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Androgens Modulate the α-Adrenergic Responsiveness of Vascular Smooth Muscle in the Corpus Cavernosum

CHRISTOPHER M. REILLY, VIVIENNE S. STOPPER, AND THOMAS M. MILLS

From the Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, Georgia.

ABSTRACT: Rat penile erection is an androgen-dependent process with castration leading to a loss of potency. The present study was designed to determine if one of the mechanisms by which androgens maintain the erectile response is the regulation of the α-adrenergic responsiveness of cavernosal smooth muscle. Electrical stimulation of the major pelvic ganglion (MPG) was used to elicit erection in untreated, castrated rats (CASTRATE) or castrated rats given testosterone replacement (TESTO). The effects of phenylephrine (an α_1-adrenergic agonist) and prazosin (an α_1-adrenergic antagonist) on the erectile response were investigated. Phenylephrine, when administered to both TESTO and CASTRATE animals during erection, resulted in a dose-dependent decrease in the intracavernosal pressure (CCP) with an ED_{50} value of 1.8 ± 0.48 μg/kg BW for TESTO rats; in the CASTRATE animals, the ED_{50} was significantly reduced to 0.29 ± 0.08 μg/kg BW. The increases in mean arterial pressure (MAP) resulting from phenylephrine injection in TESTO and CASTRATE animals were of similar magnitude and were not significantly different. Prazosin administration resulted in an enhancement of the erectile response in CASTRATE but not in TESTO animals. Taken together these results demonstrate that the cavernosal vasculature in CASTRATE animals possesses increased reactivity to α-adrenergic stimulation as compared to the sensitivity in TESTO rats. Based on these findings, we conclude that one of the mechanisms by which androgens maintain erectile function is by regulating the α_1-adrenergic responsiveness of the cavernosal smooth muscle.

Key words: Penile erection, testosterone, adrenergic, prazosin, phenylephrine.

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Penile erection results from a decrease in sympathetic tone of cavernosal smooth muscle coupled with the release of local vasodilators that lead to increased blood flow into the cavernous sinuses. Under the driving force of the mean arterial pressure (MAP), the sinuses fill with blood causing expansion of the cavernous sinuses, and this expansion leads to compression of the cavernous veins that reduces outflow. The combined increase in inflow and decrease in outflow result in erection. Detumescence is produced by a re-establishment of sympathetic tone and a decline in the release of vaso-dilating agents. For recent reviews of this topic see Argiolas and Melis (1995), Andersson and Wagner (1995), and Burnett (1995).

Prior studies from this laboratory have demonstrated that rat penile erection is androgen dependent (Mills et al, 1992; Mills et al, 1994; Mills et al, 1996). In other published reports, Heaton and Varrin (1994) described a centrally mediated role for testosterone in the erectile response and Leipheimer and Sachs (1993) have demonstrated androgen sensitivity in the vascular muscle involved in erection. While it is widely held that androgens are responsible for erectile function both centrally and peripherally, the precise mechanisms of how androgens act to maintain the erectile process remains an enigma. Studies in castrated dogs have suggested that androgen deficiency could result in higher smooth muscle tone leading to incomplete trabecular smooth muscle relaxation (Muller et al, 1988). The present studies were designed to determine if rat cavernosal smooth muscle tone is under androgenic regulation by testing the hypothesis that androgens modulate the adrenergic responsiveness of the vascular smooth muscle controlling blood flow in the penis.

Materials and Methods

Animals—Six-to-nine-months-old male Harlan Sprague Dawley (Indianapolis, Indiana) retired breeders were used in these studies. The animals were housed in environmentally controlled quarters in separate hanging cages on a 14-hour light : 10-hour dark cycle and provided food and water *ad libitum*.

Castration and Testosterone Replacement—Animals were castrated under ether anesthesia and immediately implanted subcutaneously with a 3-mm (approx. 3-mg) pellet composed of cholesterol (group designation: CASTRATE) or 50% testosterone and 50% cholesterol (group designation: TESTO). Experimental procedures were performed 6–9 days after castration and pellet implantation. At termination of the experiment, blood from the carotid artery was collected and analyzed for circulating

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Correspondence to: Thomas M. Mills, PhD, Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, Georgia 30912-3000.

