses. Once approach has been accomplished, the individuals may or may not proceed with copulatory interaction. Eventually this interaction will produce a state of positive affect. For further details, see Ågmo and Laan, Neurosci Biobehav Rev. 2022, 135, article number 104595, from which the figure is reprinted under license CC BY 4.0.

Fig. 3. Schematic drawing of the neurobiological circuits controlling the display of lordosis in female rats. For explanation, see text. Slightly modified from https://commons.wikimedia.org/wiki/File:Simplified_diagram_of_the_neurobiological_circuits_of_the_lordosis_sexual_reflex.png. Licensed under the Creative Commons Attribution-Share Alike 4.0 International license.

Fig. 4. Metabolism of testosterone.

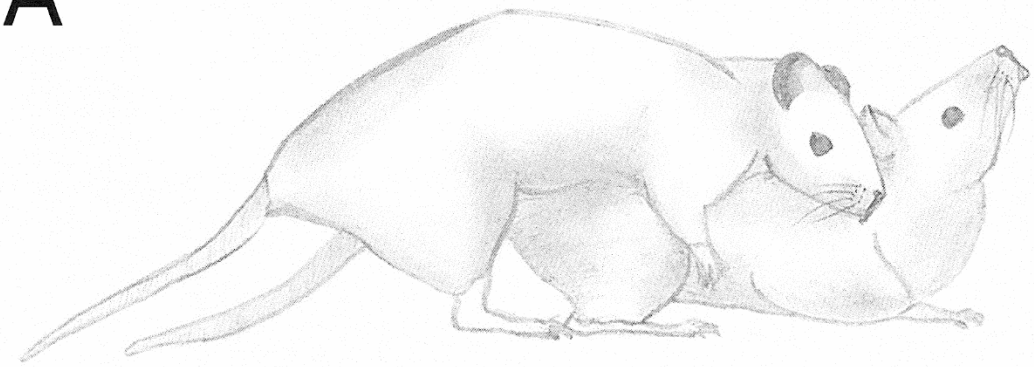
Fig. 5. **A.** The setup for evaluating the intensity of sexual approach behaviors. A sexual incentive (sexually active subject of the sex opposite to the experimental subject) and a social incentive (sexually inactive subject of the sex opposite to the experimental subject or a member of the same sex, for example an ovariectomized female or another male for the experimental subject male, or a castrated male or another female for the experimental subject female). The intensity of approach is calculated as a preference score (time spent in the vicinity of the sexual incentive / (time spent in the vicinity of that incentive + time spent in

the vicinity of the social incentive)). A score of 0.5 means no sexual motivation. A, incentive animal cage; B, incentive area. **B.** Preference score in male rats after different treatments. Intact, self-explanatory; Blank, castrated male implanted with an empty Silastic capsule; T, castrated male implanted with a capsule containing testosterone; T + F, castrated male implanted with a capsule containing testosterone plus daily treatment with 2.5 mg/kg of the aromatase inhibitor fadrozole for 21 days; DHT, castrated male implanted with two capsules containing dihydrotestosterone. The hormone levels obtained with these implants are within the physiological range. *, different from intact and T, $p < 0.05$. Thus, only the groups Intact and T approached the sexually receptive female more than they approached another male. These data are from Attila et al., Horm Behav 2010, 58, 341-351. Further experimental details are also provided in that paper.

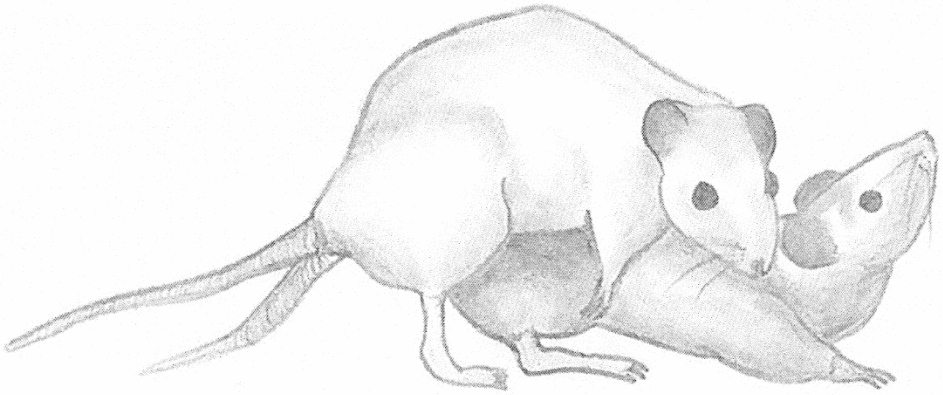
Fig. 6. The medial preoptic area (MPOA) as a connector between sensory input and motor output. Perhaps it can be conceptualized as the materialization of the central motive state.

