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Chapter

Estrogen for Male Function: Effect of Changes in the Sex Hormone Milieu on Erectile Function

Tomoya Kataoka and Kazunori Kimura

Abstract

Androgens are essential for male physical activity and normal erectile function. Moreover, estrogens also influence erectile function, and high estrogen levels are a risk factor for erectile dysfunction (ED). In this review, we summarize relevant research examining the effects of the sex hormone milieu on erectile function. Testosterone affects several organs, particularly erectile tissue. The mechanisms through which testosterone deficiency affects erectile function and the results of testosterone replacement therapy have been extensively studied. Estrogen, the female sexual hormone, also affects erectile function, as demonstrated in both clinical and basic studies. Interestingly, estradiol-testosterone imbalance is considered a risk factor for ED. Furthermore, endocrine-disrupting chemicals have estrogen-like effects and cause ED. Phosphodiesterase-5 (PDE-5) inhibitors, first-line drugs for the treatment of ED, increase the levels of testosterone and estradiol in patients with low testosterone levels. Therefore, estrogen levels should be carefully monitored in patients receiving PDE-5 inhibitors. Future studies are needed to confirm these findings using molecular tools in order to provide insights into the treatment and mechanisms of endocrine-related ED.

Keywords: estrogen, testosterone, endocrine-disrupting chemical, phosphodiesterase-5 inhibitor, erectile dysfunction, endothelial function

1. Introduction

Serum estrogen levels are correlated with symptoms of aging in men, and estrogen may therefore play an important role in aging [1, 2]. Several previous studies have suggested that estrogen levels may also affect erectile function [3–6]. Indeed, older and obese men have been found to have not only low androgen levels but also high estrogen levels. Since testosterone is metabolized to estradiol by aromatase, the particularly high aromatase levels in visceral adipose tissue may explain the elevated estradiol levels among obese men [7]. Visceral adipose tissue often accumulates among men with increasing age. Interestingly, high estrogen levels have been observed in older patients who present with a lack of sexual interest and erectile dysfunction (ED); therefore, these symptoms in the elderly are thought to involve a pathophysiological estrogen-testosterone imbalance [6, 8–10].

Accordingly, in this review, we discuss the effects of sex hormone imbalances on male erectile function.
2. Erectile function and sexual hormones

There are many reports on erectile function and sexual hormones. Erectile function is controlled by complex mechanisms [11], including the vascular and nervous systems [12–16]. One of the most important materials is a nitric oxide (NO). After NO is releasing in the penis, corporal smooth muscle relaxes. However, when NO production is decreased, the erectile function weakened, resulting in ED. The relaxant system is also important for the erectile function. The relaxant system is controlled by both the endothelial and the nervous systems. When the upper stream of smooth muscle relaxant system is weakened, ED is caused; therefore, many studies have focused on smooth muscle relaxation. In contrast, corporal smooth muscle contraction is controlled by constrictors, such as noradrenaline in the flaccid state. However, if the contraction be upregulated in some situations, ED would be caused.

Interestingly, some studies have indicated that smooth muscle relaxation and contraction balance is disturbed by abnormal activation of contractile signaling pathway such as the adrenergic regulation. In some syndromes causing ED, such as diabetes mellitus or metabolic syndrome, the contraction is enhanced [17–19]. One of the important contractile signaling pathways is the RhoA/Rho-kinase signaling pathway. The enhancement is known to occur in aged individuals. The inhibition of RhoA/Rho-kinase signaling pathway by Y-27632 has been shown to improve ED in aged animal models [20, 21]. Interestingly, the contractility of smooth muscle in the corpus cavernosum is regulated by sexual hormones and may play a significant role in erectile function.

3. Testosterone deficiency and ED

Testosterone deficiency and ED have been studied extensively [22–25]. Testosterone deficiency causes ED using castrated animal models [26]. Furthermore, the erectile function is discussed by the endothelial NO synthase (eNOS) and neuronal NOS (nNOS) signalings. In some studies, testosterone administration to the castrated animals improved NOS expression in the penis and restored the erectile function [27]. Li et al. showed that testosterone deficiency decreases the upregulating reactive oxygen species production and it decreased eNOS activity (the phospho-eNOS/eNOS ratio) [28]. They also showed the reduction in eNOS activity induced cGMP levels decreased in the penis. Testosterone also alters phosphodiesterase type 5 (PDE-5) expression in the penis. Traish et al. showed that testosterone deficiency decreases PDE-5 activity using the rabbit model [29]. Additionally, Zhang et al. showed that PDE-5 expression was decreased by castration in the rat corpus cavernosum and that testosterone replacement therapy to the rats improved the expression [30]. These results indicate that testosterone is important for regulating PDE-5 expression. Traish et al. also suggested testosterone regulates not only NOS but also PDE-5 [31].

Testosterone also affects the smooth muscle of the corpus cavernosum. Reilly et al. reported that testosterone deficiency reduces the number of α-adrenergic-1 receptors in the castrated rats’ smooth fascia [32]. Moreover, testosterone modulates the adrenergic response of the corpus cavernosum vascular smooth muscle [33]. These results indicate that when testosterone levels decrease, smooth muscle contractility also decreases. On the other hand, Sopko et al. showed that the levels of RhoA and Rho-kinase proteins are increased in the castrated rats’ corpus cavernosum [34]. Their results indicated that testosterone deficiency increased smooth muscle contractility, leading to the decreasing erectile function and
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Overall, we demonstrated that changes in the sex hormone milieu affected erectile function in rats, and our hypothesis that the sex hormone imbalance associated with ED was supported by both in vivo and in vitro experiments using pharmaco-logical tools.

