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The effects of testosterone on the cavernous tissue and erectile function

Summary A review of the current literature is conducted to explore the developmental aspects, animal and human experiences and the effects of pharmacological manipulation to explain the role androgens play in sexual function with special emphasis on erectile function and the erectile tissue. This review reveals that androgens are necessary for the normal development of the penis and their deficiency results in significant structural abnormalities. Although androgen receptors in the penis decrease after puberty, they usually do not disappear completely. Animal data show that androgens support erectile function through a direct effect on the erectile tissue. Experimental castration results in impaired erectile response to central and peripheral stimulation and decrease in penile tissue concentration of nitric oxide synthase-containing nerves. Testosterone replacement reverses these abnormalities. In the rat penis, apoptosis is induced by castration and new DNA synthesis is induced by testosterone replenishment. Human data are less clear than animal data. Castration results in loss of libido and in erectile dysfunction. However, these effects are not universal. Testosterone enhances libido, frequency of sexual acts and sleep-related erections. Its effects on erotic erections are not clear.

Normal male sexual function depends on a complex interplay of psychological, neurological, vascular, and endocrine factors. There is considerable controversy as to the relative importance of these factors in the initiation and maintenance of erection, especially of the role of testosterone. The reported incidence of endocrine disorders in the impotent population has ranged widely, from 1.7% to 35% [4, 18, 38, 46, 56, 58, 60]. In a large series by Johnson and Jarow [29], only 7 of 330 [2.1%] consecutive patients referred to a urology clinic for impotence evaluation repeatedly had abnormal serum testosterone levels. However, the literature is full of suggestions of a significant contribution of androgens to erectile function. Ellis and Grayhack [13] reported that 60% of potent men undergoing medical or surgical castration for metastatic prostate cancer became impotent, and Heim [26] noted that 69% of castrated sex offenders could not engage in sexual intercourse. Although they suggest a strong influence of androgens on erection, such reports also underscore that the role of androgens in erectile function is not clear. Indeed, some investigators propose that the principal action of androgens in human sexual function mainly or solely involves the control of libido at the level of the central nervous system rather than any direct effect on erectile tissue [26]. Frajese et al. [17] emphasize the fundamental role of testosterone in the CNS, where it activates the sexual stimulatory dopaminergic system and inhibits the inhibitory serotonergic system.

The following review of the current literature addresses several aspects of this issue, which are highly important for the understanding of the role of testosterone in sexual function in general, placing special emphasis on erectile function and dysfunction. This review discusses developmental aspects; androgen receptors in the penis; experimental animal data, including some of the author's own work; human data on androgen deprivation and replacement; and the effects of pharmacological hormonal intervention.

Developmental aspects

Given that the exact role of androgens in adult male sexual function remains unclear, considerable research has established beyond doubt that the development of the penis and the male genitalia are totally dependent on androgens. Furthermore, androgen disorders during development result in profound congenital structural

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abnormalities. In humans and mammalians the normal growth and development of the penis is completely dependent upon continuous androgenic stimulation from the differentiation of the external genitalia until the completion of puberty [14, 21, 62]. A deficiency of testosterone in utero may yield varying degrees of genital ambiguity, micropenis, and hypospadias. In such patients, preoperative androgen therapy may enlarge the penis, facilitating the operative procedure [8, 22, 27].

Androgen receptors in the penis

The recognized mediator of androgen action in the penis, as elsewhere, is the cytoplasmic androgen receptor [50]. Androgen receptors are present in large quantities in the immature phallus, but they have been found to diminish markedly with age in the rat and to be present in low quantities in the adult human phallus [50]. This may account for the loss of penile growth response to testosterone after puberty [20, 47]. With regard to erectile function, it is noteworthy that the smooth muscle in the rat penis expresses androgen receptors [61]. This expression may be integral to the mechanism by which testosterone exerts its influence, especially because smooth-muscle cells predominate in the erectile tissue of the rat penis [19]. Interestingly, there is an age-related disappearance of androgen receptors in rat penile smooth muscle, but not in penile skin or urethra [61]. The reason for this selectivity of disappearance is not known.

