The Physiological Role of Androgens in Penile Erection: Regulation of Corpus Cavernosum Structure and Function

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ABSTRACT

It is generally accepted that androgens are critical for development, growth, and maintenance of penile erectile tissue. However, their role in erectile function, especially in humans, remains controversial. Clinical and preclinical studies have suggested that venoocclusion is modulated by the tone of the vascular smooth muscle of the resistance arteries and the cavernosal tissue and a balance between trabecular smooth muscle content and connective tissue matrix. In men with erectile dysfunction, venous leakage is thought to be a common condition among nonresponders to medical management and is attributed to penile smooth muscle atrophy. In the animal model, androgen deprivation produces penile tissue atrophy concomitant with alterations in dorsal nerve structure, endothelial morphology, reduction in trabecular smooth muscle content, and increased deposition of extracellular matrix. Further, androgen deprivation results in accumulation of fat-containing cells (adipocytes) in the subtunical region of the corpus cavernosum. Androgen deficiency diminishes protein expression and enzymatic activity of nitric oxide synthases (eNOS and nNOS) and phosphodiesterase type 5 (PDE5). The androgen-dependent loss of erectile response is restored by androgen administration but not by administration of PDE5 inhibitors alone. These data suggest that androgens regulate trabecular smooth muscle growth and connective tissue protein synthesis in the corpus cavernosum. Further, androgens may stimulate differentiation of progenitor cells into smooth muscle cells and inhibit their differentiation into adipocytes. Thus, we conclude that androgens exert a direct effect on penile tissue to maintain erectile function and that androgen-deficiency produces a metabolic and structural imbalance in the corpus cavernosum, resulting in venous leakage and erectile dysfunction. Traish A, Kim N. The physiological role of androgens in penile erection: regulation of corpus cavernosum structure and function. J Sex Med 2005;2:759–770.

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Introduction

Normal erectile function is dependent upon the health of the penile vascular tissues and the perineal and ischiocavernosus muscles that support the proximal penis. Adequate arterial inflow and trapping of blood within the cavernosal bodies (venoocclusion) is critical for the development of increasing pressure and volume expansion. In addition to arterial blood pressure, contraction of the perineal and ischiocavernosus muscles enhances penile rigidity. The venoocclusive mechanism depends on the integrity of neural, vascular, and endocrine systems, as well as on the fibroelastic properties of the cavernosal tissue. It has been noted that cavernosal tissue from men with erectile dysfunction of various etiologies—whether hormonal, neurological, or vascular—exhibited reduced smooth muscle content and concomitant increase in connective tissue deposition [1,2]. It is likely that such changes in penile tissue structure contribute to venoocclusive dysfunction.
Clinical studies have suggested that surgical or medical castration results in loss of libido and erectile function [3–10]. In a double-blind correlation analysis, Aversa et al. [11,12] studied men with erectile dysfunction without vascular risk factors. The authors noted a strong direct correlation between resistive index values and free testosterone, a relationship that was maintained after adjusting for age, sex, hormone binding globulin, and estradiol. They concluded that men with erectile dysfunction and low free testosterone may have impaired relaxation of penile smooth muscle, thus providing clinical evidence for the importance of androgen in regulating erectile function. In selected men with total testosterone below 10–13 nmol/L and/or free testosterone below 200–250 pmol/L, androgen supplementation improved therapeutic efficacy of phosphodiesterase type 5 (PDE5) inhibitors [13]. In addition, hypogonadal men with confirmed lack of response to sildenafil monotherapy showed greater improvement in erectile function when treated with testosterone [14]. A relationship between restoration of serum testosterone concentrations and improvement in sexual function has been proposed by Seftel et al. [15]. In severe hypogonadal men, testosterone treatment for 6 months induced normalization of nocturnal penile tumescence activity [16]. The authors suggested that testosterone has a key role in the central and peripheral modulation of erectile function even if the specific threshold concentration of plasma testosterone remains to be established.

In laboratory studies using an animal model, Mills et al. [17–21] proposed that androgens are critical for maintaining erectile function and may act specifically to support the responsiveness of the vascular smooth muscle to vasoactive drugs. Baba et al. [22,23] showed that the intracavernosal pressure decreased significantly in castrated animals (vs. control) both after pelvic nerve stimulation and after intracavernosal papaverine injection. More importantly, testosterone replacement restored penile hemodynamics. Testosterone has also been shown to be critical for maintaining the mass of skeletal muscles in the perineum, as well as neuron size [24–26]. In addition to these trophic effects, which are presumed to be due to mechanisms involving transcriptional regulation, androgens may also regulate vascular smooth muscle contractility by nongenomic mechanisms. While these mechanisms have not been investigated in penile cavernosal tissue, testosterone has been shown to relax coronary arteries by activating potassium channels and inhibiting calcium channels [27–29].

