We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

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

hypertension. Thus, although testosterone deficiency may increase contraction, additional research is required to more fully elucidate its impact on smooth muscle contraction.

Interestingly, testosterone also directly affects smooth muscle relaxation. Using isometric tension analysis, Yue et al. showed that the smooth muscle of rabbit coronary arteries and aortas are relaxed by testosterone [35]. Others have also reported that testosterone activates smooth muscle ATP-sensitive K^+ channels and regulates the relax response of the smooth muscles [36]. These findings indicate that testosterone may regulate erectile function locally by acting on corpus cavernosum smooth muscle. These results indicate that testosterone may affect both genomic and nongenomic mechanisms of erectile function.

Testosterone also affects the structure of the penis. For example, castrated rats exhibit smooth muscle loss and fibrosis [37], and testosterone deficiency increases the volume of collagen in the internal pudendal arteries [38]. These effects of testosterone indicate that testosterone deficiency causes programmed trabecular smooth muscle cell death (apoptosis) [29]. Traish et al. also indicated that testosterone deficiency is related to the accumulation of fat-containing cells (fibroblasts or preadipocyte-like cells), particularly in the penis [39]. Interestingly, Wang et al. showed that testosterone deficiency decreases erectile function and increases collagen in the corporeal cavernosum by inhibiting autophagy and promoting apoptosis of the smooth muscle cells in rats' penis [40]. Although their report had several limitations, they discussed the important role of testosterone in regulating the structural integrity of the corpus cavernosum and erectile function. This resulted from testosterone regulating the counterregulation of autophagy and apoptosis by modulating the interactions between BECN1 and Bcl-2 (key dual regulators of autophagy and apoptosis) [41, 42].

4. Estrogen and ED in clinical studies

Estrogen, the female sex hormone, also affects erectile function. Interestingly, Tivesten et al. reported that that circulating free testosterone is positively associated with the ankle-brachial index (ABI) in a large population-based cohort of elderly males. They show that testosterone has a negative association with the degree of atherosclerotic disease in the lower extremities [43]. On the other hand, estrogen also has association with ABI negatively in the males, leading to higher estradiol levels associated with increased atherosclerosis. Besides, when lower extremity peripheral arterial disease (PAD) was defined as an ABI of less than 0.90, they showed that low serum testosterone and high serum estradiol are associated with lower extremity PAD. Moreover, both low testosterone levels and elevated estradiol levels affect erectile function and are associated with increased ED severity when present individually or concomitantly [44]. Low testosterone levels were thought to be the main effector; however, the presence of concomitantly elevated estradiol levels increased the severity of ED in patients with low testosterone levels. These reports indicated that female sex hormones also affect male health. Srilatha and Adaikan demonstrated that estradiol-testosterone imbalance is a risk factor for ED [8, 45, 46]. They showed that higher levels of estradiol were present in older patients experiencing with lack of sexual interest and ED, after adjustment for age [8]. Additionally, they concluded that the estradiol-testosterone hormonal balance may be a determinant of successful management outcomes for ED. Wu et al. also reported an association between sexual dysfunction and changes in estradiol and testosterone levels in Chinese men [47], and O'Connor et al. reported that estradiol

was associated with sexual function-related distress; higher levels were related to greater distress in 2838 men, ages 40–79 years, who completed the European Male Aging Study-Sexual Function Questionnaire [48]. These reports specifically demonstrated the relationship between high estrogen milieu and male erectile function.

Serum estrogen levels are controlled by aromatase but can be altered under some conditions. Lamba et al. reported that antiretroviral therapy is associated with sexual dysfunction and increased serum estradiol levels in men [49]. Moreover, they found that total estradiol levels may be increased based on sex hormone-binding globulin (SHBG) levels. Drugs such as phenytoin are known to cause elevations in serum estradiol and SHBG [50]. Increased levels of SHBG, for example, due to induction of aromatase or SHBG synthetase, lead to a decrease in the free androgen index. Additionally, increased levels of SHBG and/or a low free androgen index have been associated with hypertension, osteoporosis, varicose veins, sexual dysfunction, and adverse serum lipids [51–56]. All these side effects have been reported in association with antiretroviral therapy as well. SHBG, similar to other globulins, is upregulated in patients with acquired immunodeficiency syndrome and human immunodeficiency virus infection [57, 58]. Hassan et al. have also reported the association of overhydration with male sexual dysfunction and depression in hemodialysis patients [59]. They showed that overhydration in hemodialysis patients was associated with a higher prevalence of sexual dysfunction and depression, lower serum levels of total testosterone and dehydroepiandrosterone, and higher levels of serum estradiol. Intriguingly, Tivesten et al. reported that circulating estradiol is a predictor of the progression of carotid artery intima-media thickness in middle-aged men [60]. They also reported that elderly men with low serum testosterone and estradiol have increased risk of mortality and that patients with low testosterone and estradiol levels have the highest risk of mortality [61]. Serum estrogen levels can be altered by some drugs and sex hormones. Therefore, ED induced by high estrogen may be related to mortality.

5. Estrogen and ED in basic research

Interestingly, estrogen administration decreases erectile function in animal models [62, 63]. Researchers administered estradiol orally to rats, resulting in high estradiol levels and low testosterone levels. Moreover, the intracavernous pressure (ICP) response to nerve stimulation was also impaired in all treated groups, and trichrome staining demonstrated the presence of cavernosal connective tissue hyperplasia in long-term study groups [62]. Oral administration of estradiol to rabbits resulted in high estradiol levels and low testosterone levels, similar to the effects in rats. Additionally, acetylcholine induced endothelium-mediated relaxation in normal animals, but this effect was significantly attenuated in treated groups, and NO-mediated nonadrenergic, noncholinergic neurotransmission was decreased in the treatment groups [63].

In our previous studies, subcutaneous administration (s.c.) of estradiol to rats resulted in high estradiol levels and low testosterone levels, thereby decreasing erectile function [64]. Moreover, we administered testosterone to rats with high estrogen-induced testosterone deficiency; however, erectile function did not improve. Interestingly, estrogen administration increases the contraction of smooth muscle in the corpus cavernosum, upregulating the RhoA/Rho-kinase signaling pathway, which is involved in ED [18]. Vignozzi et al. demonstrated that high-fat diet-induced ED is associated with high estradiol levels, rather than low testosterone levels [65].

