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Androgens Play a Pivotal Role in Maintaining Penile Tissue Architecture and Erection: A Review

Review

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ABSTRACT: Androgens are essential for development, growth, and maintenance of penile structure, and regulate erectile physiology by multiple mechanisms. Here we provide a concise overview of the basic research findings pertaining to androgen modulation of erectile tissue architecture and physiology. A significant body of evidence exists pointing to a critical role of androgens in erectile physiology. Studies in animal models have provided fundamental knowledge on the role of androgens in modulating tissue architecture and cellular, molecular, and physiological mechanisms. Based on data from our laboratory and those reported by others, we believe that androgens play a pivotal role in maintaining the structure and function of the peripheral penile nerve network, the structural integrity of the corpora cavernosa, the tunica albuginea, and the endothelium of the cavernous spaces. Further, androgens play an important role in regulating the differentiation of precursor cells into trabecular smooth muscle. In this review, we will focus our discussion on findings pertaining to the role of androgens in regulating penile tissue architectural elements in modulating penile function. This knowledge has a profound impact on the potential use of androgens in the clinical setting to treat patients with erectile dysfunction.

Key words: Andropause, erectile dysfunction, hormone, penis, adipogenesis, androgen deficiency, corpus cavernosum, sexual dysfunction, smooth muscle.

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Erectile function is a complex neurovascular physiological process that depends on the interplay among neural, vascular, hormonal, and psychological factors, as well as the integrity of the vascular bed of the penis (Krane et al, 1989). During erection, the penis acts as a capacitor, accumulating blood under pressure (Figure 1). This hemodynamic process, known as veno-occlusive function, depends on several distinct physiological mechanisms. These include 1) sexual stimulation, which activates the parasympathetic nonadrenergic-noncholinergic nerves, releasing nitric oxide (NO); 2) dilation of cavernosal arteries and the helicine arterioles of the penis, providing flow and pressure to the corpora; 3) the relaxation of the trabecular smooth muscle, allowing expansion of the lacunar spaces and trapping of blood by compression of the draining venules; and 4) compliance of the tunica albuginea and the connective tissue matrix, permitting adequate compression of the subtunical venules and reducing blood outflow (Krane et al, 1989; Saenz de Tejada et al, 1991a,b; Nehra et al, 1996, 1998). When the trabecular smooth muscle is fully relaxed, the intracavernosal pressure is dependent on the cavernosal arterial pressure and the tissue fibroelastic properties. Thus, tissue architecture plays an important role in veno-occlusive function, and any pathology that contributes to altering tissue architecture will result in veno-occlusive dysfunction (Lue and Tanagho, 1987; Krane et al, 1989; Saenz de Tejada et al, 1991a,b; Andersson and Wagner, 1995).

Corporeal veno-occlusive dysfunction is an important cause of organic erectile dysfunction and is characterized by the need for increased flow rates to maintain erection during clinical evaluation of erection by intracavernous saline infusion (Hatzichristou et al, 1995, 1999; Nehra et al, 1996, 1998; Udelson et al, 1998; Mulhall et al, 2004). Corporeal veno-occlusive dysfunction alone or combined with arterial disease is the specific hemodynamic abnormality causing lack of response to intracavernous pharmacotherapy (Rajfer et al, 1988; Mulhall et al, 1997; Aversa et al, 2003; Wespes et al, 2005; Hwang et al, 2006). The existence of concomitant arterial and sinus smooth muscle disease makes veno-occlusive dysfunction often difficult to diagnose and treat.

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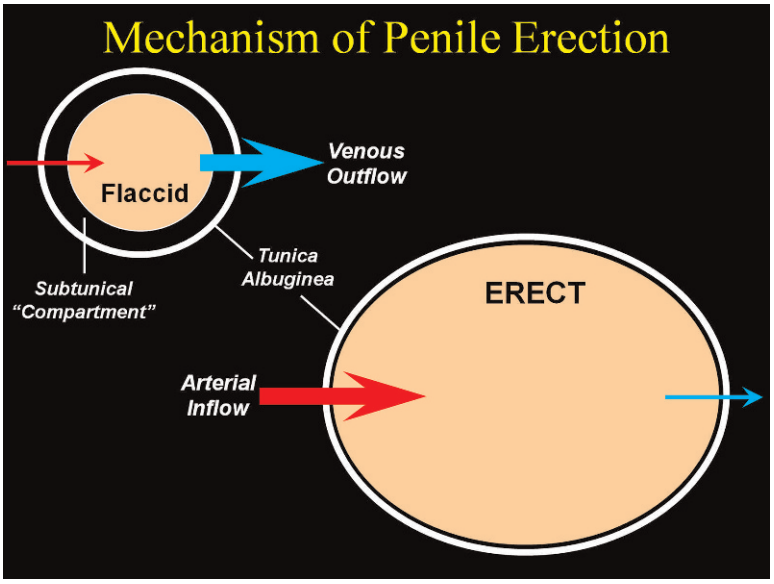