One of the least understood aspects of erectile function is the role of androgens in maintaining penile structural and functional integrity. To date, research efforts on the mechanisms by which androgens regulate penile erectile physiology have mainly focused on the role of the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway. However, androgen-dependent mechanisms that regulate tissue remodeling have been poorly defined. The objectives of this review are to summarize the existing data on the effects of androgen deficiency on specific biochemical pathways and tissue structure in the corpus cavernosum and to critically evaluate the potential effects of androgen treatment on penile tissue remodeling and erectile function.

Role of Androgens in Penile Tissue Development

It has been generally recognized that growth and development of the penis is an androgen-dependent process [30,31]. Clinical and preclinical studies indicate that testosterone undergoes conversion to 5α-dihydrotestosterone (5α-DHT) in order to modulate penile erectile growth or physiology. Consistent with this is the observation that the decline in erectile activity in orchietomized rats is prevented by testosterone alone or 5α-DHT alone, but not by coadministration of testosterone and 5α-reductase inhibitor [32]. Further, Choi et al. [33] and Charmandari et al. [34] showed that percutaneous administration of 5α-DHT was successful in promoting phallic growth in infants and children with microphallus due to 5α-reductase deficiency. Gonzalez-Cadavid et al. [35] and Lugg et al. [36] have suggested that 5α-DHT is the active androgen that promotes penile smooth muscle growth and prevents erectile failure in castrated rats. These investigators postulated that these beneficial effects are mediated, at least partially, by modulation of nitric oxide synthase (NOS) via the androgen receptor.

In our studies using male New Zealand white rabbits, we have observed that larger, older animals (4.9 ± 0.2 kg and >8 months of age) exhibit better erectile responses to pelvic nerve stimulation at low frequencies than smaller, younger animals (2.9 ± 0.5 kg and <6 months of age), while no difference was observed at higher frequencies (see Figure 1). This shift in the frequency response is typical for inhibitory modulation. In addition, the erectile tissue from the younger animals had si-
soids that were smaller than those of the older animals (see Figure 2). The New Zealand white rabbit begins sexual maturation at approximately 2 months of age and is considered a mature adult at 6 months when skeletal growth is complete [37–39]. Presumably, the “smaller younger” group in our study consists of adolescent animals, while the “larger older” group consists of fully mature animals. Thus, it may be inferred that penile tissue continues to develop over a prolonged period of time after the initial increase in testosterone levels associated with adolescence and puberty. Cavernosal tissue structure and trabecular smooth muscle function may continue to change during this time to attain optimal function when the animal reaches maturity. These observations support a role for androgens in penile tissue development and functional response to sexual stimulation.

Role of Androgens in Maintaining Erectile Tissue Innervation

Meusburger and Keast [40] have suggested that circulating androgens have potent effects on maintaining the structure and function of many pelvic ganglion neurons. Recently, Keast et al. [41] demonstrated that testosterone is critical for maturation and maintenance of terminal axon density and neuropeptide expression in the vas deferens. However, limited data are available on the role of androgens in maintaining nerve fiber structure and regulating the synthesis and distribution of neurotransmitters in the corpus cavernosum.

Using transmission electron microscopy, Rogers et al. [42] have shown that castration results in ultrastructural changes in the dorsal nerve of the rat. The dorsal nerve from sham-operated animals was filled with both myelinated and nonmyelinated nerve bundles. In tissue from castrated rats, the diameter of both the myelinated and nonmyelinated axons appeared smaller than those of the sham-operated rats. Many nonmyelinated nerve fibers became indistinct and smaller. There was also an increase in the number of nucleated Schwann cells. Testosterone treatment of castrated animals restored the nerve fibers and myelin sheath structure, which were similar to that found in the sham (control) group, suggesting that androgens are important in maintaining peripheral autonomic and sensory nerve structure and function in the penis.

Role of Androgens in Regulating NOS Isoforms in Penile Tissue

The NOS/cGMP pathway has been deemed critical for erectile function. NO mediates relaxation of the vascular smooth muscle of the resistance arteries and the trabeculae in the corpus cavernosum to facilitate penile erection. Numerous stud-
ies have reported that androgens regulate the expression of NOS isoforms in the corpus cavernosum of various species [22,32,43–53]. Orchietomy results in a rapid decrease in serum testosterone and a decreased erectile response to cavernous nerve stimulation. A marked decrease in nicotinamide adenine dinucleotide phosphate, reduced form (NADPH)-diaphorase staining, a marker for neural NOS (nNOS) expression, was also observed. Testosterone administration to orchiectomized animals restored the erectile response and normalized the staining pattern of NADPH-positive nerve fibers [23,45,52].

