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Effects of exogenous testosterone on isolated rabbit corpus cavernosum penis [1]

Sahin YILDIRIM, Tijen UTKAN[2], Kemal YILDIRIM, Yusuf SARIOGLU
(*Department of Pharmacology, Faculty of Medicine, Cumhuriyet University, 58140 Sivas, Turkey,* [2]*Department of Pharmacology, Faculty of Medicine, Kocaeli University, 41900 Kocaeli, Turkey*)

KEY WORDS testosterone；penis；electric stimulation；phenylephrine；nitroprusside；carbachol；guanethidine；atropine；N^G-nitroarginine methyl ester；potassium chloride

ABSTRACT

AIM：To study the effects of exogenous excess of testosterone on the constricting effect of phenylephrine and endothelium-dependent and -independent relaxing effects of different agonists in the corpus cavernosum penis (CCP). METHODS：Specimens of the CCP were obtained from rabbits testosterone for 1 and 2 months and untreated for 2 months after testosterone-treatment for 2 months. Preparations were mounted between two parallel platinum electrodes in organ baths. Responses to phenylephrine, carbachol, and sodium nitroprusside were obtained by adding the reagent cumulatively to the bath. RESULTS：The phenylephrine-induced contractions were decreased with no change in agonist potency (pD_2 value) after both 1 and 2 month testosterone-treatment and did not return to control values in corpus cavernosum obtained from rabbits untreated for 2 months after testosterone-treatment for 2 months. Testosterone treatment for 1 or 2 months increased the endothelium-dependent relaxations induced by carbachol and decreased the relaxations elicited by electric stimulation but did not affect the relaxations induced by sodium nitroprusside. These relaxant responses to carbachol and electric stimulation did not return to control values in corpus cavernosum obtained from rabbits untreated for 2 months after testosterone-treatment for 2 months. There were no significant changes in the pD_2 values calculated by agonist-induced relaxation responses in all testosterone-treatment groups compared with control group. CONCLUSION：The exogenous excess of testosterone plays an important role in erectile function by a direct action on the relaxant and contractile responses of CCP.

INTRODUCTION

Normal human erectile function depends on a complex interrelationship among hormonal, neurologic, vascular and psychologic factors. A defect in any of these systems may result in impotence[1]. The relationship between androgens and penile erections is complex. Androgens are necessary for the normal development of the penis and their deficiency results in significant structural abnormalities[2]. Several studies indicate that male sexual behavior is impaired by hypogonadism and improved when androgen replacement treatment is given[3,4]. On the other hand, some clinical data suggest that androgen enhances but is not essential for erection[3,5]. Although the importance of androgens for normal sexual interest and activity has been established, the amount required for both basal and optimal functions is still unknown and may have individual variations[6]. Endogenous or exogenous excess of estrogen or androgens will supress pituitary gonadotropins, leading to secondary testicular failure. The androgen excess will alter spermatogenesis but may not lead to impotence[6,7]. Furthermore, testosterone administration enhances sleep erections in eugonodal men, but only in terms of rigidity[8].

Normal erectile function is characterized by a delicate balance *in vivo* between the effects of vasoconstricting and vasorelaxing hormones on the level of corporal smooth muscle tone[9,10]. Recent *in vitro* studies have indicated that corporal smooth muscle relaxation induced by endogenous vasorelaxants may be impaired in a large proportion of impotent men[9,11]. Other investigators have provided evidence for increased α_1-adrenergic con-

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[2] Correspondence to Assoc Prof Dr Tijen UTKAN.
Fax +90-262-2335463. E-mail tijenutkan@superonline.com
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tractility of corporal smooth muscle isolated from men with organic dysfunction[9,12,13]. Although it is widely accepted that primary action of testosterone in controlling sexual behavior is in the brain[7], animal data show that androgens support erectile function through a direct effect on the erectile tissue[14]. In addition, we have recently reported that carbachol- and EFS-induced relaxations and contraction mediated by α_1-adrenoceptors were altered by castration. Testosterone replacement reverses these abnormalities[15]. However, there have not been studies assessing the effects of chronic testosterone therapy on penile erectile tissue function in isolated corpus cavernosum penis (CCP). Therefore, the aim of the present study was to determine whether the exogenous excess of testosterone have an effect on the contractions or relaxations in the CCP smooth muscles involved in penile erection.