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levels of testosterone by radioimmunoassay. Testosterone levels in CASTRATE rats averaged 80 ± 40 pg/ml, while TESTO animals had blood levels of 1,050 ± 500 pg/ml. We have previously shown that this method of testosterone replacement fully restores the erectile function to that observed in an intact animal (Mills et al, 1992).

Preparation of Animals for Measurement of Intracavernosal Pressure—The method for stimulation and measurement of the erectile response is standardly used in this laboratory (Mills et al, 1992; Mills et al, 1994; Mills et al, 1996). Briefly, the rat was anesthetized with an intramuscular injection of ketamine (87 mg/kg) combined with xylazine (13 mg/kg) and maintained on supplemental injections of ketamine and xylazine as needed. The carotid artery was cannulated with a blunted 18-gauge needle with PE 200 tubing attached to a pressure transducer and connected to a multichannel recorder to continuously monitor mean arterial blood pressure (MAP). Via the femoral artery, a fine-tipped cannula was inserted into the dorsal aorta for drug delivery. The abdominal cavity was next opened, the viscera retracted, covered in saline soaked sponges, and wrapped in cellophane to reduce evaporation and to help maintain body temperature. The tissue overlying the right aspects of the dorsal prostate was cleared of fat and adhering fascia to expose the right cavernosal nerve and major pelvic ganglion (MPG). The shaft of the penis was cleared of the overlying fascia and the right corpus cavernosum was exposed. The cavernosum was cannulated with insertion of a 30-gauge needle that was attached to PE 200 tubing (drawn to a fine tip) and attached to a pressure transducer for measurement of intracavernosal pressure (CCP).

Measurement of the Erectile Response—Stainless steel bipolar electrodes connected to a Grass stimulator were positioned on the pelvic nerve and the ganglion using a micro manipulator. Proper electrode placement was established by determining the position of electrodes that produced the maximal CCP with minimal alteration of MAP at a 5-volt stimulation (pulse duration −5 mseconds, frequency −12 Hz). After electrode placement, each animal was subjected to a series of stimulations of the MPG ranging from 1 to 6 volts while CCP and MAP were continuously measured. Stimulations lasted 1 minute with a recovery time of 1 minute between stimulations. Previous studies from this laboratory have determined that 5 or 6 volts gives the maximal erectile response (Mills et al, 1992).

Administration of Phenylephrine During Induced Erection—After determining the optimal voltage and electrode placement, the effects of intra-aortic administration of phenylephrine on intracavernosal pressure was determined. In these experiments, the CCP was allowed to rise to a maximum (after about 30 seconds) and then phenylephrine was administered into the aorta in a single bolus in doses of 0.01, 0.05, 0.1, 0.5, 1.0, 5.0, 10.0, and 50.0 μg/kg body weight (BW) in 250 μl of saline. An equal volume of saline was administered as a control. Stimulation was continued for a total of 2 minutes followed by a 2–3 minute recovery between phenylephrine doses.

Administration of Prazosin—Since prazosin is sparingly soluble in saline, it was dissolved in distilled water at a concentration of 1 mg/ml. After a control injection (intra-aortic) of 250 μl of water into the dorsal aorta followed by a 5-minute equilibration period, the animal was subjected to sequential stimulatory voltages from 1 to 6 volts for 1 minute with a recovery time of 1 minute between stimulations (PRE-PRAZOSIN). Five-hundred-μg prazosin/kg BW was then injected in 250-μl water and, 5 minutes after prazosin injection, the series of stimulation of the MPG (1–6 volts) was repeated (POST-PRAZOSIN). To determine if the rate at which blood drained out of the cavernous sinuses was altered by prazosin treatment, the intracavernosal pressure at the time that the ganglionic stimulation was terminated was compared to the intracavernosal pressure 12 seconds later. This comparison was made in the PRE-PRAZOSIN and POST-PRAZOSIN animals in both treatment groups.

