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Effect of Androgens on Penile Tissue

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There are two ways to establish that androgens play a major role in the function and integrity of erectile tissue: (1) discussing a number of physiology and molecular biology studies that have been published from experiments in animals and (2) reporting the effect of androgens on penile tissue, or in many cases the lack of androgen, in man. A variety of animal models, and also human studies, have shown the existence of androgen receptors in the corpora cavernosa. The penile erectile response in the laboratory rat is androgen dependent, and the active androgen appears to be dihydrotestosterone. There are several articles that describe the androgenic regulation of nitric oxide synthase (the enzyme responsible for production of nitric oxide), the primary agent controlling the erectile cycle. There have been few reports showing a direct end organ dependency of androgen for erectile function in the human corpora cavernosa, although there is plenty of evidence demonstrating that low or absent androgens affect a man's ability to have an erection in a sexual situation. Thus, in man androgen dependency for cavernous tissue smooth muscle function is still debatable. Extrapolating animal dependency of androgens for molecular activity in the penile tissue remains the most reasonable suggestion for androgen dependency of the cavernous tissue in man.

Key Words: Androgens; dihydrotestosterone; erectile response; testosterone; corpora cavernosa.

Introduction

There are two ways to establish that androgens play a major role in the function and integrity of erectile tissue. The first is to discuss a number of physiology and molecular biology studies that have been published from experiments in animals that clearly show the functional dependency of mammalian erectile end organ tissue on androgens. However, as in other fields, extrapolation of these data to human physiology is not absolutely certain. This first method is rather indirect, but many of the molecular messengers and processes first described in animal models, particularly rodents, have now been clearly established to be present in human tissue as well. The second method is to report the effect of androgens, or in many cases the lack of androgen, in humans; however, studies in humans have been rather sparse. Some experts have expressed the idea that the importance of androgens to the erectile cycle in men may be primarily central, affecting libido and sex drive rather than the functional integrity of end organ corpora cavernosal tissue. This review critically examines the literature that suggests a direct action of androgens on the penile erectile response. We *(1,2)* previously reviewed the role of androgens in erection in 1996 and 1999. Shabsigh *(3)* also reviewed this topic in 1997.

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Androgen Receptors

It is not unreasonable to assume that for any steroid hormone to have an effect on a tissue, receptors for that hormone must be present. A variety of animal models have shown the existence of androgen receptors (ARs) in the corpora cavernosa *(4–7)*. In the adult human male, cavernosal tissue testosterone receptors were found to be present, but low, in a small set of 11 men undergoing penile implantation *(8)*. In another report, a binding assay analysis of ARs in penile spongy tissue from adult horse, pig, and human (undergoing total penectomy for advanced penile carcinoma) showed the presence of cytosolic AR, though with low binding capacity *(9)*. In man and rat, the levels of ARs vary with age, with high levels likely contributing to the growth of the penis during puberty in the rat. However, as rats age, androgen-binding activity declines *(5–7,10,11)*. There is some controversy over whether this downregulation of AR in the penis is androgen dependent or owing to molecular mechanisms that remain to be elucidated *(5,10–12)*.

Animal Model Evidence of Direct Cavernosal Androgen Effect

The penile erectile response in the laboratory rat is androgen dependent *(1–3,13,14)*. Within 24 h of castration, intracavernosal pressure is reduced in the adult male rat, reaching maximal reduction after 1 to 2 wk and declining little thereafter *(15)*. Castration in the rat model resulted in the reduction of maximal intracavernous pressure after nerve electrostimulation and treatment with testosterone pellets

restored an almost normal erectile response. A similar dependency of the penile erection on androgen has been seen in the rabbit and canine model *(16,17)*. In another study, androgen dependency on electrostimulated erectile activity in intact vs orchectomized dogs was not shown, suggesting a species difference or the small amount of androgens needed for this effect, such as that provided by adrenal androgens, not present in the rat model *(18)*.