Experimental animal data

Animal models have been studied to establish a more direct relationship between androgens and erectile function [23, 24]. It has been noted that castrated animals exhibit diminished ejaculatory function, numbers of intromissions, and loss of mounting behavior, all of which would be normalized after the administration of testosterone [24]. Testosterone maintains the erectile and copulatory functions in castrated male rats [5, 47]. In addition, other animal studies have demonstrated that neural pathways to the penis are also modified by castration [44]. Testosterone is known to affect spinal reflex activity in animals [34, 39]. A recent in vivo study has demonstrated that androgens maintain erectile function and has suggested that androgens support the responsiveness of smooth muscle of corpora cavernosa in the rat penis [43]. In this excellent study, intracavernous pressure was measured after electrostimulation. Castration resulted in a reduction in maximal intracavernous pressure; and treatment of castrated rats with testosterone restored the normal erectile response. Similarly, cavernous nerve stimulation in castrated and noncastrated dogs has demonstrated a direct influence of serum testosterone on cavernous neurophysiological function. Despite a much higher level of stimulation, castrated animals did not achieve adequate intracavernous pressures [44].

In a recent study on the effects of castration and testosterone replacement, three groups of rats were studied, including a sham-operated control group, a castrated group, and a group receiving testosterone after castration [1]. Functional studies included centrally induced erections with apomorphine, cavernous electrostimulation, and intracavernous papaverine injection. Histology studies included immunohistochemical analysis of nitric oxide synthase-containing nerves in corpora cavernosa and dorsal nerves. The results showed that castrated rats had no erectile response to apomorphine and a full response to apomorphine after administration of testosterone. Intracavernous pressures measured after electrostimulation and papaverine injection were decreased in the absence of testosterone. The numbers of nitric oxide synthase-containing nerve fibers detected in both corpora cavernosa and dorsal nerves of castrated rats were lower than those found in controls and rats treated with testosterone. These findings suggested that testosterone acted directly on the penile nervous system to facilitate erections. In another recent study, the question as to whether testosterone or dihydrotestosterone was the active hormone in the erectile tissue was investigated using electrostimulation in castrated rats [35]. Testosterone or dihydrotestosterone was given with or without administration of the 5-alpha-reductase inhibitor finasteride. The results suggested that dihydrotestosterone was the active androgen involved in maintaining erectile function in the rat penis. A report on the effects of testosterone after castration in the rat showed that testosterone increased the number of erections occurring in response to apomorphine in a dose-dependent manner [25].

Recent work at our institution is, to our knowledge, the first to demonstrate a direct biochemical link between androgen withdrawal and penile stromal cells at the molecular biology level [53]. Rat penile cavernous and spongiosal cells were shown to undergo apoptosis in response to castration. In our study we used a castration model of androgen deprivation in the rat. We postulated that apoptosis (programmed cell death) might play a role in castration-induced erectile dysfunction. This would seem intuitive since, for example, it is well established that apoptosis is a prominent feature following castration in other androgen-dependent tissues, such as the prostate [6, 9]. The methods chosen for this study included molecular analysis of events known to occur in other organs undergoing apoptosis. Analysis of electrophoresis of high-molecular-weight DNA extracted from apoptotic tissue usually shows the typical "ladder pattern" that is due to specific DNA degradation at the internucleosomal regions [32]. We also used an in-situ histoanalytic technique, in situ end labeling (ISEL), to identify and locate the presence of apoptotic cells in tissues of penises from castrated and normal rats [42]. Finally, we analyzed the expression of clusterin (sulfated glycoprotein 2, or SGP-2), a gene product that is cons-