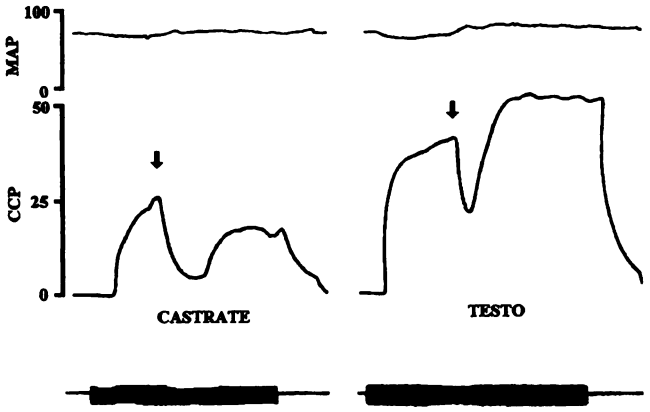

FIG. 1. Representative tracings of intracavernosal pressure (CCP) and mean arterial pressure (MAP) responses to ganglionic stimulation (solid horizontal bar) at 5 volts and injection of 1-μg phenylephrine/kg BW (↓) into the aorta of a CASTRATE and TESTO animal.

Statistical Analysis—To analyze the results of the phenylephrine injection experiment, polynomial regression was used to determine the best fit through the data points and the resulting regression lines were used to determine the ED_{50} value for the drug in each animal. The ED_{50} values for TESTO and CASTRATE animals were then compared by students *t*-test. To compare the effects of prazosin on the erectile response in TESTO and CASTRATE rats, repeated measures ANOVA was employed with *post hoc* analysis by the method of least squares. The rate of outflow was analyzed statistically using repeated measures ANOVA followed by *post hoc* analysis with Dunnett's test (Winer, 1971). $P < 0.05$ was considered statistically significant.

Results

Figure 1 shows a representative tracing of intracavernosal pressure (CCP) and mean arterial pressure (MAP) responses to stimulation of the MPG in a TESTO and CASTRATE rat. After the CCP had reached a maximum, phenylephrine was injected causing a rapid decline in CCP but an increase in MAP. While the MAP values increase to about the same extent in the TESTO and CASTRATE animals, this tracing shows three differences between the CCP response in CASTRATE rats and TESTO animals. The first difference is the magnitude of the erectile response. The CCP increase relative to the MAP rise

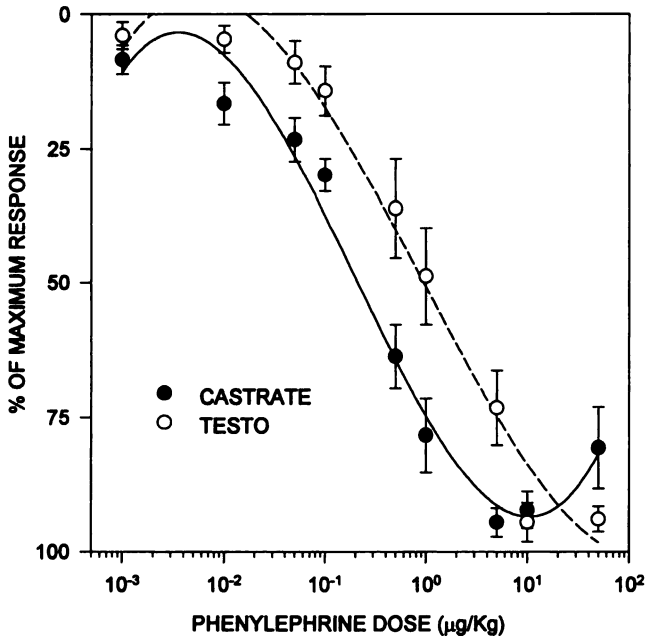

FIG. 2. The effects of increasing doses of phenylephrine on the intracavernosal pressure (CCP) during electrical stimulation of the major pelvic ganglion in CASTRATE and TESTO animals. Each point is the mean ± SEM of measurements made in 7–11 animals.