Figure 1. Mechanism of penile erection. In the flaccid state, the vasoconstriction of the cavernosal artery and the helicine arterioles limits blood inflow (dark thin red arrow). The contractility of the trabecular smooth muscle by norepinephrine and other local vasoconstrictor agents such as endothelin will not permit blood accumulation in the lacunar spaces. Further, blood outflow remains unimpeded because smooth muscle contractility does not permit compression of the subtunical venules against the tunica albuginea (light thick blue-green arrow). Upon sexual stimulation, the nonadrenergic-noncholinergic nerves stimulate the release of nitric oxide (NO), which dilates the cavernosal artery and the helicine arterioles and relaxes the trabecular smooth muscle. This neurovascular process results in increased arterial blood inflow (dark thick red arrow) and oxygen partial pressure (PO2) rises from approximately 25–40 mm Hg to 90–100 mm Hg. This physiological process further stimulates the endothelial nitric oxide synthase (eNOS) to synthesize NO, which results in further relaxation in the trabecular smooth muscle. This leads to corporal expansion against the tunica albuginea, thus stretching and occluding the draining venules and reducing blood outflow (light thin blue-green arrow). As corporal venous outflow is occluded, corporal pressure rises and reaches a plateau, thus engorging the penis. Color figure available online at www.androlgyjournal.org.

Nehra et al (1996, 1998) investigated the preoperative indices of veno-occlusive function (flow to maintain erection, venous outflow resistance, and pressure decay measurements using repeat-dosing pharmacocavernosometry) and correlated these parameters with postoperative erectile tissue computer-assisted color histomorphometry (percentage of trabecular smooth muscle to total erectile tissue area). The authors concluded that the pathophysiology of corporeal veno-occlusive dysfunction is, in part, caused by increased connective tissue deposition and reduced smooth muscle content.

Although efforts have been made by a number of laboratories to define and understand the role of androgens in regulating the cellular and molecular basis of erectile function and some progress has been made, several gaps remain. These include the role of androgens in the structural and functional integrity of the cavernosal and dorsal nerves, the growth and function of the smooth muscle, and the function of the endothelium and maintenance of connective tissue metabolism and attenuation of fibrosis. Here we present a working model of androgen action in erectile function (Figure 2). Using this framework, we discuss the role of androgens on penile structural components including 1) peripheral nerves, 2) trabecular smooth muscle, 3) differentiation of precursor pluripotent cells into smooth muscle, 4) vascular endothelium, and 5) tunica albuginea and connective tissue.

Androgens Maintain Penile Cavernosal and Dorsal Nerve Structure and Function

Androgens modulate the structure and function of pelvic ganglia (Meusburger and Keast, 2001; Keast et al, 2002). Giuliano et al (2004) suggested that androgens modulate erectile function by acting on postganglionic parasympathetic neurons. Armagan et al (2007) showed that androgen deprivation by castration altered the structure of the dorsal nerve. This observation is consistent with those made by Baba et al (2000a,b) in which castration reduced NADPH staining in the cavernosal and dorsal nerves and testosterone treatment restored these nerve fibers to control levels. Rogers et al (2003) also demonstrated that castration altered the structure of the dorsal nerve and resulted in venous leakage. Testosterone treatment immediately following castration prevented venous leakage and restored intracavernosal pressure to values similar to those of intact animals. Interestingly, treatment of castrated animals with vascular endothelial growth factor (VEGF) restored nerve structure and veno-occlusive