We also investigated the influence of estradiol-testosterone imbalance on erectile function in rats (**Figures 1–6**; **Table 1**). Male Wistar ST rats (11 weeks old, Japan SLC Inc., Hamamatsu, Japan) were separated into five groups. In the low testosterone (Low-T) group (n = 11), rats were injected with goserelin (LH-RH agonist, 0.9 mg/kg, s.c.). In the low testosterone and high estrogen (Low-T/High-E) group (n = 11), rats were injected with goserelin and estradiol (3 μg/kg/day, s.c.) daily from weeks 2 to 4. In the high estrogen (High-E) group (n = 11), rats were injected with estradiol daily from weeks 2 to 4. In the high estrogen and testosterone (High-E/High-T) group (n = 11), rats were injected with estradiol and testosterone (3 mg/kg/day, s.c.) daily from weeks 2 to 4. In the control group (n = 11), rats were not injected with any hormone. **Table 1** shows the sex hormone concentrations in rats. Goserelin injection significantly decreased serum bioavailable testosterone (control: 1.20 ± 0.13 ng/mL, Low-T: 0.55 ± 0.04 ng/mL, $P < 0.01$ versus the control; Low-T/High-E: 0.73 ± 0.06 ng/mL, $P < 0.05$ versus the control). Testosterone injection significantly increased serum bioavailable testosterone (control: 1.20 ± 0.13 ng/mL, High-E/High-T: 2.58 ± 0.31 ng/mL, $P < 0.001$ versus the control). Estradiol injection significantly increased serum estrogen (control: 102.5 ± 8.7 pg./mL, Low-T/High-E: 275.4 ± 34.4 pg./mL, $P < 0.01$ versus the control; High-E: 332.3 ± 17.4 pg./mL, $P < 0.001$ versus the control; High-E/High-T: 401.5 ± 51.6 pg./mL, $P < 0.001$ versus the control).

Figure 2 shows the erectile response to electrical field stimulation of the cavernous nerve in the different experimental groups. Analysis of the ICP/MAP ratio revealed that the ratios in the Low-T (0.52 ± 0.03), Low-T/High-E (0.46 ± 0.03), High-E (0.44 ± 0.03), and High-E/High-T (0.44 ± 0.02) groups, which represented

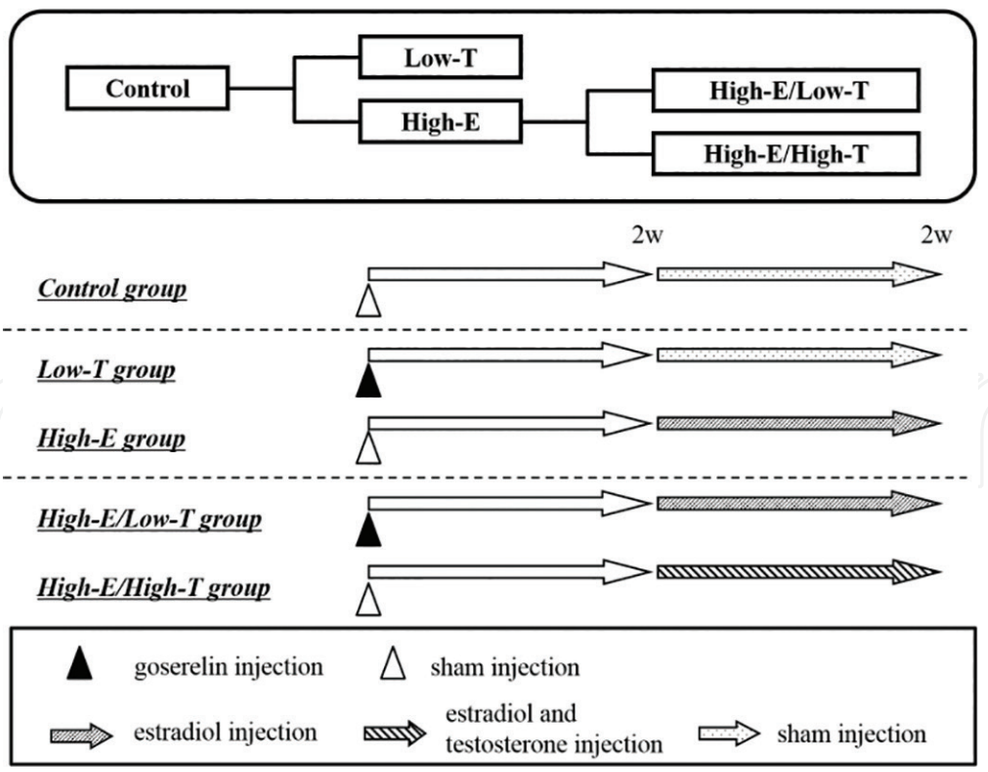

Figure 1.
Experimental design. In the control group, rats were injected with vehicle for 2 weeks. In the Low-T and High-E groups, rats were injected with goserelin acetate (LH-RH agonist, 0.9 mg/kg subcutaneously) at day 0. In the estrogen-treated (High-E) group, rats were injected with estradiol (3 mg/kg/day subcutaneously) for 2 weeks. In the estrogen- and testosterone-treated (High-E/High-T) group, rats were injected with estradiol (3 mg/kg/day subcutaneously) and testosterone (3 mg/kg/day subcutaneously) for 2 weeks. At the end of the period, rats were underwent erectile function testing in vivo or in vitro.