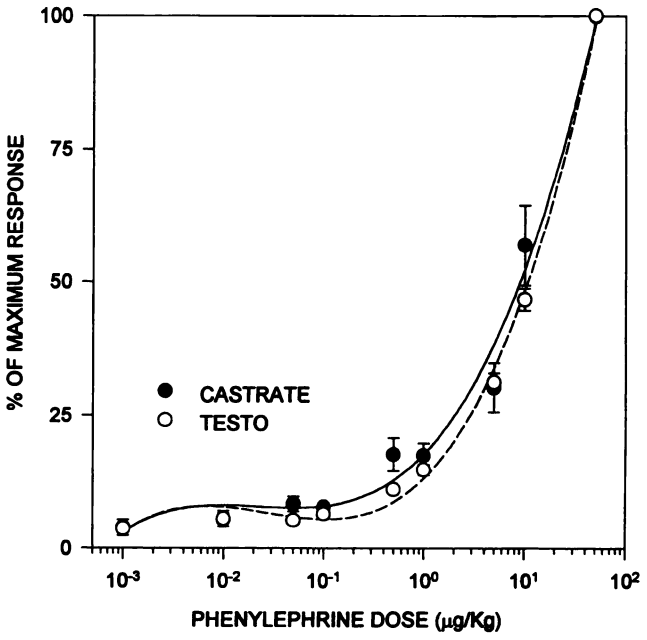

FIG. 3. The effect of increasing doses of phenylephrine on the mean arterial pressure (MAP) during electrical stimulation of the major pelvic ganglion in CASTRATE and TESTO rats. Each point is the mean ± SEM of measurements made in 7–11 animals. The responses in the two treatment groups are not significantly different.

(CCP/MAP ratio) in CASTRATE animals is about 0.3 while the ratio in TESTO animals is about 0.6. Secondly, the magnitude of the decline in the CCP/MAP ratio resulting from administration of an equal dose of phenylephrine is greater in CASTRATE rats than in TESTO animals. In this tracing, at a dose of 1-µg phenylephrine/kg BW, the CCP in the TESTO animal was reduced by about 50%, whereas in a CASTRATE animal at the same dosage, the CCP was decreased by nearly 90%. Thirdly, the degree of recovery of the CCP after drug administration in CASTRATE animals is less than the recovery in TESTO animals in which the CCP returns and often overshoots the original pressure. These differences suggest that the response of the cavernosal smooth muscle in TESTO and CASTRATE animals is not the same.

Analysis of the effects of phenylephrine on CCP is shown in Figure 2. The maximal intracavernosal pressure decrease following phenylephrine administration was set to 100% and the responses to other doses of the drug expressed as percent of this maximum. Figure 2 shows a dose-dependent decline in the CCP in both groups with administration of an increasing amount of phenylephrine and also shows a greater responsiveness in CASTRATE animals than in TESTO rats. Further analysis of the results with the determination of the ED_{50} for the response (the dose of phenylephrine that causes a 50% reduction in CCP) reveals that the CASTRATE animals are more responsive to the drug than the TESTO rats. Our calculations show that the ED_{50} for CASTRATE animals was 0.29 ± 0.08 µg/kg BW, whereas the ED_{50} value in TESTO animals was significantly increased to 1.8 ± 0.48 µg/kg BW. This shows that the responsiveness to phenylephrine is nearly six times greater in CASTRATE animals than in the TESTO rats.

To establish that the differences in phenylephrine sensitivity were specific to the corpus cavernosum and not due to generalized effects acting on the systemic vasculature, changes in MAP following drug administration were measured (Fig. 3). These results demonstrate that the dose-dependent increase in the MAP following phenylephrine in CASTRATE animals is not different from the increase in TESTO animals.

To confirm that CASTRATE animals are more responsive to α-adrenergic agonists than rats in the TESTO group, studies were completed to determine if the sensitivity of the corpus cavernosum to prazosin, an α_1-adrenergic antagonist, was different in the two treatment groups. Table 1 shows that in both the CASTRATE and TESTO groups, the MAP decreased immediately following prazosin injection and remained low for the duration of the experiment. Figure 4 demonstrates the effect of prazosin administration on the erectile response (CCP/MAP) in CASTRATE and TESTO animals and shows that there was an overall significant enhancement in the erectile response (CCP/MAP) in CASTRATE animals (PRE-PRAZOSIN vs. POST-PRAZOSIN) but not in the TESTO rats (Fig. 4).