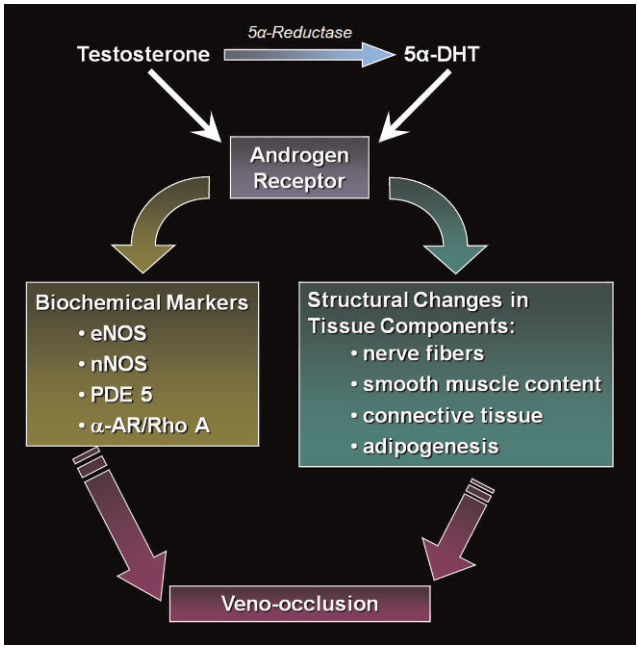

Figure 2. Proposed framework for the action of androgens in erectile function. Testosterone is metabolized to 5α-dihydrotestosterone (5α-DHT), which possesses higher affinity for the androgen receptor (AR). 5α-DHT and testosterone bind to the AR and elicit a host of biochemical signaling leading to several physiological responses. These include 1) increased expression of neural and endothelial nitric oxide synthases (nNOS and eNOS), 2) increased expression of phosphodiesterase type 5 (PDE 5), and 3) up-regulation of α-1 adrenergic receptors and down-regulation of Rho A kinase. In addition, androgens maintain the structural integrity of the penile nerve fiber network and smooth muscle growth and function. The maintenance of the tissue structural integrity and biochemical signaling is critical for veno-occlusive function and penile erection. Color figure available online at www.andrologyjournal.org.

function. Because androgens have been shown to regulate VEGF expression (Haggestrom et al, 1999), it is possible that VEGF synthesis in the corpus cavernosum is down-regulated in castrated animals and testosterone treatment induces VEGF synthesis, thus mediating the androgen-dependent effects on corpus cavernosum.

Orchiectomy produced significant reduction in intracavernosal pressure elicited by electrical field stimulation of the pelvic nerve. This was reversed by testosterone replacement, suggesting that testosterone plays an important role in the peripheral nerve network regulating penile erection (Simpson and Marshal, 1908; Müller et al, 1988; Heaton and Varrin, 1994; Mills et al, 1994; Bivalacqua et al, 1998; Traish et al, 1999; Palese et al, 2003; Suzuki et al, 2007). Further, Suzuki et al (2007) demonstrated that, in contrast to the erectile responses elicited by electrical stimulation of the cavernosal nerve, which were reduced but were not eliminated in castrated animals, erectile responses elicited by electrical stimulation of the medial preoptic area were eliminated following castration and were fully restored after testosterone replacement.

Androgens Maintain Penile Trabecular Smooth Muscle Structure and Function

Considerable evidence exists suggesting that penile trabecular smooth muscle plays an integral role in regulating erectile function (Saenz de Tejada, 2002). The exact nature of the molecular and structural alterations that occur in the smooth muscle subsequent to androgen deficiency, however, remains unknown.

Androgen deprivation in animal models, by surgical or medical castration, produced significant reduction in trabecular smooth muscle content, and increased deposition of extracellular connective tissue matrix (Traish et al, 1999). This change in tissue architecture is associated with reduction in intracavernosal pressure in response to pelvic nerve stimulation (Simpson and Marshal, 1908; Müller et al, 1988; Takahashi et al, 1991; Heaton and Varrin, 1994; Mills et al, 1994; Bivalacqua et al, 1998; Traish et al, 1999, 2003; Palese et al, 2003; Suzuki et al, 2007). Furthermore, ultrastructural studies in tissue from castrated animals documented that trabecular smooth muscle appeared disorganized, with large numbers of cytoplasmic vacuoles and decreased amounts of cytoplasmic myofilaments (Persson et al, 1989; Traish and Kim, 2005; Traish and Guay, 2006; Traish et al, 2007). The loss of smooth muscle resulting from androgen deprivation is attributed to an increase in programmed cell death, connective tissue deposition, and adipocyte differentiation from precursor cells (Shabsigh et al, 1998; Traish et al, 2005). Some notable alterations in penile tissue structural features reported in patients with erectile dysfunction were smooth muscle atrophy and accumulation of extracellular matrix, comprised primarily of collagen fibrils.