MATERIALS AND METHODS

Mature male albino rabbits weighing 2.5 − 3 kg were used. The albino rabbit was chosen as the animal model based on the close similarities that have been reported in the reactivity *in vitro* of human and rabbit CCP[16]. The rabbits were divided into four groups. Group 1 was served as control ($n = 12$). In group 2, rabbits were treated for 1 month with testosterone propionate 10 mg/d im ($n = 12$). In group 3, rabbits were treated for 2 months with testosterone propionate 10 mg/d im ($n = 12$). In group 4, rabbits were untreated for 2 months after testosterone-treatment for 2 months ($n = 14$).

CCP The rabbits were killed with iv thiopental sodium (35 mg/kg) followed by exsanguination. The penis was placed in Krebs-bicarbonate solution and tie tissue surrounding CCP was removed by sharp dissection.

Organ chamber experiments Strips of CCP measuring approximately 2 mm × 2 mm × 15 mm were in 20 mL organ chambers for isometric tension measurement. Each rabbit provided 4 strips of CCP smooth muscle which were studied separately. The strips were tied with silk to a force transducer (Grass FT 03, Quincy MA, USA) on one end and fixed with silk ties to a glass support on the other end. The chambers contained Krebs-bicarbonate salt solution: NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $NaHCO_3$ 25, $MgSO_4$ 1.2, KH_2PO_4 1.2, and glucose 11 mmol/L. The solution was gassed with 95 % O_2 + 5 % CO_2 at 37 ℃. After mounting the preparations were allowed to equilibrate for 1 h. During this time the tension adjusted to 2 g. At the end of the equilibration period, strips were depolarized with KCl 124 mmol/L in Krebs-bicarbonate solution and allowed to equilibrate for 30 min. This procedure increases and stabilizes subsequent contractile responses to phenylephrine and decreases spontaneous contractile activity. After equilibration, the contractile responses to phenylephrine (10^{-8} to 10^{-4} mol/L) were obtained cumulatively. After addition of each dose, we waited until a plateau response was obtained before adding the next one. Following completion of phenylephrine dose-response curve, tissues were washed for a further 30 min, precontracted with a submaximally concentration of phenylephrine (10^{-5} mol/L). After the contraction reached plateau, concentration-response relationships for carbachol (10^{-9} to 10^{-5} mol/L) and sodium nitroprusside were obtained by adding one of those agents to the bath in a cumulative manner. Isometric tension was recorded on a Grass model 79 E polygraph.

Electric stimulation was provided by a Grass S 88 stimulator and applied via two platinum wire electrodes set vertically within the organ bath at opposite sides of the suspended tissue. Prior to electrical stimulation tissue was treated with guanethidine (5 μmol/L) (adrenergic nerve blocker) and atropine (1 μmol/L) (muscarinic receptor blocker) for 30 min. The purpose of this treatment was to eliminate the adrenergic and cholinergic responses and to study only relaxation responses induced by stimulation of nonadrenergic noncholinergic nerves. Electric stimulation-elicited relaxation of precontracted strips of rabbit corpus cavernosum, in the presence of functional adrenergic and cholinergic blockade, was mediated by endogenous formation and release of NO. Strips were precontracted with phenylephrine at 10^{-5} mol/L. Electric stimulation was then performed: supramaximal voltage (50 V), pulse-frequency 2, 4, 8, 16, and 32 Hz, pulse-duration 0.8 ms, train-duration 5 s, train-rate 0.01 train pulse second (TPS). The strips were allowed to return to baseline precontractile tension between the tests at each frequency. Subsequently, without the strips being washed, N^{ω}-nitro *L*-arginine methyl ether (*L*-NAME) (3×10^{-5} mol/L) were added to the strips and stimulation was repeated 15 min later. Two or three agonists were tested on each preparation.