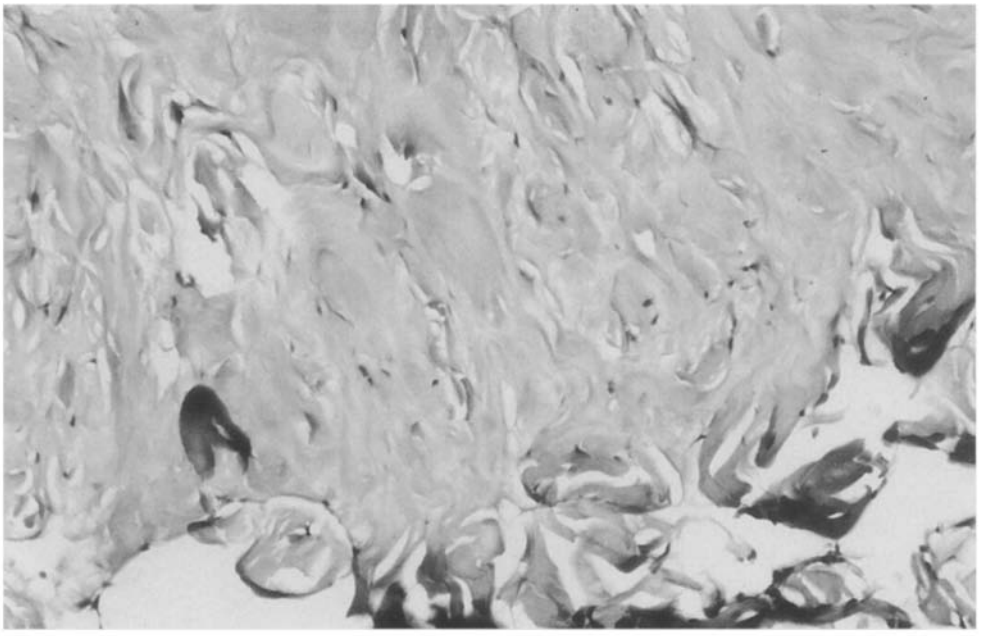

Fig. 1 Microscopic photograph of 100X magnification, showing a transverse section of the rat corpus cavernosum at 5 days after castration. The in-situ end-labeling (ISEL) technique reveals darkly stained nuclei with condensed chromatin and vacuolated cystoplasm typical of apoptotic bodies. The background is stained with methylene blue

titutively expressed in some tissues of the male genitourinary tract but is highly induced in conjunction with apoptosis in rat penises postcastration [3].

In our study we found evidence for induction of apoptosis in the rat penis following castration and located this phenomenon to a cell population in the erectile tissue of the rat penis. However, the penis as a whole organ is not as sensitive to testosterone deprivation as are other sexual accessory organs, e.g., prostate and seminal vesicles, that dramatically regress following castration. The DNA-fragmentation pattern and induction of high levels of SGP-2 observed following castration in the rat penis indicate that the process of programmed cell death occurs with androgen deprivation. The ISEL technique localizes this apoptotic activity to the penile erectile tissue (Fig. 1). The implication of this finding is that the normal growth and the survival of a population of cells in the penis are dependent upon normal levels of testosterone. The localization of these androgen-dependent cells to the erectile tissue provides a structural corollary to the induction of impotence with androgen deprivation. In conclusion, we demonstrated a relationship between androgen deprivation and the onset of apoptotic activity in a cell population of the penile erectile tissue of rats following orchiectomy. Further work on this subject will determine the relevance of the loss of these cells to erectile function. To our knowledge, this is the first direct evidence of the induction of apoptosis following androgen deprivation in an adult animal model.

In following up that work we sought to determine whether the replenishment of testosterone might stimulate stromal cellular proliferation and, if so, to determine which subset of cells was involved [51]. Our study reveals that testosterone activates new DNA synthesis in cavernosal cells of the castrated adult rat penis (Fig. 2). It represents the first biochemical documentation of the regenerative capacity of cells of the erectile tissue in response to a restored supply of androgen. Multiple stromal cell types are observed to undergo DNA synthesis, including myocytes (which predominate), fibrocytes, endothelial cells, and Schwann cells. It remains to be determined which of these cellular components is directly influenced by androgen effects and which is stimulated through one or more intermediate steps. In summary, testosterone appears integral to the physiology of penile erectile function at the level of the cavernous erectile tissue, at least in lower mammals, and its influence is pancellular.