The smooth muscle content of the corpora cavernosa relative to the connective tissue, assessed histologically with specific staining, is defined as the smooth muscle to connective tissue ratio. A decrease in the trabecular smooth muscle content concomitant with increased deposition of connective tissue matrix is expected to produce tissue fibrosis and ultimately erectile dysfunction. The severity of symptoms and clinical findings in men with erectile dysfunction was correlated with reduced tissue content of corporal smooth muscle (Nehra et al, 1996, 1998; Wespes et al, 1997, 1998). In tissue from men with ED, the smooth muscle exhibited altered morphology concomitant with sparse glycogen particles and aggregated mitochondria found throughout the cells. The nuclei displayed pleomorphic shape and the cell-cell contacts were decreased or eliminated. These studies suggested that increased collagen content (eg, connective tissue) concomitant with a compensatory decline in trabecular smooth muscle content alters penile fibroelastic properties,

reduces compliance, and results in reduced penile blood flow, producing erectile dysfunction (Persson et al, 1989; Mersdorf et al, 1991).

Androgens Regulate Differentiation of Pluripotent Precursor Cells Into Trabecular Smooth Muscle

Androgen deprivation in the animal model resulted in accumulation of adipocytes in penile tissues, particularly in the subtunical region (Traish et al, 2005). Testosterone replacement restored normal cavernosal histological appearance. The observed tissue alterations were associated with decreased intracavernosal pressure following pelvic nerve stimulation. We and others have noted the accumulation of adipocytes in penile tissue of diabetic animals (Traish and Kim 2005; Kovanecz et al, 2006). Because diabetes is associated with decreased androgen circulation, it is likely that such accumulation of adipocytes is caused by loss of androgen control of cellular differentiation. Similarly, treatment of male animals with bisphenol A, which is known to possess estrogenic activity, also resulted in accumulation of adipocytes in the corpora cavernosa (Moon et al, 2001, 2004). This suggests that estrogens may antagonize androgen action in the corpus cavernosum and result in differentiation of precursor pluripotent cells into adipocytes. Goyal et al (2005a,b; 2007a,b) have elegantly demonstrated that treatment of 2-day-old animals with estrogens resulted in reduced plasma testosterone levels and accumulation of adipocytes in the corpora cavernosa of the mature animal. Bhasin et al (2003) suggested that androgens regulate differentiation of pluripotent cells into smooth muscle and inhibit differentiation into adipocytes. This hypothesis was further supported by the findings of Singh et al (2003, 2006), who demonstrated that differentiation of pluripotent cells into smooth muscle and inhibition of adipogenesis are androgen-dependent. We postulated that accumulation of adipocytes in the interface between the tunica albuginea and the cavernosal bodies might contribute to corporo-occlusive dysfunction.

Androgens Maintain Vascular Endothelial Structure and Function

It is well established that the vascular endothelium modulates corpus cavernosum smooth muscle tone via production of NO and paracrine factors, such as prostaglandins, endothelin, platelet-derived growth factor, and transforming growth factor β1 [TGF-β1] (Moreland, 2000; Bivalacqua et al, 2003, 2005; Solomon et al, 2003; Guay 2005, 2007; Musicki and Burnett, 2007; Watts et al, 2007). Various insults on the endothelium (ie, ischemia, hypoxia, and arteriosclerosis) may produce an increased or decreased level of paracrine factors, which alters the function and growth of smooth muscle cells (Moreland, 2000). A recent study by Lu et al (2007) demonstrated that androgen deprivation by castration or 5α-reductase inhibitor treatment produced damage to the endothelium structure, as determined by electron microscopy. The endothelium from intact animals exhibited smooth surfaces with regular ultrastructural features. The endothelium from castrated animals had coarse and protuberant surfaces, and appeared to be irregular. The cell-cell contacts were altered and adhesion of red blood cells to the surface of the endothelium was noted. Administration of testosterone into castrated animals partially restored endothelial structural integrity, with few lesions remaining noticeable. The data from this study suggested that androgen deficiency produces vascular endothelial damage and that endothelial structural integrity is restored by androgen administration. Akishita et al (2007) reported that, in 187 consecutive male outpatients who underwent measurement of flow-mediated vasodilation (FMD) of the brachial artery using ultrasonography, total and free testosterone were significantly correlated with percentage FMD. This correlation was independent of age, body mass index, hypertension, hyperlipidemia, diabetes mellitus, and smoking, suggesting a protective effect of endogenous testosterone on the endothelium.

The restoration or remodeling of endothelial injury depends, in part, on a pool of premature circulating progenitor cells (PCs) and mature circulating endothelial progenitor cells (EPCs). Foresta et al (2006, 2008) investigated the effects of prolonged testosterone therapy in men with hypogonadotropic hypogonadism on PCs and EPCs. The authors suggested that hypogonadal patients had reduced levels of PCs and EPCs and that testosterone therapy resulted in a significant increase in these cells. The authors concluded that hypogonadism is associated with reduced numbers of circulating PCs and EPCs. The increase in the proliferation, migration, and colony-formation activity of EPCs induced by androgens is an AR-mediated pathway (Foresta et al, 2008).