Lugg et al. *(19)* found that the active androgen in the erectile tissue in rats is dihydrotestosterone (DHT). DHT was as effective as testosterone in restoring the erectile response to nerve stimulation in castrated rats, but treatment with a 5α-reductase inhibitor (finasteride) decreased the response to testosterone replacement, suggesting that the conversion of testosterone to DHT was essential to maintain erection in this rat model. In this study, castration induced a 75% reduction in penile nitric oxide synthase (NOS) activity, which was restored by androgen treatment. It is interesting to point out here that in a study reported by Cunningham and Hirshkowitz *(20)*, 3-mo treatment with finasteride in intact men caused a decrease in serum DHT but no change in serum testosterone levels and no change in sleep-related erections. However, these were intact men who still had measurable, but diminished, serum levels of DHT.

There are several articles that describe the androgenic regulation of NOS, the enzyme responsible for production of nitric oxide (NO), the primary agent controlling the erectile cycle. One study showed that the number of NOS-containing nerve fibers detected in the corpora cavernosa and dorsal nerves of castrated rats was lower than the number of NOS-positive fibers found in control and testosterone-treated castrated rats *(21)*. Studies from our laboratory showed a significant decline in the availability of neuronal NOS (nNOS) mRNA in the castrate rat, suggesting that testosterone acts at a genomic level to regulate the expression of the nNOS gene *(22)*. Other studies from our laboratory showed that androgens may regulate an NO-independent alternative pathway contributing to the relaxation of corporal smooth muscle, but this pathway involves cyclic guanosine 5'-monophosphate *(23)*. Later studies from our laboratory suggested that testosterone regulates NOS activity in both the arteriolar and sinusoidal smooth muscle *(24)*. Measurement of NOS enzyme protein by Western analysis showed that in castrated animals there was less than half the quantity of NOS protein as in testosterone-replaced animals *(25)*. In a study by Zvara et al. *(26)*, NADPH diasphorase staining (immunohistochemical localization of NOS activity) decreased by more than half in cavernosal nerves 10 d postcastration but returned to near normal levels following testosterone replacement.

In his review, Shabsigh *(3)* cites a study from his laboratory that showed evidence for induction of apoptosis in the rat penis following castration and located this phenomenon in a cell population in the erectile tissue of the rat penis.

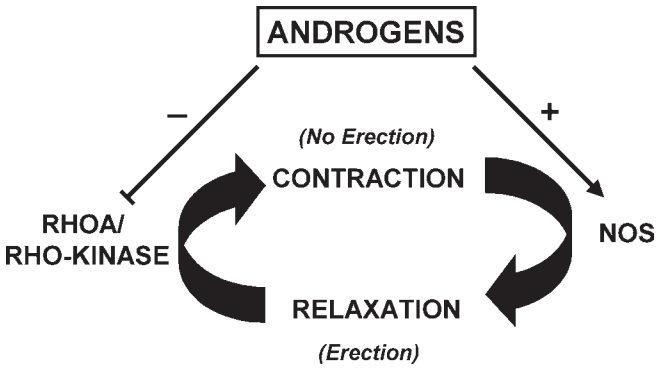

Fig. 1. Lack of androgens has a negative effect on erection by upregulating the RhoA/Rho kinase system, which produces smooth muscle contraction. On the other hand, androgens have a positive effect on erection or relaxation by enhancing NOS activity.

Insight into the mechanisms underlying the castration-related decline in erectile function comes from recent studies by Wingard et al. *(27)*. They measured the activity of the RhoA/Rho kinase calcium sensitization pathway in castration-induced erectile dysfunction (ED). The RhoA/Rho kinase pathway has been demonstrated to be a primary mediator of cavernosal smooth muscle contraction, thereby blocking the vasodilatory effects of NO and preventing erection in rats *(28)* (see Fig. 1). NO is thought to directly inhibit RhoA/Rho kinase signaling to permit smooth muscle relaxation and thus increased blood flow leading to erection. Western analysis of RhoA and Rho kinase protein demonstrated that the quantities of both proteins are upregulated in the penile tissue of untreated castrated rats compared with intact animals. In addition, intracavernosal injection of the specific Rho kinase inhibitor Y-27632, fully restored erectile function in the castrated rats. The authors go on to suggest that the quantities of NO released in response to electrical stimulation of the erectile apparatus can only partially counteract the effects of elevated Rho kinase–mediated vasoconstriction in the castrated animals. However, when Rho kinase activity was further suppressed with Y-27632, NO release was adequate to permit full erection to occur.

