











Review

# Androgens and Female Sexuality: Molecular Insights, Neuroendocrine Crosstalk and Future Therapeutic Directions

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Academic Editor: Michael H. Dahan

Submitted: 17 February 2023 Revised: 12 April 2023 Accepted: 6 May 2023 Published: 12 July 2023

## Abstract

**Objective:** The scientific community has recently directed its attention towards investigating the role of androgens in female sexuality. This narrative review aims to elucidate the central and peripheral androgen-mediated mechanisms involved in female sexual health and function. Additionally, the current state of androgen therapeutic options is discussed. **Mechanism:** We searched several scientific literature databases, including EMBASE, MEDLINE, PubMed Central, and Scopus, utilizing keywords, index terms, and MeSH terms, such as "androgen\*", "female sexuality", "female sexual function", "women's sexual dysfunctions", "androgen therapy in women", and various combinations thereof. **Findings in Brief:** Progesterone or estrogens are commonly prescribed as first-line treatments for female sexual dysfunctions. However, these medications may frequently lead to therapeutic failure and cause harm by increasing sex-hormone-binding-globulin plasma levels and decreasing testosterone plasma concentrations. Currently, there are limited androgen therapies available for women, and the evidence for their effectiveness and safety is still limited. **Conclusions:** The knowledge of neuroendocrine interactions that underlie sexual arousal and pleasure is rapidly expanding, and ongoing research is striving to develop more appropriate clinical practices for managing sexual dysfunctions in women.

**Keywords:** testosterone; menopause; sexuality; androgens

## 1. Sexuality, Sexual Health and Sexual Function and the Role of Hormones

Sexuality and sexual health (SH) are strictly connected with sexual function (SF), which encompasses the four linear phases of the human sexual response cycle: excitement, plateau, orgasm, and resolution, as defined by Masters and Johnson in the 1960s [1]. However, this linear model has been challenged over the years, particularly with regards to female SF. Basson [2] proposed in 2001 that female sexual function is based on a more complex cycle that includes psychological and social factors. Female sexual response involves intricate interactions between social, psychological, neurological, vascular, and hormonal processes, as well as the central nervous system (CNS). Sexual dysfunctions can arise from alterations in endocrine, neural, or vascular responses, which can be caused by aging, medical illness, neurological diseases, surgery, or medications [3]. While sexual health and sexual function are closely linked, there

is no clear distinction between the two, and changes at any level can significantly impact patients' quality of life [4].

Unfortunately, female sexuality and dysfunctions have received less attention than male counterparts in biomedical literature, leading to a lack of understanding and targeted medications for female sexual dysfunctions [5]. Although research into the neuroendocrine interactions that underlie sexual arousal and pleasure is ongoing, there is still much to be learned about female sexuality. Currently, first-line therapies for treating female sexual dysfunctions are often non-pharmacological, such as couples therapy, sex therapy, psychotherapy, lifestyle changes, and pelvic physical therapy, or estrogens/estrogenic [6–8]. Recently, the role of androgens in sexual health and function in women has gained significant attention, with new therapeutic options being validated and entering pharmaceutical markets. This paper aims to offer an overview of the biological role of androgens in women and to discuss potential therapeutic



tic options for female sexual dysfunction in the absence of hyperandrogenism or hypoandrogenism.

## 2. Androgens in Women

Androgens in women (AW) are essential for the maintenance of women's overall health and well-being. In addition to their crucial reproductive functions, AW have diverse effects on several aspects of health, including cardiac health, bone remodeling and mass preservation, muscle tone and mass, and brain function [9]. It is interesting to note that there is currently no clear evidence linking AW to SF [10].

Major AW listed in descending order of serum concentration include: dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T), and dihydrotestosterone (DHT).

The production of AW is both central (adrenal glands, gonads) and peripheral (liver, adipose tissue, skin). Quantitatively, the amount of circulating AW is much higher than estrogens' one, with quite significant variations over the menstrual cycle and age [11–13]. In particular, serum AW declines steeply during the early reproductive years, then gradually without a menopause effect: the postmenopausal ovary is a continuing site of T production [14].