Figure 1

A



B



C

Figure 2.

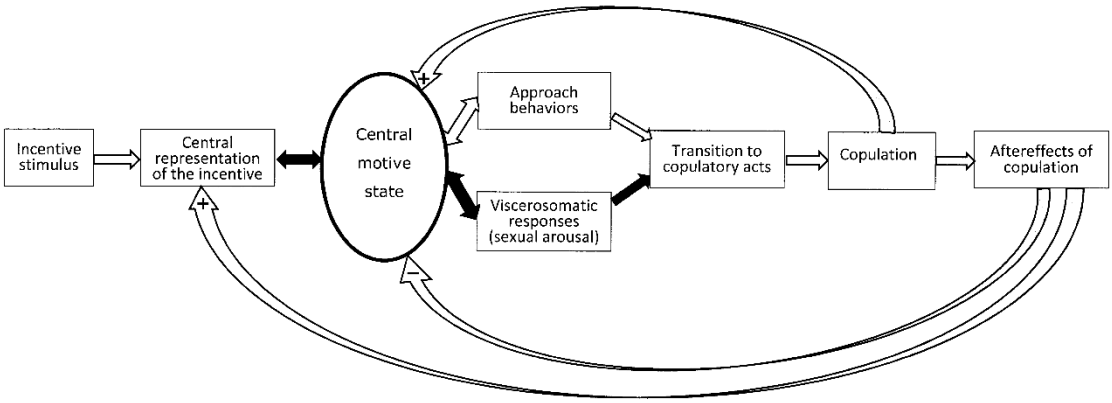


Figure 3

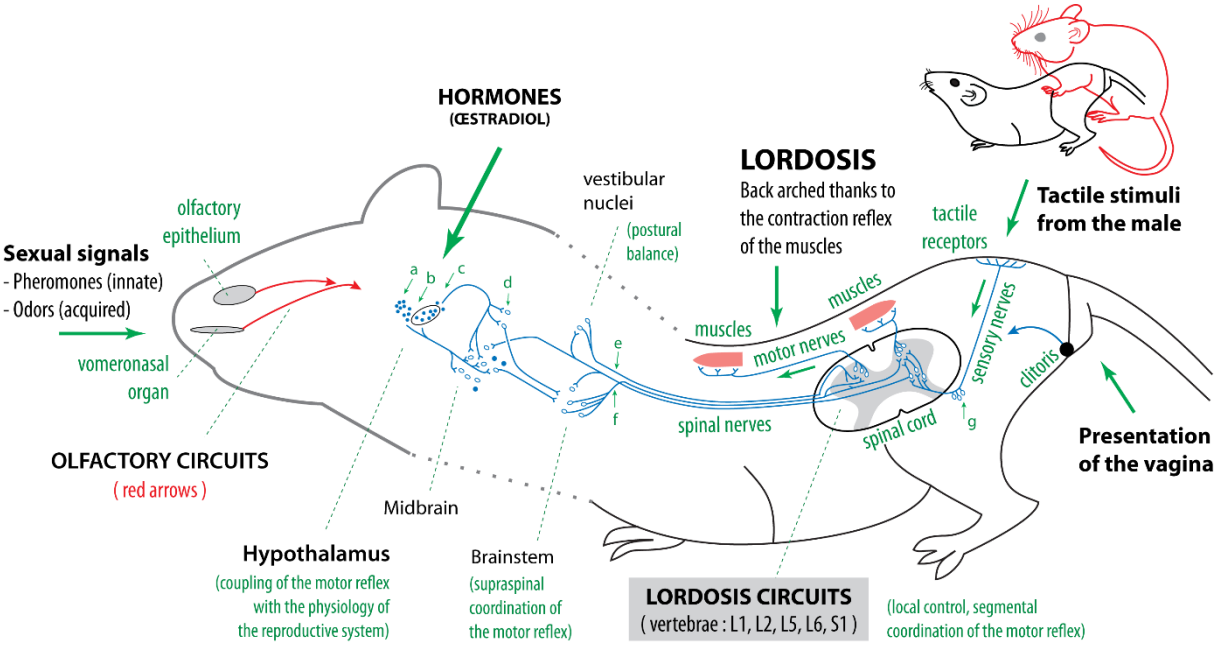


Figure 4.