Table 1. *Effect of the duration of prazosin treatment (0–15 minutes) on MAP (mm Hg) in CASTRATE and TESTO animals**

Treatment	0 minutes	1 minute	5 minutes	10 minutes	15 minutes
CASTRATE	81 ± 6	67 ± 7	66 ± 5	66 ± 3	68 ± 2
TESTO	82 ± 5	71 ± 3	70 ± 3	69 ± 4	70 ± 5

* Each value is the mean of measurements made in 4–5 animals ± 1 SEM. The MAP following prazosin administration is significantly different from that of pre-injection (0 minutes) at all times observed ($P < 0.05$). However, there was no significant difference between the mean blood pressure values in the CASTRATE and TESTO animals at any of the specific times ($P > 0.05$).

Following prazosin administration, the rate at which blood drained from the corpus cavernosum was significantly altered in both treatment groups. Figure 5 shows that when ganglionic stimulation (3–6 volts) was discontinued, drainage from the cavernous sinuses was significantly decreased in both CASTRATE and TESTO animals, but the rates of drainage were not different in the two treatment groups.

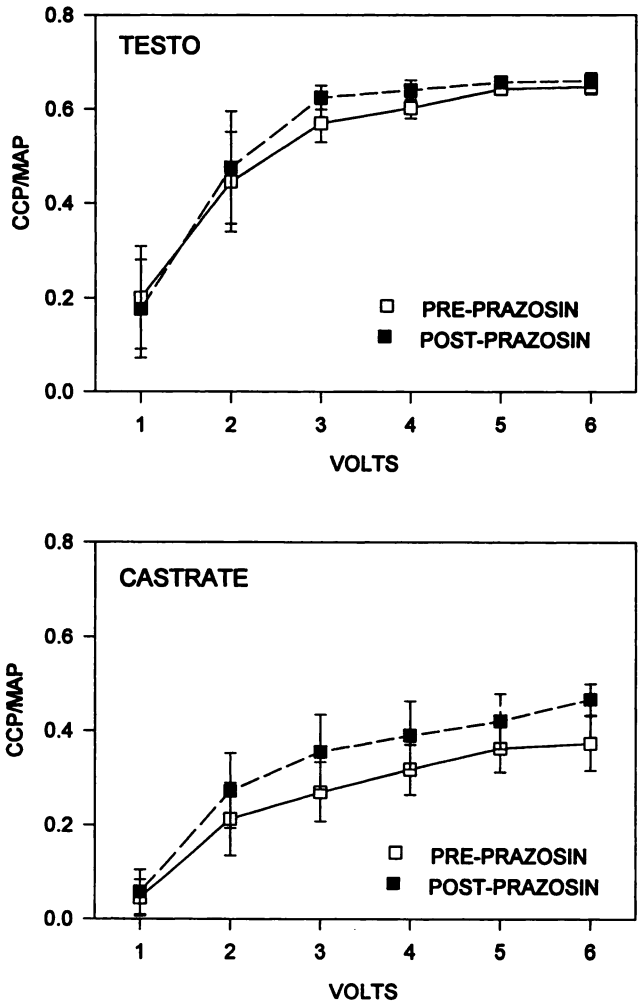

FIG. 4. Effect of stimulation of the major pelvic ganglion in CASTRATE and TESTO animals before and after prazosin administration (PRE-PRAZOSIN and POST-PRAZOSIN). Each value is the mean ± SEM of measurements made in 4–5 animals. At 5 and 6 volts the CCP/MAP ratio is significantly greater in the CASTRATE group after receiving prazosin ($P < 0.05$), while the ratio in the TESTO group remains unchanged.