Precursors, such as DHEAS, DHEA and A, can be transformed into more bioactive androgens (*i.e.*, T and DHT) in peripheral organs and target tissues [15]. T is produced in the zona fasciculata of adrenal glands (25%), in the ovarian stroma (25%), and the remaining 50% is produced from circulating A [16]. It is estimated that ovaries alone contribute up to 50% to the plasma levels of T (25% through direct secretion and 25% through a peripheral transformation of the precursors). An analysis of plasma T using mass spectrometry [17] found a mean production rate of  $1.8 \pm 0.6$   $\mu\text{g/h}$ , with the highest production rates from 04:00 to 12:00 AM. Circulating levels of T and free T are in the range of 15–45 ng/dL (0.52–1.56 nmol/L) and 1.2–6.4 pg/mL (4.16–22.2 pmol/L), respectively. Moreover, T serum levels are higher in the mid- and luteal phases of the menstrual cycle [18–20].

T, in addition to its effects on the androgen receptor (AR), acts as a precursor of DHT. In certain tissues, such as the skin, liver, and brain, the enzyme 5-reductase catalyzes the formation of DHT from T. DHT is a much more potent AR agonist than T, and its production rate is  $2.9 \pm 1.1$   $\mu\text{g/h}$  [21]. Circulating DHT has a concentration of 3–10% relative to T and is almost entirely produced by peripheral conversion [22]. DHT serum levels do not appear to fluctuate cyclically throughout the different phases of the menstrual cycle [20]. As a result, DHT acts mainly in an intracrine and paracrine manner in peripheral tissues in which it is produced [11]. Moreover, T and A are precursors for the formation of estradiol and estrone, respectively, due to the aromatase enzyme action, whereas DHT is a non-aromatizable androgen [22]. Interestingly, T and DHT are metabolized

to various glucuronides in peripheral tissues, and some authors proposed them as new markers of androgenic activity in women [23].

Sex hormones circulate in the bloodstream bound to albumin, sex hormone-binding globulin (SHBG), and a small fraction unbound. Serum SHBG can bind T and estrogens, and SHBG levels are higher in women than in men. The relative occupancy of SHBG steroid-binding sites differs between men and women, with only 20% occupied in women and 80% occupied in men, reflecting men's significantly higher plasma T concentrations. SHBG steroid occupancy is further reduced in women who use oral contraceptives because they promote substantial increases in serum SHBG levels while additionally lowering ovarian sex steroid production [24].

Although T or other androgen blood levels remain debated [25,26], clinically meaningful alterations of blood values are recognized in cases of hypo- and hyperandrogenism, which we will briefly discuss. Causes of T and/or other androgen deficiency (or diminished functional activity) in women can be attributed to various causes, including aging (especially after menopause), oophorectomy, chemical oophorectomy (*i.e.*, gonadotropin-releasing hormone antagonists, chemotherapy, radiotherapy), oral estrogen or combined hormone therapy (COC), hypothalamic amenorrhea, hyperprolactinemia, premature ovarian failure/early menopause, primary or secondary adrenal insufficiency, hypopituitarism, drugs (*e.g.*, spironolactone, cyproterone acetate), and female androgen insufficiency syndrome [27]. Conversely, hyperandrogenism in women can arise from multiple causes, including but not limited to polycystic ovary syndrome, idiopathic hirsutism, congenital adrenal hyperplasia, late-onset 21-hydroxylase deficiency, and secondary conditions such as androgen-secreting tumors of the ovary and adrenal gland, hyperprolactinemia, Cushing syndrome, acromegaly, and rare conditions such as steroidogenic enzyme deficiencies [28].

## 3. Androgens and Central Control of Sexual Function

To date, evidence about the CNS control over SF needs to be further elucidated. Several recent studies in women have used functional magnetic resonance imaging (fMRI) to identify brain regions associated with sexual arousal and erotic stimuli [29]. Specific areas of the CNS are activated by sexual stimulation, including the medial preoptic region, the anterior hypothalamic region, and the related limbic hippocampal structures. This stimulates the transmission of signals via the parasympathetic and sympathetic pathways. At the supraspinal levels, many factors influence the excitability of spinal sexual reflexes, including gonadal hormones, non-sexual hormones (vasopressin, oxytocin, dopamine, serotonin, norepinephrine), genital sensory information through the myelinated spinothalamic

pathway and the unmyelinated spinoreticular pathway, and input from higher cortical cognition centers [30–32].

AW have multiple binding sites in the brain. In women, high concentrations of AR-containing neurons are observed in the hypothalamus and extrahypothalamic sites, such as the preoptic area, bed nucleus of the stria terminalis, amygdala, lateral septum, olfactory bulb, cortex, and hippocampus. The androgen receptors are clustered in areas involved in reproductive behavior and hormonal secretion. From these areas, signals communicate to other parts of the brain [33]. T has binding sites in the paraventricular nucleus of the hypothalamus, which activation stimulates the olfactory and genital centers. At the cortical, limbic and hypothalamic level, AW initiates sexual desire, with the subsequent support of estrogen (permitting) and progesterone (receptivity) through a real balance of neurotransmitters such as dopamine, serotonin, noradrenaline, gamma-aminobutyric acid (GABA) and other neuropeptides/neuromodulators [30].