Human data on the effects of androgen deprivation and replacement

The role of androgens in human male sexual function is derived from clinical data obtained in men after androgen deprivation and replacement. Many of these studies have not been well documented. The majority of castrated sex offenders had a decrease in libido and erectile ability, but some of those men retained normal sexual function for years after castration [26]. Orchiectomy for prostate cancer frequently causes impotence [13, 26]. However, even with castration, erectile dysfunction is not universal [26]. These studies did not include an objective assessment of erectile function, for example, by nocturnal penile tumescence (NPT) monitoring. A review of the literature by Schiavi and White [54] suggested that lowering of serum androgen levels decreased both sexual activity and erectile function. Androgen replacement in hypogonadal males has been shown to increase sexual interest and activity [11, 31, 36, 40, 57]. In such clinical studies it is difficult to separate libido from erectile

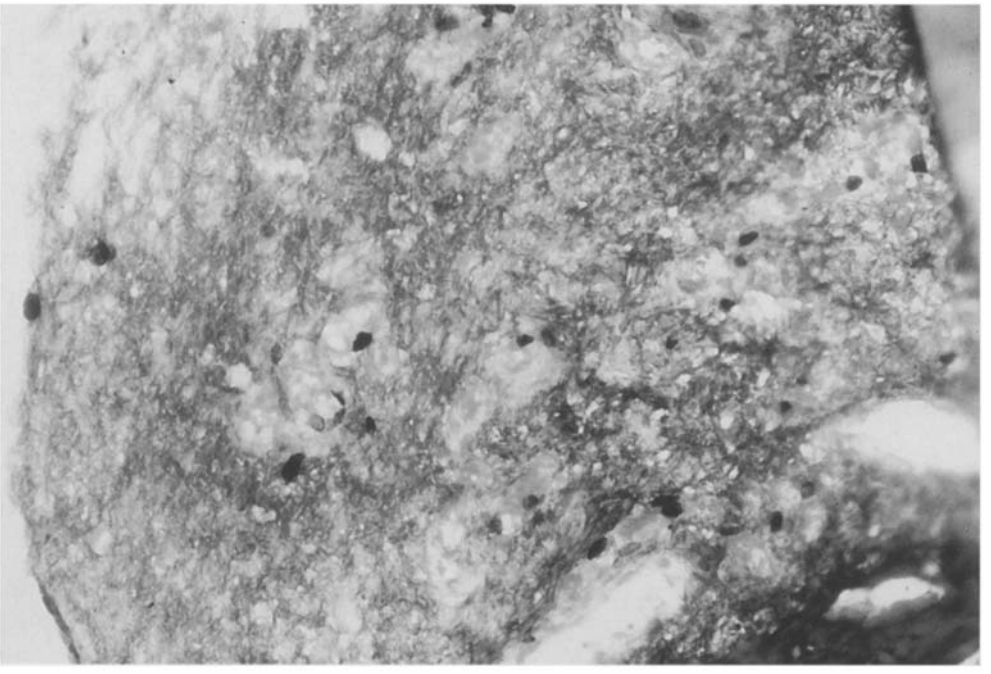

Fig. 2 Microscopic photograph of 100X magnification, showing a transverse section of the rat corpus cavernosum at 4 days after the administration of testosterone to a castrated rat. The bromodeoxyuridine staining technique reveals many cells with stained nuclei typical of new DNA synthesis

function and, therefore, it is difficult to find a cause-effect relationship between androgen deprivation and erectile dysfunction [57]. Double-blind controlled studies in hypogonadal men have shown evidence suggesting that erection is androgen-dependent [36]. These studies showed that androgen replacement in hypogonadal men had a significant effect on sexual function that was dose-dependent and could not be reproduced with placebo.

Data in the literature suggest that sleep-related erections and erotic erections have two different physiological mechanisms [9]. The former may be androgen-dependent and the latter, androgen-independent. Indeed, in humans there is a positive relationship between serum testosterone levels and the frequency of erections during NPT monitoring [2, 10, 11, 15, 36, 48]. Sleep erections are thought to occur without the interference of psychogenic stimuli. In addition, human studies have shown a significantly positive correlation between both the latency time to maximal penile tumescence and the magnitude of erection and serum testosterone levels [33, 52].

A major clinical review of the medical literature attempted to determine the association between testosterone and erectile function [45]. A Medline search of the English literature published between 1975 and 1992 was conducted. In all, 12 original reports of the effect of testosterone administration on sexual function in men with low serum testosterone levels were accepted into this review, which resulted in 3 conclusions. First, testosterone enhances libido, including sexual thoughts and perceived sexual arousal. Second, testosterone leads to increased frequency of sexual acts. It is unknown whether this would lead to a net increase in the success rate of intercourse. Third, testosterone increases the frequency of sleep-related erections but has no effect on fantasy or visually induced erections.