Analysis of data Experimental values expressed as the $\bar{x} \pm s$. Contractile responses to phenylephrine were calculated as percentage of the maximal contraction caused by potassium chloride (124 mmol/L). Relaxant effects of agonists were expressed as a percentage of the precontraction to phenylephrine. To evaluate the effects

of agonists；pD_2 values calculated. Agonist pD_2 value (appearent agonist affinity constants；$-\lg ED_{50}$) were calculated from each agonist dose-response curve by linear regression analysis of the linear portion of the curve and taken as a measure of the sensitivity of the tissues to each agonist.

Statistical comparision between groups were performed using ANOVA followed by t-test.

Drugs Phenylephrine hydrochloride (Sigma), sodium nitroprusside (Nipruss, Adeca), atropine sulfate (Sigma), guanethidine sulfate (Sigma), carbachol chloride (Sigma), testosterone propionate (Sustanon；Organon), N^{ω}-nitro-*L*-arginine methyl ester (*L*-NAME) (Sigma). All drug solutions were prepared daily.

RESULTS

Serum testosterone concentrations in all experimental groups were listed in Tab 1.

Tab 1. Serum testosterone levels in testosterone-treated and control groups ($\mu g \cdot L^{-1}$). $\bar{x} \pm s$. $^bP<0.05$ *vs* control.

	Serum testosterone/ $\mu g \cdot L^{-1}$	*n*
Control	0.8 ± 1.4	10
Testosterone-treated for 1 month	16 ± 26^b	10
Testosterone-treated for 2 months	19 ± 15^b	8
Untreated for 2 months	3 ± 4^b	9

The cumulative addition of phenylephrine (10^{-8} to 3×10^{-4} mol/L) produced concentration-dependent contractions of corpus cavernosum isolated from the rabbits. The contractility of the strips decreased significantly in both 1 and 2 month testosterone-treatment groups compared to controls ($P<0.05$) and did not return to control values in corpus cavernosum obtained from animals untreated for 2 months after testosterone-treatment for 2 months (Fig 1).

However, no change in pD_2 value for phenylephrine from all testosterone-treatment rabbits compared with controls was detected (Tab 2).

The contractions elicited by KCl 124 mmol/L did not change in the CCP of all testosterone-treated than in those of control rabbits. (Fig 2).

Sodium nitroprusside (10^{-8} to 3×10^{-5} mol/L) produced concentration-dependent relaxation in precontracted submaximally (60－70 % of maximal contraction) by

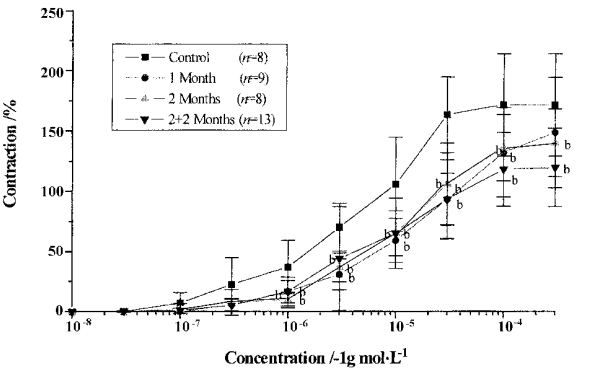

Fig 1. Phenylephrine concentration-response curves in isolated rabbit CCP strips. Each point = % of the contraction induced by KCl 124 mmol/L. Values are arithmetic $\bar{x} \pm s$, n = number of animals. $^bP<0.05$ *vs* control.

