19 Male Sex Hormones in Andrology Today

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19.1 Introduction

Male sexual function is the result of the communication among organic relational and intrapsychic components, which mutually interact supporting and maintaining a satisfying sexual relationship [1–9]. Endocrine and nervous systems represent the key messengers connecting and regulating all the involved phases. Both systems detect all the environmental changes affecting the body and work together to provide the best appropriate response to such events. The nervous system is based on electrical stimulations to communicate, whereas hormones a heterogeneous group of steroid or peptide-derived molecules, produce a messenger system regulating distant target organs.

Sexual sensations collected through the sense organs such as sight, hearing, smell, and touch are detected by peripheral nerves and the codified information reaches the most important centers within the central nervous system, including the septal nuclei, the amygdala, and the hippocampus [5, 10, 11]. The latter are brain areas widely interconnected with each other and with other regulatory centers of endocrine activity, such as the hypothalamus. At the appropriate time, the symphonic activity of hormones and neurotransmitters determines the readiness towards sexuality, which eventually results in intense vascularization of the corpora cavernosa and, eventually in penile erection.

Several hormonal pathways are involved in the latter process. Testosterone (T) represents the most important hormonal regulator of male sexuality acting either at central or peripheral level [11, 12]. Thyroid system seems to be more involved in the regulation of the ejaculatory reflex, although a possible contribution in sexual desire as well as in penile erection has also been supposed [12–15]. Prolactin (PRL) is mainly involved in the modulation of sexual desire, whereas its contribution in the pathogenesis of erectile dysfunction (ED) is more conflicting [12, 16]. Similarly, the role of other hormonal pathways in the regulation of male sexual response appears negligible [12].

In the following sections, the available evidence supporting the role endocrine system in the regulation of male sexual response will be summarized and critically discussed. In particular, the specific contribution on sexual desire erectile function and ejaculation will be analyzed in details.

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19.2 Steroids

Testosterone (T) is the main circulating sex steroid in males, essentially derived from testis production (daily production 5–10 mg) with a negligible contribution of the adrenal glands [17–19].

About 6–8% of daily T production is reduced into the more potent androgen, dihydrotestosterone (DHT), through the action of two distinct 5 α reductase (5αR) isoforms, 5αR type 1 and 2 [19]. In addition, T and its precursor, Δ4 androstenedione, can be actively transformed, through P450 aromatase, to other bioactive metabolites, such as estrone and 17-β-estradiol (E2) (daily production about 45 μg), which activate estrogen receptors (ERs).

During fetal life, androgens play a crucial role in regulating the differentiation of internal (mainly T) and external (mainly DHT) genitalia. During puberty, the new T rise contributes to the development of secondary sexual characteristics, growth acceleration, and body composition as well as to psychological modifications, which eventually allow reaching the adulthood male appearance. During adulthood, androgens, and T in particular, are mainly involved in maintaining and sustaining the psycho-biological modifications occurred during puberty [19–21]. The regulation of male sexual response is probably one of the most important functions modulated by T during adulthood and aging [18, 22–24]. According to the results derived from the European Male Aging Study (EMAS), a survey performed on more than 3400 community-dwelling men recruited from eight European centers, sexual symptoms—particularly ED, reduced frequency of morning erections, and reduced libido—are the most sensitive and specific symptoms in identifying patients with reduced T levels [25]. Similar results were thereafter reported by our group investigating a large sample ($n = 4890$) of subjects seeking medical care for ED [26]. Conversely, the role of other sex steroids including DHT and estrogens in regulating male sexual functioning is more conflicting. In the following section, the specific role of sex steroids on the regulation of sexual desire, erectile function, and ejaculation will be analyzed more in details.

19.2.1 Sexual Desire

T represents the fuel of sex drive and it is the most important determinant of the motivation to seek sexual contact (Table 19.1). Data derived from the general population [25, 27] as well as those detected from subjects consulting for ED [28, 29] have clearly documented an inverse relationship between circulating T levels and sexual desire. Similar data were observed in subjects undergoing androgen deprivation therapy for prostate cancer [30–32] or in those with hypogonadism related to androgenetic steroid abuse [33]. Accordingly, several clinical trials have documented that T replacement therapy (TRT) significantly improves sexual desire, spontaneous sexual thoughts, and attractiveness to erotic stimuli in hypogonadal (total T below 12 nmol/L; 3.5 ng/mL) subjects [34–39]. Data derived from animal studies and using functional magnetic resonance imaging (fMRI) have clearly documented that androgen receptors (AR) are widely expressed in specific brain areas, including temporal, preoptic, hypothalamus, amygdala, midbrain, frontal and prefrontal cortex areas, and cingulate gyrus which play an essential role in regulating male sexual drive [40]. Accordingly, the acute T administration activates most of them, as derived from fMRI [41]. Similarly, erotic visual stimulation, in healthy volunteers, leads to