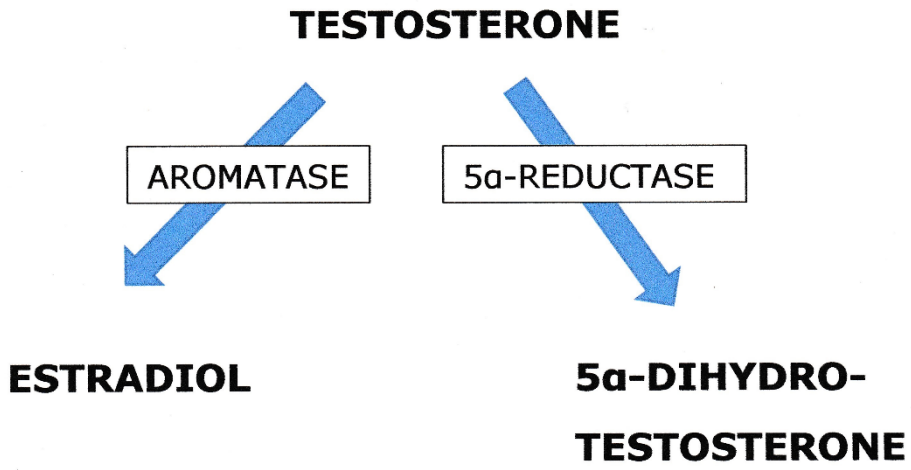
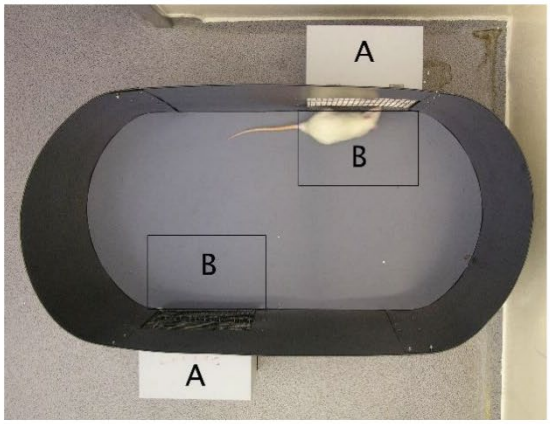

TESTOSTERONE
AROMATASE
5α-REDUCTASE
ESTRADIOL
5α-DIHYDRO-
TESTOSTERONE

Figure 5.

A


A
B
B
A

B

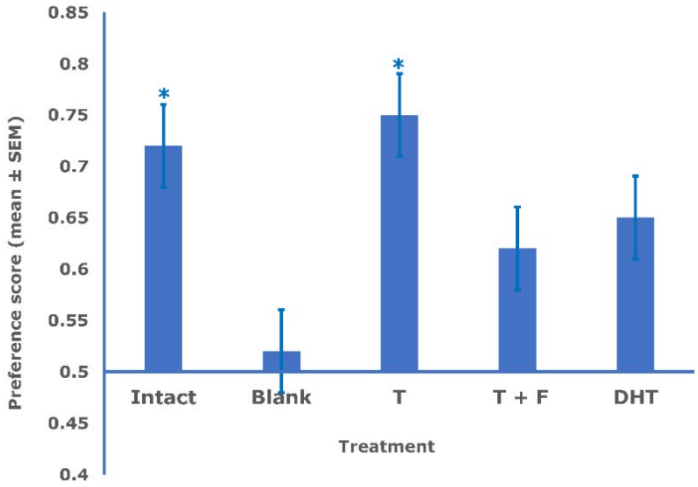

0.85
0.8
0.75
0.7
0.65
0.6
0.55
0.5
0.45
0.4
Preference score (mean ± SEM)
*
*
Intact
Blank
T
T + F
DHT
Treatment

Figure 6.