Effects of pharmacological intervention

Several hormonal pharmacological manipulations can result in sexual dysfunction of varying degrees of decreased libido, erectile dysfunction, and orgasmic and/or ejaculatory dysfunction. These medications include luteinizing hormone-releasing hormone (LHRH) analogues, antiandrogens, and 5-alpha-reductase inhibitor. LHRH analogues such as leuprolide and gosereline shut down the hypothalamic-pituitary-testicular axis and produce a castration level of serum testosterone. Flutamide and bicalutamide are antiandrogens indicated for use in combination with an LHRH analogue for maximal androgen blockade in the treatment of prostate cancer. Finasteride is a 5-alpha-reductase inhibitor that inhibits the conversion of testosterone to dihydrotestosterone and is indicated for the treatment of benign prostatic hyperplasia.

In a study on flutamide therapy for advanced prostate cancer [59], 72 patients received flutamide at 250 mg t.i.d. for an average of 12.5 months. Prior to flutamide therapy, 51% (37/72) were potent. During flutamide therapy, 87% (32/37) remained potent. In an open trial of the efficacy and safety of neoadjuvant maximal androgen blockade prior to radical prostatectomy for prostate cancer [7], 30 patients received an injection of depot leuprolide at 7.5 mg and oral flutamide at 250 mg t.i.d. Libido decreased during the therapy and returned to prior levels after its discontinuation. In a study on 40 men receiving flutamide for the treatment of metastatic prostate cancer [12], 67% (10/15) of the sexually potent patients retained potency during flutamide therapy. In a comparison of flutamide with stilbestrol in a prospective randomized study [37], 40 patients received either stil-

bestrol at 3 mg qd or flutamide at 250 mg t.i.d. for 12 months. All patients receiving stilbestrol experienced impotence. Patients receiving flutamide had no change in libido or erectile function. Another investigation compared flutamide with estramustine in metastatic prostate cancer [28]. A total of 30 patients received flutamide or estramustine phosphate until relapse. All patients receiving estramustine (15/15) and 20% (3/15) of patients receiving flutamide experienced loss of libido. In a pilot study, concomitant flutamide at 125 mg t.i.d., later increased to 250 mg t.i.d., plus finasteride at 5 mg qd were given to patients with advanced prostate cancer [16]. After 3 months of therapy, 8/10 patients reported normal libido and erectile function and 2/10 patients experienced loss of libido and erectile dysfunction. In the finasteride clinical trials, although this 5-alpha-reductase inhibitor caused a statistically significantly higher incidence of erectile dysfunction than did placebo, the overall incidence was low (finasteride versus placebo: impotence 3.7% versus 1.1%, decreased libido 3.3% versus 1.6%, and decreased volume of ejaculate 2.8% versus 0.9%, respectively) [5, 30, 49, 55].

Conclusions

The following conclusions can be drawn from this literature review:

1. Androgens, including testosterone and dihydrotestosterone, are absolutely necessary and highly important for the normal development of the penis in humans and mammalians, and their deficiency results in congenital structural anomalies.
2. Androgen receptors are present in the penis, including the erectile tissue. Levels of these receptors decrease after puberty but may not disappear completely.
3. Animal data provide strong evidence that androgens play a direct role in the rat in supporting the erectile function at the level of the erectile tissue, most likely by maintaining intact innervation and neurotransmitter systems. Castration results in functional abnormalities, including impaired response to apomorphine, cavernous nerve electrostimulation, and intracavernous papaverine injection. These abnormalities are reversible with the replacement of testosterone. Similarly, castration results in structural abnormalities in the erectile tissue, including a reduction in the number of nitric oxide synthase-containing nerves. Testosterone replacement reverses these abnormalities. In the rat penis, apoptosis (programmed cell death) is induced after castration, and new DNA synthesis is induced after testosterone replacement.
4. Human data are less clear than animal data. In the human adult male, medical or surgical castration results in loss of libido and in erectile dysfunction. However, these effects are not universal. Treatment of hypogonadism with testosterone restores sexual function. Testosterone enhances libido and the frequency of sexual acts. Although it enhances sleep-related erections, its effects in terms of erotic erections are not clear. Further prospective, well-structured studies in humans are needed to provide accurate answers to the questions related to androgens and erectile function.

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