Table 19.1 Role of several hormonal pathways in the control of male sexual response

	Sexual desire	Erection	Ejaculation
Steroids			
Testosterone	+++	+++	++
DHT	++ –	+++	– – –
Estrogens	+ – –	– – –	+ – –
DHEA/DHEAS	– – –	– – –	– – –
Glucocorticoids	+ – –	– – –	– – –
Aldosterone	– – –	+ – –	– – –
Other hormones			
Thyroid hormones	+ – –	+ – –	++ –
Prolactin	+++	+ – –	+ – –
Oxitocyn	– – –	+ – –	+ – –
Melacortin	– – –	– – –	– – –

DHT dihydrotestosterone, *DHEA* dehydroepiandrosterone, *DHEAS* dehydroepiandrosterone sulfate

a significant activation of the inferior frontal lobe, cingulate gyrus, insula gyrus, corpus callosum, thalamus, caudate nucleus, globus pallidus, and inferior temporal lobe [42]. Interestingly, the same results were not confirmed when hypogonadal men were considered [42]. Finally, in line with previous results, Stoleru et al. [43] using positron emission tomography (PET) documented that sexually explicit visual stimulation is able to produce T plasma level increase and to activate several paralimbic areas. Hence, taking together the aforementioned results support a strong role of T through AR activation in regulating male sexual desire [40]. However, given the possibility that other sex steroids, besides T, can support its role within the brain, acting on AR or through T, conversion to estrogens on ERs cannot be ruled out.

The role of DHT is quite conflicting (Table 19.1). Data derived from a clinical model of congenital 5αR type 2 deficiency, characterized by the impairment of T into DHT, showed that affected subjects often report normal sexual desire [44]. Similarly, data derived from population-based studies showed no relationship between mass-derived DHT and sexual desire [45]. In apparent contrast with the previous results, data derived from studies using 5αR inhibitors (5ARIs) for androgenetic alopecia [46] or prostate hyperplasia (BPH; [47]) showed an association with an increased risk of ED and reduced sexual desire. An intriguing working hypothesis supports the concept that 5ARIs can impair the formation of other 5α-reduced steroid metabolites, acting as neurosteroids in modulating sexual desire [48].

Limited evidence supports a possible role of estrogens (Table 19.1). In a double-blind placebo-controlled randomized controlled trial (RCT), Finkelstein et al., [49] by experimentally inducing a clinical condition of secondary hypogonadism through the administration of GnRH-analogue in 400 healthy men, aged from 20 to 50 years, reported that either E2 or T contributed to the observed decline of sexual desire. In line with the latter evidence, data derived from men with aromatase deficiency showed that transdermal E2 administration was able to improve sexual desire [50]. Conversely, adrenal hormones including dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) [51], as well as cortisol and aldosterone, seem to not be involved in the regulation of male sexual desire [12] (Table 19.1).

19.2.2 Erectile Function

Data derived from animal models and in vitro studies have documented that T controls most of the signaling pathways involved in the control of penile erection, including nitric oxide (NO) production and degradation, adenosine signaling, calcium sensitization through the RhoA-ROCK pathway, and even penile smooth muscle differentiation [52] (Table 19.1). Despite this evidence, data derived from clinical studies showed only a milder association between self-reported severe ED and circulating T levels [11, 53, 54]. Conversely, more solid data support the association between sleep-related erections and T levels [55–57]. These observations deserve a better discussion. Penile erection is essentially a neurovascular phenomenon characterized by the increase in blood flow within the lacunar spaces of the penis. Increasing age and associated morbidities can largely reduce the influence of T on erectile function by impairing penile vascular flow. Accordingly, we recently reported that age and comorbidities were the best predictors of the relationship between prostaglandin E1 (PGE1)-stimulated penile blood flow and T levels in a cohort of more than 2500 men complaining of sexual dysfunction [11]. Similar data were previously reported by us [58] and other groups [59, 60]. Hence, the main physiological action of T is to timely adjust the erectile process as a function of sexual desire, therefore finalizing erections with sex. However, it should be important to recognize that we recently reported that the combination of low T and associated morbidities could often result in more severe sexual problems [58].