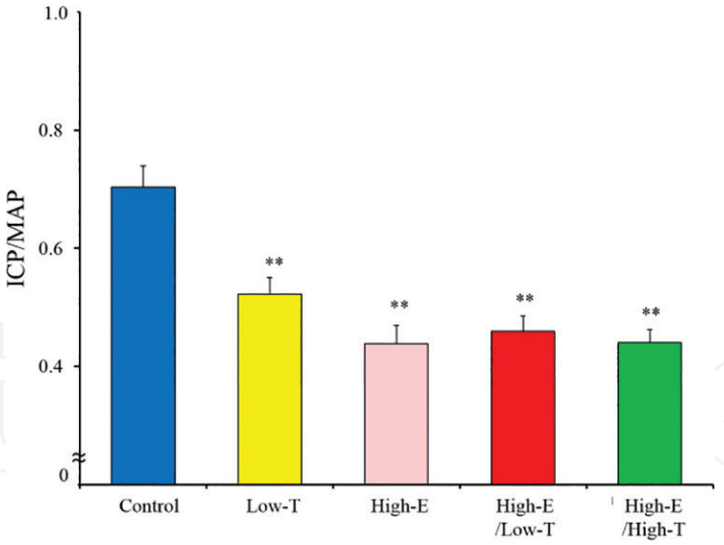

Figure 2.
*Measurement of intracavernous pressure (ICP). Maximum ICP changes during electrical stimulation of the cavernous nerve in the control, Low-T, High-E, High-E/Low-T, and High-E/High-T groups. Data represent the means ± standard errors of the means (n = 6 per group). **P < 0.01 versus the control group by analysis of variance and Bonferroni-type multiple t-tests.*

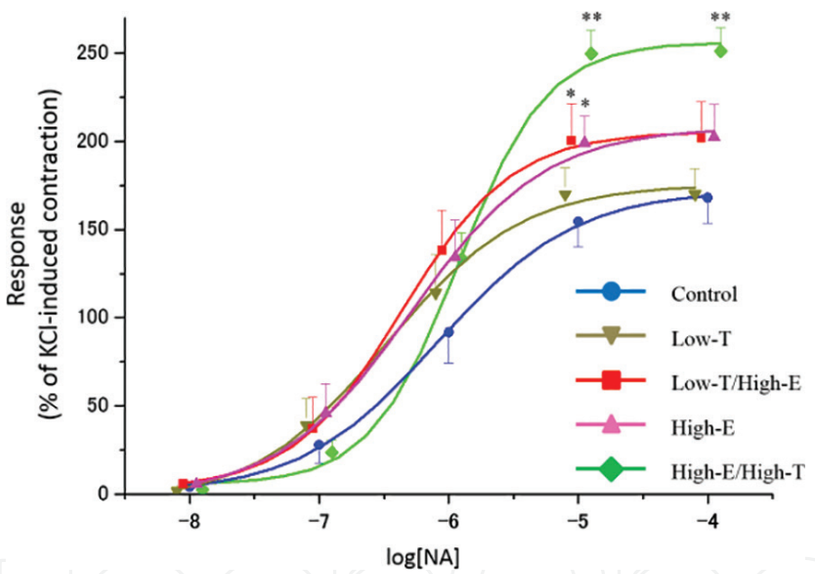

Figure 3.
*The contraction curves induced by noradrenaline (NA) in rat corpus cavernosum strips. The contractile tone induced by 80 mM KCl was taken as 100%. Data reported in all graphs represent the means ± standard errors of the means (n = 5 per group). *P < 0.05, **P < 0.01 versus the control group by analysis of variance and Bonferroni-type multiple t-tests. Emax values are reported in the text.*

all treated rats, were significantly lower than in the control group (0.70 ± 0.04, $P < 0.01$). These data suggested that erectile responses were decreased in rats with a sex hormone imbalance.

Figure 3 shows the contractile response of rat corpora cavernosa strips to increasing concentrations of noradrenaline (NA). Increasing concentrations of NA were found to contract rat corpora cavernosa strips in all groups. In particular, 10 μM NA resulted in statistically significant differences in the in vitro penile contractile response among the experimental groups (control: 154.5 ± 14.1%, Low-T: 169.8 ± 14.8%, Low-T/High-E: 200.2 ± 21.1%, High-E: 198.9 ± 15.3%, High-E/High-T: 249.7 ± 13.5%). Although the contractile response did not differ between the control

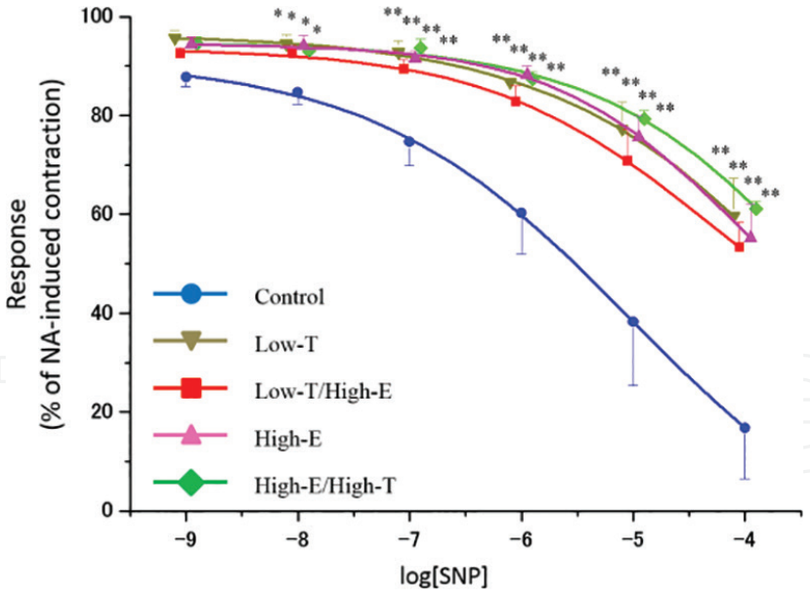

Figure 4.
*The relaxation curve induced by sodium nitroprusside (SNP) in rat corpus cavernosum strips. The strips were precontracted using 10^{-5} M NA. Data reported in all graphs represent the means ± standard errors of the means (n = 5 per group). *P < 0.05, **P < 0.01 versus the control group by analysis of variance and Bonferroni-type multiple t-tests. Emax values are reported in the text.*