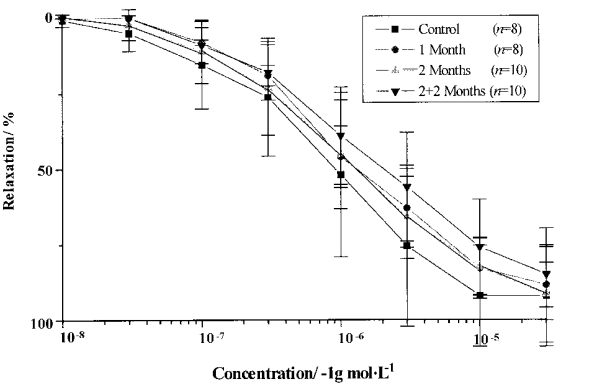

Fig 2. Sodium nitroprusside concentration-response curves in strips precontracted with phenylephrine 10^{-5} mol/L. Each point = % of the contraction induced by phenylephrine. Values are arithmetic $\bar{x} \pm s$, n = number of animals.

phenylephrine 10^{-5} mol/L CCP strips obtained from control and testosterone-treated rabbits. The relaxations induced by sodium nitroprusside did not change in CCP of all testosterone-treated rabbits (Fig 2).

There was no significant change in the pD_2 values in sodium nitroprusside-induced relaxations of strips from all testosterone-treated rabbits compared with controls (Tab 2).

Carbachol (10^{-9} to 10^{-5} mol/L) produced concentration-dependent relaxation in phenylephrine 10^{-5} mol/L precontracted submaximally strips obtained from control and testosterone-treated rabbits. Treatment with *L*-NAME (0.03 mmol/L) abolished the carbachol-induced relaxation and increased basal tonus in all strips. Relaxations to carbachol were increased in CCP strips from 1 and 2 month testosterone-treated rabbits compared to the

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Tab 2. pD_2 values of phenylephrine, carbachol, sodium nitroprusside and maximum responses of 124 mmol/L KCl (g) in corpus cavernosum strips obtained from testosterone treated for both 1 and 2 months, untreated for 2 months after treated with testosterone for 2 months and control rabbits. Values are arithmetic $\bar{x} \pm s$, n = number of observations.

	Phenylephrine	n	Carbachol	n	SNP	n	KCl	n
Control	5.35±0.11	8	7.30±0.06	8	6.10±0.09	8	1.4±1.0	12
Testosterone treated for 1 month	5.16±0.15	9	7.22±0.20	8	6.05±0.14	8	1.5±0.6	10
Testosterone treated for 2 months	5.22±1.98	8	7.49±0.29	10	6.00±0.28	12	1.8±0.8	10
Untreated for 2 months	5.26±3.25	13	7.31±0.22	13	6.10±0.26	14	1.7±0.9	12

controls ($P<0.05$) and these relaxant responses to carbachol did not return to control values in untreated for 2 months after testosterone-treatment for 2 months group (Fig 3).

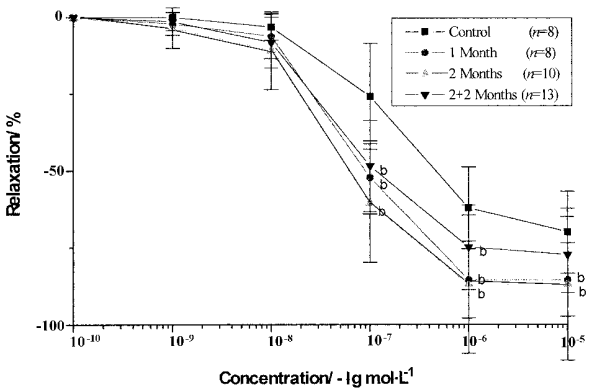

Fig 3. Carbachol concentration－response curves in strips precontracted with phenylephrine 10^{-5} mol/L. Each point = % of the contraction induced by phenylephrine. Values are arithmetic $\bar{x} \pm s$, n = number of animals. $^bP<0.05$ *vs* control.