In line to what derived from clinical evidence, all the available meta-analyses have shown that TRT is able to significantly improve erectile function in hypogonadal (total T < 12 nmol/L, 3.5 ng/mL) subjects [36, 37, 39, 61]. Interestingly,

however, TRT induced a modest 8% increase in International Index of erectile function domain score [11, 39], which should be considered clinically meaningful only in patients with milder forms of ED according to Rosen et al. [62]. Accordingly, the effects of TRT are more limited in more complicated patients such as those with obesity and diabetes mellitus [11, 35, 39]. The combination between phosphodiesterase type 5 inhibitors (PDE5i) and TRT has been suggested a possible strategy to overcome the limited effects of TRT in more severe ED. However, the present data are still conflicting and final conclusions cannot be drawn [11, 63].

Data derived from animal models seem not to support any difference when T is compared to DHT in the regulation of the main androgen-dependent pathway involved in penile erection and detumescence [18, 52] (Table 19.1). Accordingly, the possible association between the use of 5ARIs and ED seems more related to a drug effect rather than to reduction of DHT circulating levels. In line with the latter hypothesis, experimental studies showed that 5ARIs induce a structural and functional alteration in penile tissue, resulting in penile fibrosis through a modulation of cholinergic and adrenergic sensitivity, with no apparent changes in PDE5 expression and activity [64].

Estrogens and adrenal androgens (DHEAS and DHEA) play a negligible role in regulating erectile function, whereas limited evidence supports a possible role of glucocorticoids and mineralocorticoids [12] (Table 19.1).

19.2.3 Ejaculation

As previously reported for erectile function and sexual desire, T is deeply involved also in the modulation of ejaculatory reflex acting either at central or peripheral level [15, 65] (Table 19.1). Several central brain areas, including medial preoptic area, the bed nucleus of the stria terminalis, the median amygdala, and the posterior thalamus, are crucial for the supraspinal control of ejaculation express AR [15, 65]. In addition, bulbo-cavernosus muscle as well as other muscles of the pelvic floor involved in the ejection of the seminal bolus are under T control [15, 65]. Furthermore, T positively modulates also the emission phase by regulating the integrated system NO-PDE5, which represents one of the most important factor involved in the contractility of the male genital tract [65, 66]. In line with this evidence, we originally reported that low T levels and the presence of hypogonadal symptoms are associated with an overall lower propensity to ejaculate [66–68].

Accordingly, TRT is able to improve ejaculatory domain and orgasm when hypogonadal (total T < 12 nmol/L, 3.5 ng/mL) patients are considered [11, 69].

ERs have been identified in the epididymis of several animal species including humans [15]. At this level, estrogens are involved in the regulation of luminal fluid reabsorption and sperm concentration [15]. In addition, a possible role in the modulation of epididymal contractility has been also suggested [15]. In particular, estrogens might positively regulate endotelin-1 (ET-1) and oxytocin (OT)-mediated contractility either by increasing the expression of OT receptors or by activating a common downstream effector of the contractile mechanisms: the calcium-sensitizing RhoA/Rho-kinase system (see below; [70]) (Table 19.1).

No evidence supports a role of adrenal androgens (DHEAS and DHEA) as well as glucocorticoids and mineralocorticoids in the control of ejaculatory reflex [12, 15]. Similarly, no specific effect of DHT has been supposed [15] (Table 19.1).

19.3 Prolactin

PRL is a polypeptide secreted by the anterior pituitary and mainly regulated through tonic hypothalamic inhibition, by dopamine (DA) secretion [71, 72]. Hence, disruptions of the latter pathway or portal circulation perturbation, as well as sellar or parasellar tumors, are all associated with the development of marked hyperprolactinemia. The same condition can be associated with a primary hypothyroidism, since thyroid-

stimulating hormone (TRH) exerts positive effects on PRL secretion, or with the use of drugs blocking dopaminergic or increasing serotoninergic transmission such as antipsychotics or antidepressants [16]. The prevalence of milder forms of hyperprolactinemia (MHPRL, PRL >420 mU/L or 20 ng/mL) in male subjects with sexual dysfunction ranges from more than 13% [73] to less than 2% [74]. Conversely, more severe forms (SHPRL, PRL > 735 mU/L or 35 ng/mL) are less frequently observed (less than 1%; [74, 75]). In the presence of MHPRL, repeat blood sampling, in adequate conditions, results in normal PRL values in about 50% of cases, most probably due to venipuncture stress [74]. False positive cases can be derived from the presence of macroprolactin (around 10%), in the presence of SHPRL [74]. The latter is a biologically inactive complex of PRL and IgG which can be easily ruled out by reproducible polyethylene glycol (PEG) test [76]. Finally, it is also important to recognize that SHPRL is frequently (around 60%) supported by an organic problem in the hypothalamic-pituitary region, whereas a drug-induced condition can be found in almost 1/3 of cases [74].