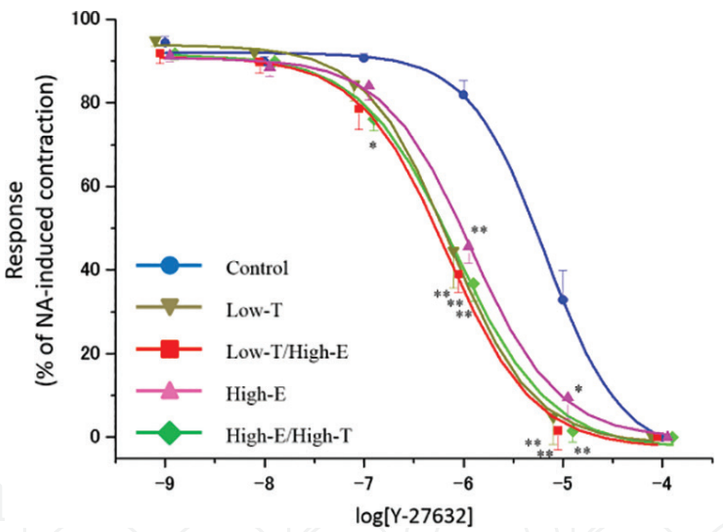

Figure 5.
*The relaxation curves induced by Rho-kinase inhibitor Y-27632 in rat corpus cavernosum strips. The strips were precontracted using 10^{-5} M NA. Data reported in all graphs represent the means ± standard errors of the means (n = 5 per group). *P < 0.05, **P < 0.01 versus the control group by analysis of variance and Bonferroni-type multiple t-tests. IC_{50} values are reported in the text.*

group and the Low-T group ($P > 0.05$), the contractile responses in the Low-T/High-E, High-E, and High-E/High-T groups were higher than the response in the control group ($P < 0.05$).

Figures 4 and **5** show the relaxant response of NA-precontracted rat corpora cavernosa strips to increasing concentrations of sodium nitroprusside (SNP) and Y-27632. In all groups, increasing concentrations of the NO donor SNP relaxed rat corpora cavernosa strips (control: Emax = 16.8 ± 10.3%, Low-T: Emax = 59.7 ± 7.6%, Low-T/High-E: Emax = 53.4 ± 5.0%, High-E: Emax = 55.2 ± 6.8%, High-E/High-T: Emax = 61.1 ± 1.5%). In the treated groups, the sensitivities to SNP were significantly lower than in the control group ($P < 0.01$). Increasing concentrations of

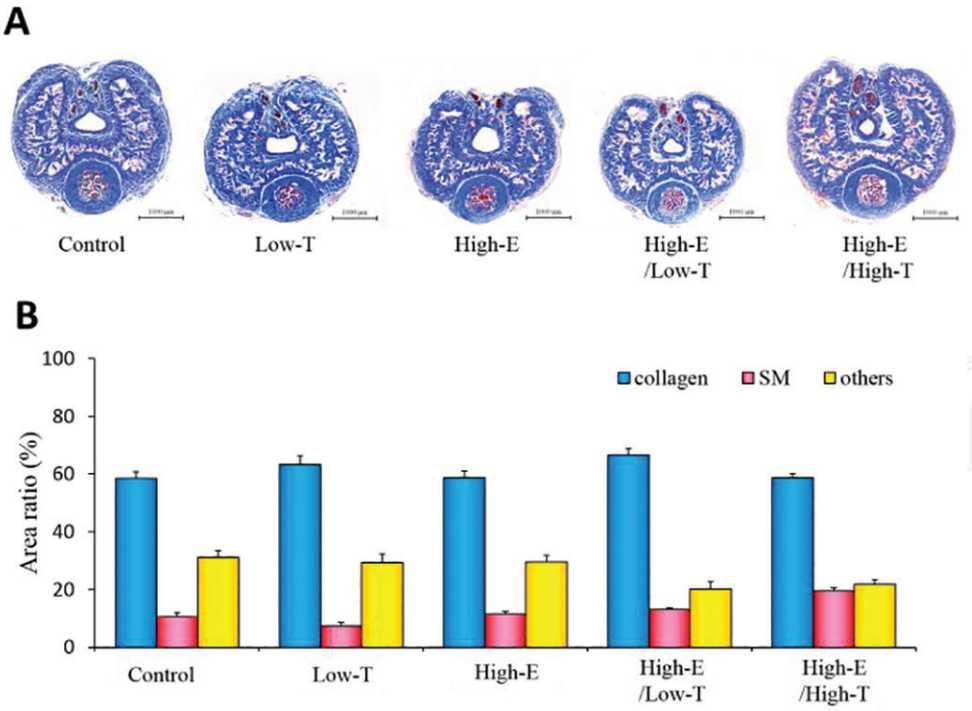

Figure 6.
The rat penis sections of Masson's trichrome staining. (A) Representative specimens of corpus cavernosum of each group rats. (B) Histological evaluation of the tissues. The area ratios of the collagen fibers, smooth muscle (SM), and others were calculated using computerized image analysis. Data reported in all graphs represent the means ± standard errors of the means (n = 3 per group).

	Bio-T (ng/mL)	Estrogen (pg/mL)
Control	1.20 ± 0.13	102.5 ± 8.7
Low-T	0.55 ± 0.04**	51.2 ± 4.2
High-E	0.90 ± 0.12	332.3 ± 17.4**
High-E/Low-T	0.73 ± 0.06*	275.4 ± 34.4**
High-E/High-T	2.58 ± 0.31**	401.5 ± 51.6**

*Data are expressed as means ± standard errors of the means. *P < 0.05, **P < 0.01 versus the control group by analysis of variance and Bonferroni-type multiple t-tests (n = 6 per group).*

Table 1.
Serum levels of estrogen and bioavailable testosterone (bio-T) in rats.

Rho kinase inhibitor Y-27632 completely relaxed rat corpora cavernosa strips in all groups (control: half-maximal inhibitory concentration [IC_{50}] = 1.22×10^{-6} M, Low-T: $IC_{50} = 2.43 \times 10^{-7}$ M, Low-T/High-E: $IC_{50} = 1.31 \times 10^{-7}$ M, High-E: $IC_{50} = 2.26 \times 10^{-7}$ M, High-E/High-T: $IC_{50} = 1.25 \times 10^{-7}$ M). When using 10^{-6} M and 10^{-5} M Y-27632, the sensitivities to Y-27632 in the treated groups were significantly lower than in the control group ($P < 0.01$); thus, the graphs for the treated groups were shifted to the left.