#### 4. Androgens and Peripheral Control of Sexual Function

The process of genital arousal and orgasm during sexual stimulation involves the activation of spinal cord reflexes that are controlled by genital afferents originating from the pudendal nerve. The efferent arms involve a combination of sympathetic, parasympathetic, and somatic activities. Afferent signaling during sexual stimulation is transmitted to higher brain centers via the spinothalamic and spinoreticular pathways after entering the spinal cord in the sacral segments [31]. Vaginal engorgement during sexual arousal involves vasodilation and significant changes in vaginal tone, resulting in relaxation and lengthening of the vaginal tissue. This process is regulated by cholinergic mechanisms and contraction of striated muscle. The vaginal nerve fibers contain vasoactive intestinal polypeptide (VIP), nitric oxide synthase (NOS), calcitonin gene-related peptide (CGRP) and substance P (SP), all of which contribute to the relaxation of the vaginal tissue [34]. The neuroregulatory mechanisms for clitoral and penile smooth muscle appear to be similar, with immunohistochemical staining of human clitoral cavernosal tissue revealing the expression of NOS subtypes, suggesting the involvement of nitric oxide (NO) in the regulation of clitoral smooth muscle contractility and the development of clitoral engorgement [31]. The findings of Comeglio *et al.* [35] suggest that T relaxes smooth muscles through the NOS-cGMP pathway, and along with  $17\beta$ -estradiol, maintains the intermittent contractile function of the clitoris in female rats. The peripheral control of SF is complex and not yet fully understood. In rabbits, clitoral smooth muscle relaxation is enhanced by sildenafil, and the expression of phosphodiesterase type 5 in the vagina suggests an involvement of cGMP [27,36].

Additionally, Cellai *et al.* [37] found that supplementing DHEA on vaginal cells and vaginal smooth muscle cells obtained through biopsies increased the production of  $\delta 4$ -androstenedione, resulting in increased secretion of T and DHT. Compared to ovaries, these tissues have a higher mRNA expression of proandrogenic steroidogenic enzymes (HSD3B1/B2, HSD17B3/B5), indicating that the human vagina is an androgenic target capable of synthesizing androgens from precursors. Furthermore, DHT has been shown to have an anti-inflammatory effect on vaginal tissue. Studies investigating the involvement of human vagina smooth muscle cells in the inflammatory response have found that DHT treatment reduces the expression and secretion of several pro-inflammatory mediators (*e.g.*, COX2, IL-1, IL-2, IL-6, IL-12A, IFN $\gamma$ ) [38]. These findings support the potential use of androgens as a therapeutic target in a range of sexual dysfunctions.

#### 5. Medications and Their Influence on Androgens and Sexual Function: The Status Quo

Hormone replacement therapy (HRT) is a treatment used to alleviate symptoms associated with menopause. HRT can lead to a decrease in T and other AW bioavailability, and these changes, mediated by estrogens, can have negative clinical implications for susceptible individuals [39,40]. As discussed earlier, SHBG plasma levels are increased during HRT or COC treatments, resulting in less relative occupancy by steroid hormones. SHBG plasma levels are directly related to the different molecules used in HRT/COC, with ethinylestradiol increasing the circulating levels of SHBG by 119%, estradiol valerate by 40%, and estriol having no effect [41]. Monophasic preparations containing levonorgestrel induce an average SHBG increase of around 50%, while COC containing desogestrel or gestodene causes an average SHBG increase of 200–300%. A preparation with cyproterone acetate causes a 300–400% SHBG increase. Other authors have found a 150% SHBG increase with norgestimate and a 250–300% increase with drospirone and dienogest [42]. Additionally, several clinical studies have found a significant worsening of premenstrual syndrome, emotional side effects, decreased frequency of sexual thoughts, and decreased psychosexual arousability after initiation of HRT/COC therapies depending on the active substances contained in the medication [43–45].