Despite the well-known role of PRL in promoting breast-feeding in females, the specific role of this hormone in males is still not completely clarified. However, much evidence documented that elevated PRL levels in males are associated with a negative perturbation of sexual function [12, 16, 18, 29]. In the following sections, the specific contribution of PRL perturbation on male sexual function will be analyzed in details.

19.3.1 Sexual Desire

PRL receptors (PRLR) are expressed in brain, testis, accessory glands, and even at penis level [16]. A large body of evidence has clearly documented that SHPRL is tightly associated with reduced sexual desire in males [28, 29, 74, 77], whereas milder forms of hyperprolactinemia are less frequently associated with reduced libido [28, 77, 78] (Table 19.1). The specific molecular mechanisms through which PRL can impair sexual desire are not completely clarified. PRL can interfere with gonadotropin releasing hormone (GnRH) inducing a development of secondary hypogonadism. However, the latter can explain, only partially, the association between SHPRL and reduced libido [72]. Accordingly, TRT is not effective in restoring sexual desire in patients with SHPRL [79]. Hence, possible direct mechanisms of PRL have been advocated. Accordingly, PRL can modulate the turnover of DA in several brain areas partially involved in the regulation of sexual behavior such as the nigrostriatal and the mesolimbic tracts [72] Furthermore, experimental data have documented that PRL is involved in decreasing DA pathway in the diencephalic incertohypothalamic dopaminergic system, which represents the most important area for the control of motivational and consummatory aspects of sexual behavior [16, 80]. In line to what reported above, DA agonists such as bromocriptine and cabergoline are considered the first line treatments for SHPRL, particularly in patients with PRL-secreting adenomas [81]. Conversely, when possible, the modification or the withdrawn of interfering drugs should be advocated [81]. DA can normalize sexual desire and T levels in up to 90% of patients [16]. If hypogonadism persists, even after PRL normalization, TRT can be added resulting in better outcomes [16].

19.3.2 Erectile Dysfunction

The role of PRL in the regulation of erectile process is more conflicting (Table 19.1). Some studies have reported worse erectile function in subjects with SHPRL [73, 75]. However, we were unable to detect any association between SHPRL and severe ED after adjustment for T levels [74]. The latter observation suggests that PRL plays a major indirect effect (SHPRL-induced hypogonadism) on ED. Interestingly, we more recently reported that low PRL (<10 ng/mL or 210 mU/L) rather than high PRL was associated with arteriogenic ED in a large sample of patients seeking medical care for sexual dysfunction [82]. These results were confirmed in the general pop-

ulation [78, 83]. The latter observations support a positive effect of PRL on initiating or maintaining sexual behavior. The specific mechanisms underlying these findings are still unclear. However, an intriguing hypothesis supports the view that low PRL, in the peripheral circulation, could mirror, within the hypothalamus, both an increase of dopaminergic and a decreased serotoninergic signaling [16].

19.3.3 Ejaculation

Several observational studies have reported a PRL increase following male orgasm [84–86], supporting a possible role of PRL in the regulation of the postorgasmic refractory period [16]. However, it should be important to recognize that the observed postorgasmic rise in PRL is similar in men and women, which are less inclined to experience postorgasmic refractoriness. Hence, it is conceivable support that the observed PRL increases during orgasm reflect the emotional and stressful situation related to the sexual stimulation [16].

Similar to what was reported for ED, we originally documented that relatively low PRL levels were associated with a higher risk of premature ejaculation (PE) even after adjustment for confounders [82] (Table 19.1). In the same study, we did not observe any difference in the risk of PE when lifelong or acquired forms were considered [82]. Hence, by supporting PE-related *Waldinger's neurobiological hypothesis*, dealing with a disturbance in the central serotonin pathway, our data support the view that even secondary causes of PE would act mainly influencing the brain serotonergic system [16].

19.4 Thyroid Hormones

Free fractions (FT3 and FT4) represent the biological active fraction of the thyroid hormones (TH) produced by thyroid glands under thyroid-stimulating hormone (TSH) control [15]. TH are involved in regulating protein, fat, and carbohydrate metabolism so that no organs or tissues can be unaffected by thyroid diseases [87]. Accordingly, thyroid receptors are widely expressed within male genitalia tract, although the specific role of TH on male sexual function is still conflicting.