Direct Androgen Effect on Corpora Cavernosal Tissue in the Human

There have been few reports showing direct end organ dependency on androgen for erectile function in the human corpora cavernosa, although there is plenty of evidence demonstrating that low or absent androgens affect a man's ability to have an erection in a sexual situation. Primary or secondary hypogonadism is often associated with ED, but even surgical or medical castration does not always result in loss of erectile function. Androgens are produced by the adrenal gland in man, and these androgens may be all that

is necessary to maintain erectile capabilities in the penis. Hormonal dependency for penile erection seems to vary regarding the type of erection setting, whether it is in a sexual situation, it is associated with rapid eye movement sleep, or it is initiated by visual sex stimulation. One of the most intriguing studies to demonstrate this difference was by Greenstein et al. *(29)* in 1995. Sixteen previously potent men who were either medically or surgically castrated (10 by surgical orchiectomy) and reported neither spontaneous erections nor possible vaginal intercourse were investigated. These men were challenged with an erotic videotape, and penile erection was measured by a penile strain gage connected to a recorder. The quality of the erection was self-evaluated, as well as by the lead author of this study. Four of the patients, all who had surgical castration, had an erection judged to be adequate for sexual intercourse during the visual sex stimulation. There was no difference in the responders and nonresponders regarding erection score before castration, age at castration, duration since castration, libido, smoking habits, or comorbidity score. However, levels of free testosterone, although at castrate levels in all patients, was statistically significantly higher in the 4 obtaining erections vs the remaining 6 surgically castrated patients or the 12 surgically or medically castrated patients who did not achieve an erection. Greenstein et al. *(29)* suggested two conclusions. First, there was a difference in erections that occur in sexual situations compared with those resulting from visual sex stimulation. Second, there seemed to be a testosterone level dependency for visual sex–stimulated erection to occur, even though testosterone levels were very low.

Several investigators have reported that the three different types of erection—erections with sexual partners, nocturnal erections, and erections induced by visual sex stimulation—may have different androgen dependency thresholds *(30–32)*. Those patients with severe degrees of hypogonadism (i.e., serum testosterone <1.4 ng/mL) have impaired erection in sexual situations and in nocturnal erections. Patients with a less severe decrease in serum testosterone (i.e., levels between 2 and 3.5 ng/mL) maintain normal nocturnal erections but still have impaired erections in sexual situations. Erections during visual sex stimulation did not show much androgen level dependency. Granata et al. *(32)* reported a serum testosterone threshold level of about 200 ng/dL required to maintain sleep-related erections in a study of 201 men.

In a literature review of English language articles published between 1975 and 1992, Mulligan and Schmitt *(33)* considered that based on available data, testosterone replacement therapy in men with low testosterone levels is important for sleep-associated erections but not for erections in response to fantasy or visual erotic stimulation. Bancroft and Wu *(34)* showed that in eight hypogonadal men, erections in response to erotic films were not significantly different from in control subjects before and after androgen treatment. However, erections in response to erotic fantasy were fewer in the hypogonadal men compared with age-matched control subjects. The erectile response to fantasy was improved by androgen replacement in the hypogonadal men, becoming not significantly different from that in control subjects. Reported frequency of sexual acts per week was significantly improved in these eight hypogonadal men after androgen treatment.

Cunningham et al. *(35)* showed a significant decline over time in the number of nocturnal penile tumescence (NPT) episodes, maximum penile circumference, total tumescent time, and mean penile rigidity as measured by buckling pressure after im administration of 200 mg of testosterone cypionate in six hypogonadal men. In these studies, NPT was obtained within 1 wk of therapy and was compared to the response 7 to 8 wk after therapy. However, after 7 to 8 wk none of the hypogonadal men had NPT parameters that would classify their erectile response as organic based on all NPT changes including duration, rigidity, and maximum circumference change compared to expected normals for these parameters. By contrast, this same group of investigators had reported diminished NPT in 6 of 6 men identified as androgen deficient and untreated out of 172 men with complaints of ED *(36)*. Carani et al. *(37)* showed that testosterone injection in eugonadal young men with no sexual dysfunction did not change the frequency of NPT events or duration of circumference change. However, their study did show increased rigidity in these normal men, suggesting an enhancement of end organ function in these normal subjects. Another study showed maintenance of frequency of sexual acts and normal NPT parameters in 11 patients treated first with a gonadotropin-releasing hormone agonist followed by either high- or low-dose testosterone for 9 wk. This study clearly showed the futility of using testosterone therapy in those patients with testosterone in the low range of normal to improve erectile function and suggests that testosterone has to be at extremely low levels to effect sexually related erections or nocturnal sleep-related erections *(38)*.