Figure 6 shows the histological analysis of the rats' corpora cavernosa. The area ratio of the cavernous smooth muscle was analyzed (control: 10.5 ± 1.4%, Low-T: 7.4 ± 1.1%, Low-T/High-E: 13.2 ± 0.4%, High-E: 11.6 ± 0.1%, High-E/High-T: 19.4 ± 1.1%). Similarly, the area ratio of the collagen fiber was analyzed (control: 58.4 ± 2.5%, Low-T: 63.2 ± 3.0%, Low-T/High-E: 66.5 ± 2.3%, High-E: 58.8 ± 2.2%, High-E/High-T: 58.7 ± 1.4%). No statistically significant differences between the experimental groups were observed in the overall area ratios of smooth muscle, collagen fiber, and other parameters according to χ^2 tests for independence ($P > 0.05$).

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 pharmacological 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-α, and ER-β and that endothelial cells were negative for AR, sporadically positive for ER-α, and positive for ER-β [67]. Jesmin et al. have demonstrated that ER-α was predominantly localized in the sensory corpuscle of the glans penis [68]. On the bother hands, they also reported that the ER-β 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-β 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-β* gene at the mRNA and protein levels in the corpus cavernosum of diabetic rats [70–72]. They had shown the expression of *ER-β* mRNA in male rat aortas before and after balloon denudation injury. Interestingly, the expression of *ER-α* mRNA in vascular endothelial and smooth muscle cells was very low levels after injury; however, the expression of *ER-β* 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-β, not ER-α [73]. Shirai et al. also demonstrated that the functionally predominant form of ER in the rat corpus cavernosum was ER-β and that age-related alterations in ER-β 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

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, subtunical 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.

Author details

Tomoya Kataoka[1] and Kazunori Kimura[1,2]*

1 Department of Clinical Pharmaceutics, Graduate School of Medical Sciences, Nagoya City University, Japan

2 Department of Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Japan

*Address all correspondence to: kkimura@med.nagoya-cu.ac.jp

References

[1] Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. European Journal of Endocrinology. 2008;**159**:507-514

[2] Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman JM, Tan HM, et al. Endocrine aspects of sexual dysfunction in men. Journal of Sexual Medicine. 2004;**1**:69-81

[3] Diaz-Arjonilla M, Schwarcz M, Swerdloff RS, Wang C. Obesity, low testosterone levels and erectile dysfunction. International Journal of Impotence Research. 2009;**21**:89-98

[4] Yassin A, Saad F, Gooren LJ. Metabolic syndrome, testosterone deficiency and erectile dysfunction never come alone. Andrologia. 2008;**40**:259-264

[5] Corona G, Mannucci E, Fisher AD, Lotti F, Petrone L, Balercia G, et al. Low levels of androgens in men with erectile dysfunction and obesity. Journal of Sexual Medicine. 2008;**5**:2454-2463

[6] Shabsigh R, Arver S, Channer KS, Eardley I, Fabbri A, Gooren L, et al. The triad of erectile dysfunction, hypogonadism and the metabolic syndrome. International Journal of Clinical Practice. 2008;**62**:791-798

[7] Cohen PG. The role of estradiol in the maintenance of secondary hypogonadism in males in erectile dysfunction. Medical Hypotheses. 1998;**50**:331-333

[8] Srilatha B, Adaikan PG, Chong YS. Relevance of oestradiol-testosterone balance in erectile dysfunction patients' prognosis. Singapore Medical Journal. 2007;**48**:114-118

[9] Greco EA, Pili M, Bruzziches R, Corona G, Spera G, Aversa A. Testosterone:Estradiol ratio changes associated with long-term tadalafil administration: A pilot study. Journal of Sexual Medicine. 2006;**3**:716-722

[10] Basar MM, Aydin G, Mert HC, Keles I, Caglayan O, Orkun S, et al. Relationship between serum sex steroids and aging male symptoms score and international index of erectile function. Urology. 2005;**66**:597-601

[11] Andersson KE, Wagner G. Physiology of penile erection. Physiological Reviews. 1995;**75**:191-236

[12] Hotta Y, Hattori M, Kataoka T, Ohno R, Mikumo M, Maeda Y, et al. Chronic vardenafil treatment improves erectile function via structural maintenance of penile corpora cavernosa in rats with acute arteriogenic erectile dysfunction. Journal of Sexual Medicine. 2011;**8**(3):705-711

[13] Hotta Y, Ohno R, Kataoka T, Mikumo M, Takahata Y, Ohno M, et al. Effects of chronic vardenafil treatment persist after end of treatment in rats with acute arteriogenic erectile dysfunction. Journal of Sexual Medicine. 2012;**9**(7):1782-1788

[14] Abe Y, Hotta Y, Okumura K, Kataoka T, Maeda Y, Kimura K. Temporal changes in erectile function and endothelium-dependent relaxing response of corpus cavernosal smooth muscle after ischemia by ligation of bilateral internal iliac arteries in the rabbit. Journal of Pharmacological Sciences. 2012;**120**(3):250-253

[15] Shiota A, Hotta Y, Kataoka T, Morita M, Maeda Y, Kimura K. Oral L-citrulline supplementation improves erectile function in rats with acute arteriogenic erectile dysfunction. Journal of Sexual Medicine. 2013;**10**(10):2423-2429

[16] Musicki B, Bhunia AK, Karakus S, Burnett AL. S-nitrosylation of NOS pathway mediators in the penis contributes to cavernous nerve injury-induced erectile dysfunction. International Journal of Impotence Research. 2018;**30**:108-116

[17] Wingard C, Fulton D, Husain S. Altered penile vascular reactivity and erection in the Zucker obese-diabetic rat. Journal of Sexual Medicine. 2007;**4**:348-363

[18] Morelli A, Chavalmane AK, Filippi S, Fibbi B, Silvestrini E, Sarchielli E, et al. Atorvastatin ameliorates sildenafil-induced penile erections in experimental diabetes by inhibiting diabetes-induced RhoA/Rho-kinase signaling hyperactivation. Journal of Sexual Medicine. 2009;**6**:91-106

[19] Wingard CJ, Moukdar F, Prasad RY, Cathey BL, Wilkinson L. Reversal of voltage-dependent erectile responses in the Zucker obese-diabetic rat by rosuvastatin-altered RhoA/Rho-kinase signaling. Journal of Sexual Medicine. 2009;**6**:269-278

[20] Rajasekaran H, White S, Baquir A, Wilkes N. Rho-kinase inhibition improves erectile function in aging male Brown-Norway rats. Journal of Andrology. 2005;**26**:182-188