6. Estrogen receptors (ERs) in erectile function

Several reports have suggested an association between ERs and ED. Schultheiss et al. have shown the ER distribution in the corpus cavernosum penis of adult humans [66]. Additionally, Dietrich et al. have demonstrated that the corpus cavernosum and corpus spongiosum smooth muscles were immunoreactive for the androgen receptor (AR), ER-\(\alpha\), and ER-\(\beta\) and that endothelial cells were negative for AR, sporadically positive for ER-\(\alpha\), and positive for ER-\(\beta\)[67]. Jesmin et al. have demonstrated that ER-\(\alpha\) was predominantly localized in the sensory corpuscle of the glans penis [68]. On the other hand, they also reported that the ER-\(\beta\) was localized around the neurovascular bundle, artery, and nerve [68]. Spyridopoulos et al. have shown that the potential antiapoptotic effects of estrogen were impaired by reduced ER-\(\alpha\) expression, and loss of antiapoptotic genes in the rat corpus cavernosum was associated with the pathogenesis of ED [69]. These reports indicate that the ER exists in the corpus cavernosum and has various functions. Moreover, the ER has been reported to be altered under some conditions. Shirai et al. have demonstrated that vascular endothelial growth factor treatment restores erectile function through stimulation of the insulin-like growth factor system and ER-\(\alpha\) gene at the mRNA and protein levels in the corpus cavernosum of diabetic rats [70–72]. They had shown the expression of ER-\(\alpha\) mRNA in male rat aortas before and after balloon denudation injury. Interestingly, the expression of ER-\(\alpha\) mRNA in vascular endothelial and smooth muscle cells was very low after injury; however, the expression of ER-\(\beta\) mRNA in vascular endothelial cells was high after injury. Thus, the vascular protective effects of estrogen on endothelial and smooth muscle cells were exclusively mediated by ER-\(\alpha\), not ER-\(\beta\)[73]. Shirai et al. also demonstrated that the functionally predominant form of ER in the rat corpus cavernosum was ER-\(\alpha\) and that age-related alterations in ER-\(\alpha\) expression were likely related to the pathogenesis of ED in older rats. Thus, they concluded that downregulation of sex hormone receptors in the corpus cavernosum of aging rats is associated with ED [74]. Goyal et al. demonstrated the influence of estrogen on the structure of the corpus cavernosum [75–79] and showed that exposure to antiandrogens induces permanent structural abnormalities, including accumulation of fat cells, loss of smooth muscle cells and sinusoids, and reduced thickness of connective tissue trabeculae and tunica albuginea in the corpora cavernosa [76]. They also demonstrated that the ER and AR mediate cavernous smooth muscle cell differentiation, as shown by downregulation of MYH11 expression at the mRNA and protein levels and by reduced immunohistochemical staining of smooth muscle alpha actin using rats [79]. Therefore, a high estrogen milieu and alterations in ER expression may affect erectile function.

7. Endocrine-disrupting chemicals and ED

Some endocrine-disrupting chemicals have physiological effects similar to those of estrogen. Bisphenol A (BPA) is a widely used endocrine-disrupting chemical that is thought to have adverse health effects [80]. BPA has been widely produced and used as a common ingredient in the manufacture of plastics. Humans are mainly
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exposed to BPA through ingestion of foods containing BPA, and increasing evidence supports its association with impaired male reproductive function [81]. Manfo et al. reported that BPA also decreases erectile function [82], and Li et al. showed that BPA-exposed workers had significantly increased risk of ED (odds ratio = 4.5, 95% confidence interval: 2.1–9.8) [83, 84]. Moon et al. were the first to report the influence of BPA on erectile function using animal model [85]. They observed thickening of tunica albuginea, sub tunical deposition of fat, and decreased sinusoidal space with subsequent increases in trabecular smooth muscle content by histological analysis in BPA-treated animals and demonstrated endothelial dysfunction in BPA-treated rabbits. Kovanecz et al. also reported that BPA decreases nNOS and vascular endothelial growth factor expression in rats [86, 87]. In these reports, BPA-induced ED was similar to high estrogen-induced ED. Thus, the relationship between endocrine-disrupting chemicals and ED should be carefully considered.

8. ED treatment and estrogen

PDE-5 inhibitors are the first choice for patients with ED. Recently, some interesting papers on PDE-5 inhibitors and estrogen have been published. Greco et al. reported a reduction in estrogen levels in patients with ED after chronic exposure to tadalafil, a PDE-5 inhibitor, and a concomitant increase in the testosterone-estrogen ratio [88]. They also showed that increased testosterone-estrogen ratios were not related to increases in testosterone serum levels, but rather to the possible effects of tadalafil on aromatase activity. Aversa et al. also demonstrated that daily tadalafil decreases serum estradiol levels [9]. In contrast, Spitzer et al. have reported that the PDE-5 inhibitor sildenafil increased estradiol levels in 40 men (ages 40–70 years) with ED, despite increasing testosterone levels [89]. Additionally, several reports have demonstrated that PDE-5 inhibitors increase testosterone levels [90–96]. When testosterone is low, estradiol levels may also be low because testosterone is metabolized to estradiol by aromatase. PDE-5 inhibitors can increase not only testosterone but also estradiol in patients with low testosterone levels. Therefore, estrogen levels should be carefully monitored in patients receiving PDE-5 inhibitors.

9. Conclusions

The sex hormone milieu affects erectile function, and sex hormone imbalances, particularly low testosterone levels combined with high estrogen levels, cause ED. Interestingly, estradiol has protective effects on female health, but harmful effects on male erectile function. Overall, these results provide insights into the possible treatments of endocrine-related ED. Future research should confirm these findings in more specific experiments using molecular tools.

Conflict of interest

The authors declare no conflicts of interest.
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Estrogen