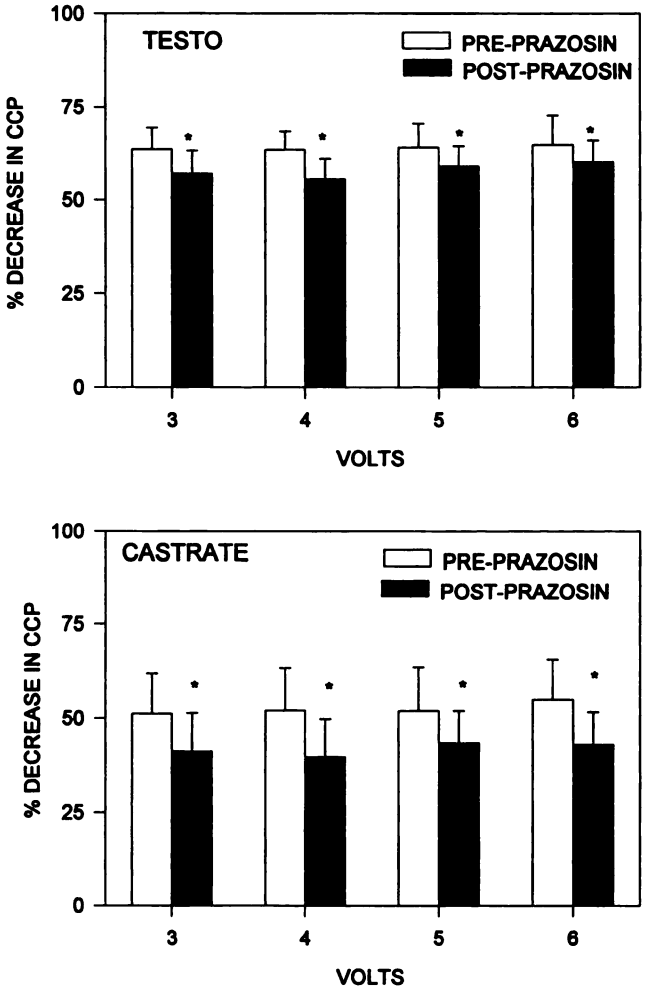

FIG. 5. Effect of prazosin administration on the rate of drainage in the corpora cavernosa after stimulation in CASTRATE and TESTO animals. Each value is the mean ± SEM of measurements made in 4–5 animals. The rate of drainage in both CASTRATE and TESTO animals is significantly decreased with prazosin administration (*$P < 0.05$) after a 3-, 4-, 5-, or 6-volt stimulation.

Discussion

While the role of the muscarinic cholinergic system in the erectile response remains controversial, the adrenergic system has been shown to be critically important. Both α- and β-adrenergic receptors have been identified in the corpus cavernosum, with α receptors outnumbering β receptors 10 to one (Levin and Wein, 1980; Christ et al, 1990). Systemic administration of β-adrenergic antagonists either failed to affect, or in some instances inhibited, penile function. On the other hand, α-adrenergic antago-

nists substantially enhanced erectile function when used in conjunction with non-adrenergic non-cholinergic vasodilators (Wagner and Brindley, 1980; Blum et al, 1985; Adaikan and Ratnam, 1988; Levin et al, 1994; Truss et al, 1994). Specifically, a tri-injection cocktail containing papaverine and PGE_1 (to facilitate vasodilation) and phentolamine (to decrease sympathetic tone) has been used successfully to elicit erection sufficient for intercourse in otherwise impotent men. In other clinical studies, intracavernous injection of the α_1-adrenergic antagonist, prazosin (Blum et al, 1985; Holmquist et al, 1990; Christ et al, 1992) or the α_1,α_2-adrenergic antagonist, phentolamine (Diederichs and Lue, 1991) resulted in an increase in CCP and partial erection. Idazoxin (an α_2 antagonist) has little effect, suggesting that the α_1 subtype is the predominant receptor involved (Argiolas and Melis, 1995). In cases of priapism, injection of phenylephrine (an α_1 agonist) into the corpus cavernosum is often used to re-establish detumescence (Dittrich et al, 1991). Taken together, these reports confirm that elevated sympathetic tone maintains detumescence and the necessity for a decrease in sympathetic tone for erection to occur. Furthermore, the target of α-adrenergic agonists in the regulation of cavernosal blood flow would have to be the smooth muscle of the cavernosal arterioles since arteriolar flow controls organ blood flow (Berne and Levy, 1992).