[21] Jin L, Liu T, Lagoda GA, Champion HC, Bivalacqua TJ, Burnett AL. Elevated RhoA/Rho-kinase activity in the aged rat penis: Mechanism for age-associated erectile dysfunction. FASEB Journal. 2006;**20**:536-538

[22] Kataoka T, Kimura K. Testosterone and erectile function, a review of evidence from basic research. In: Sex Hormones in Neurodegenerative Processes and Diseases. London: IntechOpen; 2017. pp. 257-272

[23] Kataoka T, Hotta Y, Maeda Y, Kimura K. Assessment of androgen replacement therapy for erectile function in rats with type 2 diabetes mellitus by examining nitric oxide-related and inflammatory factors. Journal of Sexual Medicine. 2014;**11**(4):920-929

[24] Kataoka T, Hotta Y, Maeda Y, Kimura K. Testosterone deficiency causes endothelial dysfunction via elevation of asymmetric dimethylarginine and oxidative stress in castrated rats. Journal of Sexual Medicine. 2017;**14**(12):1540-1548

[25] Hotta Y, Shiota A, Kataoka T, Motonari M, Maeda Y, Morita M, et al. Oral L-citrulline supplementation improves erectile function and penile structure in castrated rats. International Journal of Urology. 2014;**21**(6):608-612

[26] Mills TM, Lewis RW, Stopper VS. Androgenic maintenance of inflow and veno-occlusion during erection in the rat. Biology of Reproduction. 1998;**59**:1413-1418

[27] Armagan A, Kim NN, Goldstein I, Traish AM. Dose-response relationship between testosterone and erectile function: Evidence for the existence of a critical threshold. Journal of Andrology. 2006;**27**:517-526

[28] Li R, Meng X, Zhang Y, Wang T, Yang J, Niu Y, et al. Testosterone improves erectile function through inhibition of reactive oxygen species generation in castrated rats. PeerJ. 2016;**4**:e2000

[29] Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I. Effects of castration and androgen replacement on erectile function in a rabbit model. Endocrinology. 1999;**140**:1861-1868

[30] Zhang XH, Morelli A, Luconi M, Vignozzi L, Filippi S, Marini M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil

in rat corpus cavernosum. European Urology. 2005;**47**:409-416

[31] Traish AM, Goldstein I, Kim NN. Testosterone and erectile function: From basic research to a new clinical paradigm for managing men with androgen insufficiency and erectile dysfunction. European Urology. 2007;**52**:54-70

[32] Reilly CM, Stopper VS, Mills TM. Androgens modulate the alphaadrenergic responsiveness of vascular smooth muscle in the corpus cavernosum. Journal of Andrology. 1997;**18**:26-31

[33] Reilly CM, Lewis RW, Stopper VS, Mills TM. Androgenic maintenance of the rat erectile response via a non-nitric-oxide-dependent pathway. Journal of Andrology. 1997;**18**:588-594

[34] Sopko NA, Hannan JL, Bivalacqua TJ. Understanding and targeting the Rho kinase pathway in erectile dysfunction. Nature Reviews in Urology. 2014;**11**:622-628

[35] Yue P, Chatterjee K, Beale C, Poole-Wilson PA, Collins P. Testosterone relaxes rabbit coronary arteries and aorta. Circulation. 1995;**91**:1154-1160

[36] Han DH, Chae MR, Jung JH, So I, Park JK, Lee SW. Effect of testosterone on potassium channel opening in human corporal smooth muscle cells. Journal of Sexual Medicine. 2008;**5**:822-832

[37] Dai YT, Stopper V, Lewis R, Mills T. Effects of castration and testosterone replacement on veno-occlusion during penile erection in the rat. Asian Journal of Andrology. 1999;**1**:53-59

[38] Alves-Lopes RU, Neves KB, Silva MA, Olivon VC, Ruginsk SG, Antunes-Rodrigues J, et al. Functional and structural changes in internal pudendal arteries underlie erectile dysfunction induced by androgen deprivation. Asian Journal of Andrology. 2017;**19**:526-532

[39] Traish AM, Toselli P, Jeong SJ, Kim NN. Adipocyte accumulation in penile corpus cavernosum of the orchiectomized rabbit: A potential mechanism for veno-occlusive dysfunction in androgen deficiency. Journal of Andrology. 2005;**26**:242-248

[40] Wang XJ, Xu TY, Xia LL, Zhong S, Zhang XH, Zhu ZW, et al. Castration impairs erectile organ structure and function by inhibiting autophagy and promoting apoptosis of corpus cavernosum smooth muscle cells in rats. International Urology and Nephrology. 2015;**47**:1105-1115

[41] Lian J, Karnak D, Xu L. The Bcl-2-Beclin 1 interaction in (−)-gossypol-induced autophagy versus apoptosis in prostate cancer cells. Autophagy. 2010;**6**:1201-1203

[42] Kang R, Zeh HJ, Lotze MT, Tang D. The Beclin 1 network regulates autophagy and apoptosis. Cell Death and Differentiation. 2011;**18**:571-580

[43] Tivesten A, Mellström D, Jutberger H, Fagerberg B, Lernfelt B, Orwoll E, et al. Low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men. The MrOS Study in Sweden. Journal of the American College of Cardiology. 2007;**50**(11):1070-1076

[44] El-Sakka AI. Impact of the association between elevated oestradiol and low testosterone levels on erectile dysfunction severity. Asian Journal of Andrology. 2013;**15**(4):492-496

[45] Srilatha B, Adaikan PG. Oestrogen-androgen crosstalk in the pathophysiology of erectile dysfunction. Asian Journal of Andrology. 2003;**5**(4):307-313

[46] Srilatha B, Adaikan PG. Endocrine milieu and erectile dysfunction: Is oestradiol-testosterone imbalance, a risk factor in the elderly? Asian Journal of Andrology. 2011;**13**(4):569-573

[47] Wu F, Chen T, Mao S, Jiang H, Ding Q, Xu G. Levels of estradiol and testosterone are altered in Chinese men with sexual dysfunction. Andrology. 2016;**4**(5):932-938

[48] O'Connor DB, Lee DM, Corona G, Forti G, Tajar A, O'Neill TW, et al. The relationships between sex hormones and sexual function in middle-aged and older European men. Journal of Clinical Endocrinology and Metabolism. 2011;**96**(10):E1577-E1587