There were no significant changes in the pD_2 values of corpus cavernosum strips for carbachol from all testosterone-treated rabbits compared with controls (Tab 2).

In preparations precontracted submaximally by phenylephrine 10^{-5} mol/L, electric stimulation evoked frequency-dependent relaxations. Treatment with *L*-NAME (3×10^{-5} mol/L) decreased the relaxations and incresed basal tonus in all strips. The relaxations elicited by electric stimulation were significantly decreased in testosterone-treatment for 1 and 2 months groups compared to corresponding controls ($P<0.05$) (Fig 4). These relaxant responses to electric stimulation did not return to control values in untreated for 2 months after testosterone-treatment rabbits (Fig 4).

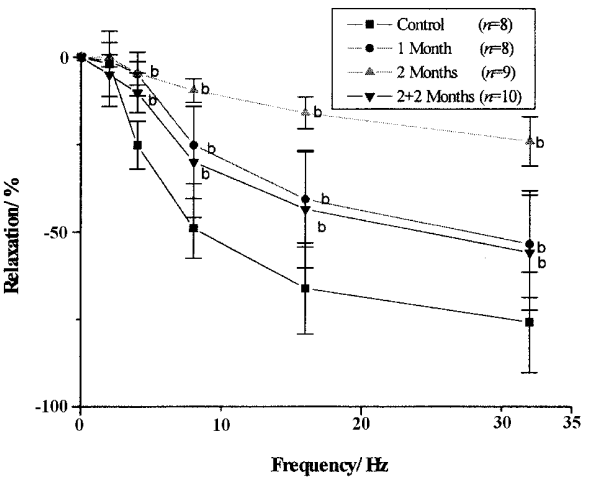

Fig 4. Relaxation responses evoked by electric stimulation on strips precontracted with phenylephrine 10^{-5} mol/L. Each point = % of the contraction induced by phenylephrine. Values are arithmetic $\bar{x} \pm s$, n = number of animals. $^bP<0.05$ *vs* control.

DISCUSSION

In this study we have examined the effects of exogenous testosterone on relaxant and contractile responses of corpus cavernosum tissue from the male rabbits. All testosterone-treated rabbits showed a functional impairment of neurogenic relaxation and phenylephrine-induced contraction but an increment of carbachol-induced relaxation (endothelium-dependent) corpus cavernosum tissue.

The mechanisms underlying the relaxation of penile smooth muscles are not fully understood but both muscarinic stimulation and release of relaxant NANC transmitters including NO seem to be involved[17]. The endothelium and autonomic nerves are independent sources of NO, mediating the corpus cavernosum smooth muscle relaxation[11,17]. *In vitro* studies using electrical field stimulation of rabbit and human corpus cavernosal tissue during muscarinic and adrenergic blockade have elicited NANC neurogenic relaxation[11,16]. The abolition of electrical field stimulation-induced rabbit cavernous smooth muscle relaxation by tetrodotoxin indicates that the effect of EFS is mediated by neurotransmitter[16]. In the present study, after tissue treatment with *L*-

NAME, a specific inhibitor of nitric oxide synthase, both neurogenic and carbachol-induced relaxation of corporeal tissue from testosterone-treated and control groups was depressed, suggesting that NO is required for the response.

Animal studies demonstrated numerous inconsistencies in the effects of androgens on male sexual behaviour. Some authors reported that there is no relationship between serum testosterone level and erectile function and that testosterone mainly acts on the brain and not on the penis[14,18]. In contrast, it has been suggested that penile erection in the rat is completely dependent on androgens because of their role in the maintenance of penile NOS activity[19]. Although in an animal model of penile erection testosterone increases the number of erections in a dose-dependent manner in castrated rats, doses in excess of that needed to produce a normal rate of erection decrease the erectile function[14]. Similarly, Buena *et al*[20] concluded that erectile function and sexual behaviour are restored by relatively low testosterone levels with poor correlation between serum testosterone levels and sexual function when testosterone values are within the normal range. Furthermore, other studies have evaluated whether a threshold exists for serum testosterone in the supraphysiological range, which might influence sexual behaviour. In one such study on sexual arousal and sexual behaviour increased arousability, without any effect on sexual behaviour was observed in eugonodal men with pharmacologically induced supraphysiological serum testosterone levels[21].