Previous studies from this laboratory have demonstrated that the magnitude of the erectile response in castrated animals receiving testosterone replacement is similar to that of intact animals, whereas untreated, castrate animals display a significant decrease in the erectile response (Mills et al, 1992, 1994, 1996). The present studies were undertaken to investigate the underlying mechanisms by which androgens act to maintain the erectile response. The results in Figure 2 show that cavernosal smooth muscle from CASTRATE rats is nearly six times more responsive to phenylephrine than smooth muscle from TESTO rats. However, it is not apparent from these findings how the loss of testosterone leads to the increase in responsiveness to the α agonist. There are several possible mechanisms by which the androgen could exert this action. Zhang and coworkers (1991) suggested steroid hormones could regulate anion metabolism and Ca^{+2} transport across smooth muscle cell membranes. Other possible mechanisms include androgenic regulation of smooth muscle cell division (Fujimoto et al, 1994), a direct relaxation effect of testosterone on smooth muscle cells (Yue et al, 1995), or a change in the number of receptors for sympathetic affecter molecules. With regard to this latter possibility, it is known that androgens (Leipheimer and Sachs, 1993), as well as estrogens (Colucci et al, 1982), influence the sensitivity of smooth muscle cell α-adrenergic receptors. Also reported was the finding that elderly men and men suffering from diabetes possess heightened sensitivity to α-adrenergic agonists; men in these two groups also show a higher frequency of erectile dysfunction (Christ et al, 1992). We suggest that testosterone could regulate the number of α receptors either by down regulation of receptor synthesis or by increasing the rate of receptor turnover although there is no evidence in the present report to support either possibility. Normally in the corpus cavernosum, the number of α receptors outnumbers the number of β receptors by 10 to one (Levin and Wein, 1980) and the number of β receptors in smooth muscle decreases with age (Hishimoto et al, 1995). The loss of testosterone support could alter the ratio of α- and β-adrenergic receptors and thereby alter the sympathetic tone of the tissue. If castration leads to a decline in the number of smooth muscle cells in the corpora cavernosa, then a reduction in cell number would limit the amount of nitric oxide produced, resulting in a reduced erectile response.

The quantity of prazosin injected into the animal was similar to the dose used by Waeber et al (1983), who showed that this dose of the α-adrenergic antagonist caused a 15–20 mm Hg decrease in MAP for a period of 30–45 minutes. Studies from this and other laboratories reported that when MAP is increased or decreased during erection, CCP changes proportionally (Giuliano et al, 1993; Mills et al, 1994). We find that after prazosin injection, the response to ganglionic stimulation changed little in TESTO animals, whereas the response increased significantly in CASTRATE rats. This finding, in conjunction with the findings of other investigators, shows that the suppression of sympathetic tone is essential to full erectile function (Diederichs and Lue, 1991; Diederichs et al, 1991; Costa et al, 1993; Giuliano et al, 1993).

Following the cessation of ganglionic stimulation of prazosin-treated rats, blood drained from the penis at a decreased rate in both CASTRATE and TESTO animals. Thus, the sympathetic tone of cavernosal smooth muscle also influences the rate of drainage of blood from the penis. Although we could not establish a direct relationship between androgen administration and the rate of outflow, it is evident that sympathetic activity is involved. Possibly, the prazosin treatment slowed the rate at which sympathetic tone was re-established in the cavernosal arteries. This could result in continued high rates of flow of blood into the cavernous sinuses to partially maintain the veno-occlusive mechanism and slow the rate of drainage. Alternatively, the findings could reflect a direct action of phenylephrine on the veno-occlusive mechanisms, although this seems unlikely based on our published findings detailing the unresponsive nature of the veno-occlusive mechanism to vasoactive drugs (Mills et al, 1994).

In summary, these studies suggest that sympathetic activity in the corpus cavernosum is regulated, in part, by testosterone. Testosterone acts to reduce the responsive-

ness to α_1-adrenergic agonists and the reduced sympathetic tone permits greater blood inflow and higher intracavernosal pressure.

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