19.4.1 Sexual Desire

In a first open-label observational pilot study, Carani et al. [13] reported that hypothyroidism was associated with low sexual desire, which was improved after normalizing TH levels. Similar results were reported by other authors [88]. Although the raised PRL levels due to hypothyroidism status have been advocated as a possible supporting mechanism mediating the negative effects of low TH on sexual desire, a direct action of TH on the serotoninergic system has been also suggested [12, 18]. However, it should be important to recognize that no association between low TH and sexual desire has been reported in a larger series of subjects either from the general population or from patients seeking medical care for sexual dysfunction [14]. Hence, more studies are advisable to better clarify the role of TH on sexual desire (Table 19.1).

19.4.2 Erectile Dysfunction

Similar to what was reported for sexual desire, the role of TH in regulating male erectile function is still conflicting (Table 19.1). Limited evidence has documented a possible association between either hypo or hyperthyroidism and ED [13, 88–90]. In addition, some authors also reported that the restoration of normal TH was associated with an amelioration of erectile function [13, 88, 89]. The largest study published so far including 3203 subjects seeking medical care for sexual dysfunction and more than 3400 patients enrolled in the EMAS study showed that hyperthyroidism but not hypothyroidism was associated with an increased risk of severe ED, after adjusting for confounding factors [14]. The latter results were confirmed by Keller et al. [91] in a retrospective analysis of a Health Insurance Database representative of Taiwan's general

population. Data derived from animal models have shown that hyperthyroidism is associated with an impairment of NO-dependent relaxation of corpora cavernosa (CC; [92, 93]). In addition, in the same experimental model either acetylcholine- or electrical field stimulation-induced relaxation of CC was impaired, whereas sensitivity to the NO donor, sodium nitroprusside, was unchanged [93]. However, it is important to recognize that the prevalence of thyroid disorders in patients seeking medical care for ED is rather low (<1%) and not different from that observed in the general population [94]. The latter observations limit the specific direct role of TH on erectile function.

19.4.3 Ejaculation

More robust data have supported a possible role of TH in the regulation of the ejaculatory reflex (Table 19.1). In 2004, we originally reported, for the first time, a significant association between hyperthyroidism, even in the subclinical form, and PE in a consecutive series of 755 men presenting with sexual dysfunction [95]. In line with this observation, Carani et al. [13] thereafter confirmed an association between PE and hyperthyroidism and that the opposite condition, hypothyroidism, resulted in a twofold increase in ejaculatory latency. Similar results were confirmed by other authors [66, 96]. Data from animal models showed that experimentally induced hyperthyroidism in rats caused an increased frequency of seminal vesicle contraction and bulbospongiosus muscle contractile activity, supporting the role of TH in regulating either the emission or the expulsion phases of the ejaculation process [97]. To further support the possible contribution of TH in the modulation of ejaculation, the aforemtioned studies also documented that achieving euthyroidism at follow-up was associated with an improvement of PE [13, 96] or reduction in ejaculatory time [13], respectively. Finally, more recently a meta-analysis of the available data confirmed that hyperthyroidism was associated with twofold increased risk of PE and that delayed ejaculation was related to hypothyroid [98]. The same study also confirmed that treatment of underlining thyroid disorders improved the mean intravaginal ejaculatory latency time measures of the subjects [98].

19.5 Other Hormones

Oxytocin (OT): is a short peptide synthesized in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus and released by posterior pituitary. OT in men is released during sexual activity and orgasm and it can activate the secretion of ET-1 and OT itself in the epididymis, creating a reciprocal and synergic cross-activation of contractile factors involved in the regulation of male genitalia tract contractility favoring sperm progression [15]. Despite this evidence, the role of OT in regulating penile erection is limited and still conflicting [12] (Table 19.1).

Other hormones Limited evidence has documented a possible contribution of other hormones in the regulation of male sexual functioning, including growth hormone [99] and melanocortin [100]; however, available data are too preliminary and not supported by robust evidence-based data [12] (Table 19.1).

19.6 Conclusions

A large body of evidence supports the crucial role of T in the regulation of male sexual response. PRL is mainly involved in modulating sexual desire, whereas TH plays a major role in regulating ejaculatory reflex. All available guidelines strongly encourage investigating T levels in all subjects complaining of sexual dysfunction [18, 22–24]. TRT can improve all aspects of sexual function and should be considered the first treatment, especially in hypogonadal patients with milder forms of ED. Dopaminergic drugs are highly effective in restoring male sexual desire in subjects with severe hyperprolactinemia, whereas the treatment of underlying thyroid diseases can improve ejaculatory problems. Further studies are advisable to better characterize the role of other hormones.

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