Hirshkowitz et al. *(39)* showed that in young healthy men sleep-related erections were decreased but not eliminated with a 12-wk treatment with a luteinizing hormone–releasing hormone agonist. Sleep parameters did not differ between placebo- and finasteride-treated groups. In hypogonadal men, treatment with oral testosterone to elevate serum testosterone to normal levels resulted in variable return of libido and erectile activity *(40)*. This, however, is not surprising since in man there are often multifactorial etiologies for the ED. Carani et al. *(41)* did show a more predictable response to oral testosterone therapy in hypogonadal men by using free testosterone levels as a guide.

In a study reported by Becker et al. *(42)*, cavernous and systemic testosterone levels were obtained in normal men during different phases of erection in response to visual stimulation. Penile erection was found to be accompanied by a significant increase in cavernous and systemic testosterone plasma levels. During the flaccidity and detumescence

Table 1
Human Evidence
of Direct Androgen Effect on Corpora Cavernosal Tissue

- Presence of ARs in corpora cavernosal tissue
- Sexual stimulation–dependent erections (depending on local tactile and central sensory activity) more sensitive to androgen levels than visual erotic film–induced erections (more central activity); nocturnal sleep-related erections sensitive to intermediate levels of androgen
- Increased rigidity of erection measured by Rigiscan (NPT associated) in eugonadal men treated with testosterone, suggesting end organ effect; no effect on frequency of events or duration of circumference change
- Systemic and cavernosal plasma testosterone levels higher in erect state compared with nonerect state, with a decrease in cavernosal levels posterection, suggesting corpora cavernosal binding of testosterone during erection

Table 2
Animal Model Evidence
of AndrogenEffect on Corpora Cavernosa

- Presence of ARs in corpora cavernosa
- Decrease in cavernosal tone after castration
- Decrease in response to nerve-stimulated induced erections after castration restored by exogenous testosterone (rodents, rabbit, dog)
- Active androgen mediator is DHT
- Seventy-five percent reduction in penile NOS produced by castration; restored by androgen treatment
- Significant decrease in nNOS mRNA in castrated rat
- Apoptosis in penile erectile tissue after castration in rat
- RhoA and Rho kinase proteins (mediators of penile smooth muscle contraction) upregulated in castrate rat model

states, penile cavernous blood was shown to have significantly lower levels of testosterone compared with systemic levels, suggesting a binding of testosterone in the cavernous space *(42)*.

Conclusion

In man androgen dependency for cavernous tissue smooth muscle function is still debatable (see Table 1). The androgen dependence of sexual function may be only central. However, testosterone receptors remain present in the cavernous tissue throughout life, although at higher levels during puberty, when penile growth occurs. Some investigators have shown significant differences in measurable testosterone during erection, suggesting active binding of testosterone in the cavernous tissue in man *(42)*. Carani et al. *(37)* did show an increase in penile rigidity without an effect on other parameters when eugonadal men were treated with testosterone, suggesting an end organ effect of the androgen. Erections associated with sexual activity between partners, in which there is usually more involvement of penile tactile factors and the sensory lumbar arc, appear to have higher thresholds for circulating testosterone, whereas sleep erections, which are thought to be more centrally dependent, and erections associated with visual stimulation or fantasy are either dependent on lower circulating testosterone or independent of circulating levels. Since the erections occurring in these three different conditions are variable in the same individual at the same time in his life, an end organ effect dependent on different levels of circulating androgen from those in which there is more involvement of a lower sacral arc might again suggest an end organ or direct cavernous tissue effect as one explanation of these differences. Extrapolating animal dependency of androgens or molecular activity in the penile tissue remains the final suggestion for androgen dependency of the cavernous tissue in man (see Table 2). This, too, is indirect, but molecular events first discovered in animal models have led to a significant understanding of normal erection and translational value for treatment of ED in man. It is doubtful that the same will not be true in man for androgens, but species differences still have to be taken into account.

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