[49] Lamba H, Goldmeier D, Mackie NE, Scullard G. Antiretroviral therapy is associated with sexual dysfunction and with increased serum oestradiol levels in men. International Journal of STD and AIDS. 2004;**15**(4):234-237

[50] Heroz AG, Levesque LA, Drislane FW, Ronthal M, Schomer DL. Phenytoin-induced elevation of serum oestradiol and reproductive dysfunction in men with epilepsy. Epilepsin. 1991;**32**:550-553

[51] Gyllenborg J, Rasmussen SL, Borch-Johnsen K, Heitmann BL, Skakkebaek NE, Juul A. Cardiovascular risk factors in men: The role of gonadal steroids and sex hormone-binding globulin. Metabolism. 2001;**50**:882-888

[52] Legrand E, Hedde C, Gallois Y, et al. Osteoporosis in men: A potential role for the sex hormone binding globulin. Bone. 2001;**29**:90-95

[53] Scopacasa F, Horowitz M, Wishart JM, Morris HA, Chatterton BE, Need AG. The relation between bone density, free androgen index, and oestradiol in men 60 to 70 years old. Bone. 2000;**27**:145-149

[54] Ciardullo AV, Panico S, Bellati C, et al. High endogenous oestradiol is associated with increased venous distensibility and clinical evidence of varicose veins in menopausal women. Journal of Vascular Surgery. 2000;**32**:544-549

[55] Aversa A, Isidori AM, De Martino MU, et al. Androgens and penile erection: Evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. Clinical Endocrinology. 2000;**53**:517-522

[56] Phillips GB, Jing TY, Laragh JH, Sealey JE. Serum sex hormone levels and renin-sodium profile in men with hypertension. American Journal of Hypertension. 1995;**8**:626-629

[57] Martin ME, Benassayag C, Amiel C, Canton P, Nunez EA. Alterations in the concentrations and binding properties of sex steroid binding protein and corticosteroid-binding globulin in HIV+ patients. Endocrinological Investigation. 1992;**15**:597-603

[58] Laudat A, Blum L, Guéchot J, Picard O, Cabane J, Imbert JC, et al. Changes in systemic gonadal and adrenal steroids in asymptomatic human inmmunodeficiency virus-infected men: Relationship with the CD4 cell counts. European Journal of Endocrinology. 1995;**133**:418-424

[59] Hassan K, Elimeleh Y, Shehadeh M, Fadi H, Rubinchik I. The relationship between hydration status, male sexual dysfunction and depression in hemodialysis patients. Therapeutics and Clinical Risk Management. 2018;**14**:523-529

[60] Tivesten A, Hulthe J, Wallenfeldt K, Wikstrand J, Ohlsson C, Fagerberg B. Circulating estradiol is an independent predictor of progression of carotid artery intima-media thickness

in middle-aged men. Journal of Clinical Endocrinology and Metabolism. 2006;**91**(11):4433-4437

[61] Tivesten A, Vandenput L, Labrie F, Karlsson MK, Ljunggren O, Mellström D, et al. Low serum testosterone and estradiol predict mortality in elderly men. Journal of Clinical Endocrinology and Metabolism. 2009;**94**(7):2482-2488

[62] Adaikan PG, Srilatha B. Oestrogen-mediated hormonal imbalance precipitates erectile dysfunction. International Journal of Impotence Research. 2003;**15**(1):38-43

[63] Srilatha B, Adaikan PG. Estrogen and phytoestrogen predispose to erectile dysfunction: Do ER-alpha and ER-beta in the cavernosum play a role? Urology. 2004;**63**(2):382-386

[64] Kataoka T, Hotta Y, Ohno M, Maeda Y, Kimura K. Limited effect of testosterone treatment for erectile dysfunction caused by high-estrogen levels in rats. International Journal of Impotence Research. 2013;**25**(6):201-205

[65] Vignozzi L, Filippi S, Comeglio P, Cellai I, Morelli A, Marchetta M, et al. Estrogen mediates metabolic syndrome-induced erectile dysfunction: A study in the rabbit. Journal of Sexual Medicine. 2014;**11**(12):2890-2902

[66] Schultheiss D, Badalyan R, Pilatz A, Gabouev AI, Schlote N, Wefer J, et al. Androgen and estrogen receptors in the human corpus cavernosum penis: Immunohistochemical and cell culture results. World Journal of Urology. 2003;**21**(5):320-324

[67] Dietrich W, Haitel A, Huber JC, Reiter WJ. Expression of estrogen receptors in human corpus cavernosum and male urethra. Journal of Histochemistry and Cytochemistry. 2004;**52**(3):355-360

[68] Jesmin S, Mowa CN, Matsuda N, Salah-Eldin AE, Togashi H, Sakuma I, et al. Evidence for a potential role of estrogen in the penis: Detection of estrogen receptor-alpha and -beta messenger ribonucleic acid and protein. Endocrinology. 2002;**143**(12):4764-4774

[69] Spyridopoulos I, Sullivan AB, Kearney M, Isner JM, Losordo DW. Estrogen-receptor-mediated inhibition of human endothelial cell apoptosis. Estradiol as a survival factor. Circulation. 1997;**95**(6):1505-1514

[70] Shirai M, Yamanaka M, Shiina H, Igawa M, Ogishima T, Fujime M, et al. Androgen, estrogen, and progesterone receptor gene regulation during diabetic erectile dysfunction and insulin treatment. Urology. 2004;**64**(6):1244-1249

[71] Shirai M, Yamanaka M, Shiina H, Igawa M, Kawakami T, Ishii N, et al. Vascular endothelial growth factor restores erectile function through modulation of the insulin-like growth factor system and sex hormone receptors in diabetic rat. Biochemical and Biophysical Research Communications. 2006;**341**(3):755-762

[72] Yamanaka M, Shirai M, Shiina H, Shirai M, Tanaka Y, Fujime M, et al. Loss of anti-apoptotic genes in aging rat crura. Journal of Urology. 2002;**168**(5):2296-2300

[73] Lindner V, Kim SK, Karas RH, Kuiper GG, Gustafsson JA, Mendelsohn ME. Increased expression of estrogen receptor-beta mRNA in male blood vessels after vascular injury. Circulation Research. 1998;**83**(2):224-229