The role of androgen-containing drugs in improving female SF is controversial. Currently, available data about T used as medication for this purpose are not robust enough to draw firm conclusion, and the long-term effects are not well-established. In the past, estrogen-androgen HRT was found to improve sexual desire, satisfaction and frequency in postmenopausal women dissatisfied with estrogen-only therapy. In particular, SF improved with estrogen-androgen therapy, even though circulating estrogen levels were lower

than those measured during previous estrogen therapy [46]. T administration in postmenopausal women with a symptomatic SH impairment is promising [47]. However, there is no data to support T use in women without any symptoms or clinical conditions or for disease prevention, mainly because no cutoff blood level can be used for any measured circulating androgen to differentiate women with and without sexual dysfunction, and data are inconclusive or insufficient [48]. The National Institute for Health and Care Excellence (NICE) Menopause Guideline (NG23) recommends that a trial of conventional HRT is given before T supplementation is considered. Furthermore, switching women with hypoactive sexual desire disorder (HSDD) from oral to transdermal estrogen can be beneficial as this can increase the proportion of circulating free T without requiring exogenous T [49]. The use of oral formulations is limited by the potential for adverse changes in blood lipid profiles. Other potential side effects of T therapy are acne, hirsutism, and mood or personality changes. Moreover, when considering androgen therapy in females of reproductive age, inadvertent exposure of a developing fetus must be considered a significant potential risk [50]. Shifren *et al.* [51] reported that in women who have undergone oophorectomy and hysterectomy, transdermal T improved SF and psychological well-being. In 2019, the “Global Consensus Position Statement on the use of testosterone therapy for women” [48] published findings on the potential use of transdermal T therapy (patch delivering 300 µ/day) for naturally or surgically postmenopausal women experiencing HSDD, with or without concurrent estrogen therapy. Non-oral routes, such as transdermal or injectable, are preferred due to their lack of statistically significant adverse effects on lipid profiles in the short term, as opposed to oral administration. In addition, the prescription of transdermal T therapy does not appear to be associated with an increased risk of cardiovascular events or other serious adverse events in women. It should be noted, however, that safety data for T therapy at physiologic doses beyond 24 months of treatment are not available [47,48,52]. Although transdermal T patches would be the preferred medication for females electing T therapy but are no longer available in the United States and Europe. Topical T formulations, such as 1% T cream, ointment, or gel, are available but have limitations including inconsistent concentrations of testosterone, variable absorption and bioavailability, potential adverse effects in children due to secondary exposure to the skin of an adult who had recently applied the medication, and limited data on safety and efficacy for any indication, including improvement of female SF [47].

Regarding DHEA medications, they can be used to treat HSDD in postmenopausal women in the presence of vulvovaginal atrophy or dyspareunia [48,53]. Preliminary studies of vaginal DHEA suggest effectiveness and safety, but further data are needed [54,55]. DHEA is available as a vaginal suppository (active ingredient called prasterone,

6.5 mg) and as a nutritional supplement. However, the use of nutritional supplements is not recommended, as they are not regulated by regulatory bodies such as the European Medicines Agency (EMA) and/or Food and Drug Administration (FDA). It may be appropriate to use DHEA at a dose of 25 or 50 mg/day following counselling regarding its experimental nature, although caution should be exercised [56].

## 6. Conclusions

Over time, there has been a growing awareness of the involvement of androgens in female sexuality and SH. However, there is still a dearth of established T or other androgen cutoff levels in blood that can differentiate between women with or without sexual dysfunction. Currently, validated therapeutic options for female sexual dysfunction include transdermal T therapy, which is beneficial for naturally or surgically postmenopausal women with HSDD, and vaginal suppository DHEA, which is indicated for vulvovaginal atrophy.

Discussion of androgen therapy with the patient must include a full explanation of the potential benefits and risks. Patients should be made aware that there is limited safety and efficacy data available, particularly with regards to long-term use or use without concomitant estrogen therapy.

## Author Contributions

Contributors: GM and GB conceived the article. GM, GB and MC wrote the initial draft of the manuscript. MC, LT, ASL, VC, AG, AE, GG, GC, EC, MR, and VC retrieved and analyzed data and edited the manuscript into its final form. All authors contributed to overall supervision. All authors provided approval for publication. All authors have made important intellectual contributions and have seen and approved the manuscript for submission.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of Interest

The authors have no conflicts of interest. Erich Cosmi, Andrea Giannini and Antonio Simone Laganà are serving as the Editorial Board members of this journal. Andrea Giannini, Giovanni Buzzaccarini, Antonio Simone Laganà, Gaspare Cucinella and Giuseppe Gullo are serving as Guest editors of this journal. We declare that Erich Cosmi, Giovanni Buzzaccarini, Andrea Giannini, Antonio Simone Laganà, Gaspare Cucinella and Giuseppe Gullo had no involvement



in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

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