We propose that androgen deficiency–induced injury to endothelial cells lining the vascular bed of the penis increases synthesis and release of TGF-β1, endothelin, and contractile prostanoids, but decreases NO. The outcome of such biological insults to the endothelium would bring about changes in the smooth muscle phenotype, leading to increased extracellular matrix deposition (fibrosis), cell atrophy, and an inhibition of cell growth (hypoplasia). Fibrosis, therefore, may contribute to altered contractility and decreased compliance (as determined clinically), leading to vasculogenic erectile dysfunction.

Androgens Maintain Tunica Albuginea Structural Integrity and Connective Tissue Matrix Fibroelastic Properties

Shen et al (2003) demonstrated, in castrated animals, a significant reduction in the thickness of the tunica albuginea when compared with intact animals. In intact animals, the tunica is rich in elastic fibers, and the architecture of such fibers showed typical regular arrangements. In contrast, the tunica albuginea from castrated animals showed reduced density of elastic fibers and replacement of these fibers with collagen. The authors concluded that androgens are indispensable for maintenance of normal ultrastructure of penile tunica albuginea.

Androgen ablation by castration in animal models produced a marked increase in the extracellular matrix, with concomitant reduction in smooth muscle to connective tissue ratio by approximately 2-fold (Takahashi et al, 1991; Traish et al, 1999, 2003). This reduction in the tissue fibroelastic properties compromises penile tissue compliance and attenuates penile hemodynamics, resulting in erectile dysfunction (Wespes et al, 1990, 1991; Jevtich, 1991; Nehra et al, 1996). Several studies have suggested that androgens modulate the extracellular matrix through expression of growth factors (Natoli et al, 2005). This, however, need to be further investigated in penile tissue. The decrease in elastic fibers and changes in microscopic features may contribute to erectile dysfunction by impairing the veno-occlusive function of the tunica albuginea (Gentile et al, 1996; Akkus et al, 1997). Recent case studies have corroborated the restoration of erectile function in men with erectile dysfunction attributed to venous leakage after androgen treatment (Yassin et al, 2006; Kurbatov et al, 2008a,b). These observations suggest that androgens play a role in maintaining erectile tissue architecture.

Summary and Conclusions

A significant body of evidence exists, suggesting that androgens regulate the structure and function of penile nerves, vascular endothelium, trabecular smooth muscle, connective tissue matrix, and the tunica albuginea. Further, androgens regulate differentiation of precursor cells into trabecular smooth muscle and inhibit differentiation into adipocytes. In humans, androgen deficiency manifests itself in clinical pathologies, such as 1) inadequate development of the penis and 2) loss of erectile function in patients with prostate cancer or benign prostatic hyperplasia managed with medical or surgical castration or antiandrogen therapy. Androgen supplementation in hypogonadal patients improves sexual function. These clinical observations, together with the preclinical data, suggest that testosterone restores tissue structural elements and improves penile hemodynamics.

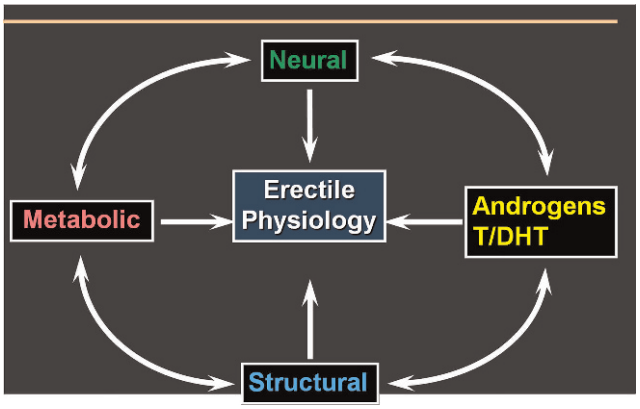

Figure 3. The interplay between androgen action and the structural, hormonal, neural, and metabolic function of penile tissue. This framework suggests that erectile function is a complex process that requires metabolic, structural, and neural integrity mediated by androgens. Color figure available online at www.androlgyjournal.org.

In summary, androgens play a pivotal role in maintaining erectile tissue architecture (Figure 3), and erectile physiology by modulating penile neural function and structural integrity of the smooth muscle, endothelium, and connective tissue matrix, as well as metabolic and signaling pathways.

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