The etiology of organic erectile dysfunction in men may be due to pharmacologic abnormalities at the level of the corporeal smooth muscle[13,10]. Testosterone has been reported to have various effects on the density of some autonomic receptors[22]. Authors reported that low testosterone level induced by castration reduced relaxant responses of corpus cavernosum and testosterone replacement therapy increased these responses. Thus, authors suggested that testosterone plays an important role in erectile function by a direct action on the corpus cavernosum penis[15,23]. As it is well known, the *L*-arginine-NO system may be modulated by several factors, including the sexual hormones. Chronic oestrogen treatment enhances some endothelium-dependent relaxations[24]. Conversely, Andersson *et al*[25] reported that castration enhanced NANC nerve mediated relaxation in corpus cavernosum tissue from rabbits, speculating that the hormonal changes caused by castration may stimulate the synthesis and/or release of NO. The observation in our study that testosterone-treatment impairs neurogenic relaxation of trabecular smooth muscle, would suggest a possible common pathophysiologic mechanism with alteration in the nitric oxide/c-GMP pathway or testosterone may impair relaxation of trabecular smooth muscle or diminish its sensitivity to NO. However, these possibilities are unlikely since corporeal strips relaxed well to the nitric oxide producing vasodilator sodium nitroprusside. Sodium nitroprusside is known to contain a NO moiety in its structure and the guanylate cyclase-activating property of the drug is thought to result from generation of free NO[26]. Therefore it is possible that testosterone impairs the synthesis or availabilty of nitric oxide in nerve tissue. According to our present study, testosterone-treated rabbits showed an increased relaxant response to carbachol. It can be speculated that the increased response to carbachol in testosterone-treated rabbits might be due to up-regulation of muscarinic receptor on endothelial cells of the sinusoidal spaces. The change of receptor density may be an adaptive phenomenone due to decreased EFS-responses and/or may be caused by androgenic hormones.

The importance of sympathetic nervous activity and α-adrenoceptor function for keeping the penis in the flaccid state is generally accepted[13,27,28]. It is well known that systemic administration of drugs blocking α-adrenoceptors, such as prazosin, may on rare occasions produce erection and even priapism[29]. Brindley[30] showed that intracavernosal injection of the selective α_2-adrenoceptor blocker idazoxan had no effect which means that α_1-adrenoceptor blockade seems to be required for an erectile response. In some cases, impotence can be secondary to changes in alpha-adrenoceptor function[9,12,13]. It is reported that phenylephrine-induced contractility of the corpus cavernosum decreased significantly in the castration group as compared with control group[15,23]. In this study phenylephrine-induced contractions are reduced in all testosterone-treated rabbits when compared to controls. There were not differences in KCl contractile responses of all experimental groups. It means that contractile mechanisms were intact in corpus cavernosum smooth muscles. Therefore, it can be speculated that the decreased response to phenylephrine in testosterone-treated rabbits is a hormonal influence of steroid hormones which are known to directly influence the levels of neurotransmitter receptors.

In conclusion, testosterone-treated rabbits had a diminished contractile response to phenylephrine and neurogenic relaxant response to EFS and an increased endothelium-dependent relaxant response to carbachol. These results clearly indicate that the exogenous excess of testosterone plays an important role in

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erectile function by a direct action on the relaxant and contractile responses of corpus cavernosum penis.

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外源性睾酮对离体家兔阴茎海绵体的影响[1]

关键词 睾酮；阴茎；电刺激；苯福林；硝普盐；卡巴胆碱；胍乙啶；阿托品；N^G-硝基精氨酸甲酯；氯化钾

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