[74] Shirai M, Yamanaka M, Shiina H, Igawa M, Fujime M, Lue TF, et al. Downregulation of androgen, estrogen and progesterone receptor genes and protein is involved in aging-related erectile dysfunction. International Journal of Impotence Research. 2003;**15**(6):391-396

[75] Goyal HO, Braden TD, Williams CS, Dalvi P, Williams JW, Srivastava KK. Exposure of neonatal male rats to estrogen induces abnormal morphology of the penis and loss of fertility. Reproductive Toxicology. 2004;**18**(2):265-274

[76] Simon L, Avery L, Braden TD, Williams CS, Okumu LA, Williams JW, et al. Exposure of neonatal rats to anti-androgens induces penile mal-developments and infertility comparable to those induced by oestrogens. International Journal of Andrology. 2012;**35**(3):364-376

[77] Goyal HO, Braden TD, Williams CS, Dalvi P, Mansour MM, Mansour M, et al. Abnormal morphology of the penis in male rats exposed neonatally to diethylstilbestrol is associated with altered profile of estrogen receptor-alpha protein, but not of androgen receptor protein: A developmental and immunocytochemical study. Biology of Reproduction. 2004;**70**(5):1504-1517

[78] Goyal HO, Braden TD, Cooke PS, Szewczykowski MA, Williams CS, Dalvi P, et al. Estrogen receptor alpha mediates estrogen-inducible abnormalities in the developing penis. Reproduction. 2007;**133**(5):1057-1067

[79] Okumu LA, Bruinton S, Braden TD, Simon L, Goyal HO. Estrogen-induced maldevelopment of the penis involves down-regulation of myosin heavy chain 11 (MYH11) expression, a biomarker for smooth muscle cell differentiation. Biology of Reproduction. 2012;**87**(5):109

[80] Dodds EC, Lawson W. Synthetic strogenic agents without the phenanthrene nucleus. Nature. 1936;**137**:996

[81] Yamada H, Furuta I, Kato EH, Kataoka S, Usuki Y, Kobashi G, et al. Maternal serum and amniotic fluid bisphenol A concentrations in the early second trimester. Reproductive Toxicology. 2002;**16**:735-739

[82] Manfo FP, Jubendradass R, Nantia EA, Moundipa PF, Mathur PP. Adverse effects of bisphenol A on male reproductive function. Reviews of Environmental Contamination and Toxicology. 2014;**228**:57-82

[83] Li D, Zhou Z, Qing D, He Y, Wu T, Miao M, et al. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. Human Reproduction. 2010;**25**(2):519-527

[84] Li DK, Zhou Z, Miao M, He Y, Qing D, Wu T, et al. Relationship between urine bisphenol-A level and declining male sexual function. Journal of Andrology. 2010;**31**(5):500-506

[85] Moon DG, Sung DJ, Kim YS, Cheon J, Kim JJ. Bisphenol A inhibits penile erection via alteration of histology in the rabbit. International Journal of Impotence Research. 2001;**13**(5):309-316

[86] Kovanecz I, Gelfand R, Masouminia M, Gharib S, Segura D, Vernet D, et al. Chronic high dose intraperitoneal bisphenol A (BPA) induces substantial histological and gene expression alterations in rat penile tissue without impairing erectile function. Journal of Sexual Medicine. 2013;**10**(12):2952-2966

[87] Kovanecz I, Gelfand R, Masouminia M, Gharib S, Segura D, Vernet D, et al. Oral Bisphenol A (BPA) given to rats at moderate doses is associated with erectile dysfunction, cavernosal lipofibrosis and alterations of global gene transcription. International Journal of Impotence Research. 2014;**26**(2):67-75

[88] Aversa A, Fittipaldi S, Francomano D, Bimonte VM, Greco EA, Crescioli C, et al. Tadalafil improves lean mass

and endothelial function in nonobese men with mild ED/LUTS: In vivo and in vitro characterization. Endocrine. 2017;**56**(3):639-648

[89] Spitzer M, Bhasin S, Travison TG, Davda MN, Stroh H, Basaria S. Sildenafil increases serum testosterone levels by a direct action on the testes. Andrology. 2013;**1**(6):913-918

[90] Kang S, Park S, Kim MJ, Oh SM, Chung KH, Lee S. A sensitive and selective LC-MS/MS analysis coupled with an online sample enrichment technique for H295R steroidogenesis assay and its application in the investigation of the effect of sildenafil on steroidogenesis. Analytical and Bioanalytical Chemistry. 2013;**405**(29):9489-9496

[91] Andric SA, Janjic MM, Stojkov NJ, Kostic TS. Sildenafil treatment in vivo stimulates Leydig cell steroidogenesis via the cAMP/cGMP signaling pathway. American Journal of Physiology. Endocrinol and Metabolism. 2010;**299**(4):E544-E550

[92] Yigitaslan S, Ozatik O, Ozatik FY, Erol K, Sirmagul B, Baseskioglu AB. Effects of tadalafil on hemorrhagic cystitis and testicular dysfunction induced by cyclophosphamide in rats. Urology International. 2014;**93**(1):55-62

[93] Janjic MM, Stojkov NJ, Bjelic MM, Mihajlovic AI, Andric SA, Kostic TS. Transient rise of serum testosterone level after single sildenafil treatment of adult male rats. Journal of Sexual Medicine. 2012;**9**(10):2534-2543

[94] Mostafa T, Rashed LA, Kotb K. Testosterone and chronic sildenafil/tadalafil anti-apoptotic role in aged diabetic rats. International Journal of Impotence Research. 2010;**22**(4):255-261

[95] Santi D, Granata AR, Guidi A, Pignatti E, Trenti T, Roli L, et al. Six months of daily treatment with vardenafil improves parameters of endothelial inflammation and of hypogonadism in male patients with type 2 diabetes and erectile dysfunction: A randomized, double-blind, prospective trial. European Journal of Endocrinology. 2016;**174**(4):513-522

[96] Jiang T, Zheng L, Su XM, Peng JQ, Sun DC, Li QL, et al. Long-term testosterone supplementation is useful for ED with testosterone deficiency. Asian Journal of Andrology. 2013;**15**(5):699-700