Western blot analyses and biochemical assays showed that castration of adult male rats reduces by half the activity of penile nNOS and endothelial NOS. These metabolic and physiological changes were restored by androgen administration [47,50,54]. Reilly et al. [55] also demonstrated that the erectile response in the rat penis is androgen-dependent and may be mediated by NO-independent, as well as NO-dependent, pathways. Interestingly, both of these pathways appear to involve the synthesis of cGMP. In other studies, analyses of mRNA for NOS isoforms in penile tissue from intact and castrated rats treated with or without testosterone suggested that androgens enhance nNOS gene expression in the penile corpus cavernosum of rats and that DHT was more potent than testosterone [53].

Aging-related impairment of penile erection can be corrected by administration of exogenous androgens [46]. However, enzymatic and semi-quantitative Western blot assays found no significant variations in either NOS activity or NOS levels between untreated aged rats or those treated with testosterone. Thus, the authors suggested that aging-related erectile dysfunction in the intact rat may be responsive to androgen therapy, but this correction is not associated with an increase in the basal levels of penile nNOS, in contrast with that observed in castrated rats.

**Role of Androgens in the Regulation of PDE5 Expression in Penile Tissue**

PDE5 is the predominant enzyme responsible for cGMP hydrolysis in trabecular smooth muscle. Activation of PDE5 terminates NO-induced, cGMP-mediated smooth muscle relaxation, resulting ultimately in restoration of basal smooth muscle contractility and penile flaccidity. Following sexual stimulation, PDE5 inhibitors act to enhance cGMP-mediated smooth muscle relaxation, resulting in improved penile erection in men with erectile dysfunction.

We have reported that castration resulted in reduced expression and activity of PDE5 in the rabbit model and that androgen treatment upregulated the expression of PDE5 activity [56]. This observation was also confirmed in the rat model in our laboratory (A. Traish, unpublished observation). Using real-time reverse transcript polymerase chain reaction (RT-PCR) and Western blot analyses, Morelli et al. [57,58] have also observed that androgen deprivation reduced PDE5 expression, while testosterone supplementation restored PDE5 gene and protein expression in rabbit corpus cavernosum. In addition, organ bath assays with isolated cavernosal tissue strips showed that androgen deprivation reduced the facilitative effect of sildenafil on neurogenic relaxation, and this facilitation was restored in tissues of castrated animals treated with testosterone. These data suggest that androgens are critical for maintaining normal expression of PDE5 in rabbit penis.

In a separate study, we tested if administration of PDE5 inhibitor to animals that were surgically or medically (LH–RH agonist treated) castrated enhances erectile function in response to pelvic nerve stimulation [59]. Both surgical and medical castration significantly decreased plasma androgen concentration compared with intact control animals. Administration of PDE5 inhibitor 10 minutes before nerve stimulation enhanced erectile function in intact animals. However, administration of PDE5 inhibitor to surgically or medically castrated animals did not enhance erectile function. Taken together, these observations suggest that androgens are critical not only for NOS activity but also for modulating PDE5 activity.

**Role of Androgens in Maintaining Penile Trabecular Smooth Muscle Structure and Function**

Trabecular smooth muscle is an important component of the penis, regulating detumescence and erection [60]. In surgically or medically castrated animal models, we have demonstrated that androgen deprivation results in a significant reduction in trabecular smooth muscle content and marked increase in connective tissue deposition [56,59]. These structural alterations are also associated with loss of erectile function as demonstrated by the reduction in intracavernosal pressure in response to electrical stimulation of the pelvic nerve.
In preliminary studies using transmission electron microscopy, we have noted marked differences in the trabecular smooth muscle from castrated animals compared with that of intact (sham) animals. In castrated animals, the smooth muscle appeared disorganized, with a large number of cytoplasmic vacuoles, whereas in the intact animals, the smooth muscle cells exhibited normal morphology and were arranged in clusters (Figure 3). These observations are supported by the studies of Rogers et al. [42], who assessed the effects of androgen deprivation and supplementation on cavernosal tissues, using quantitative analysis of the smooth muscle content (by alpha smooth muscle actin staining) and transmission electron microscopy. The authors noted that there was no significant difference in the smooth muscle content between intact, castrated, and testosterone-treated castrated animals. However, transmission electron microscopy showed marked differences in the morphology of the smooth muscle cells. In sham-operated rats, the smooth muscle cells were arranged in clusters and separated by fine strands of fibroelastic tissue. The intercellular spaces between myocytes were usually quite narrow, with many gap junctions connecting individual cells, and the cytoplasm contained abundant contractile myofilaments and dense bodies. In contrast, myocytes in cavernosal tissue from castrated animals exhibited larger intercellular spaces and decreased amounts of cytoplasmic myofilaments. Tissue from testosterone-treated castrated rats had myocytes that were similar in appearance to those of sham-operated animals.

These results suggest that androgens have a profound effect on the ultrastructure of the corpus cavernosum and that these alterations may be responsible for the loss of physiological function. However, limited investigations have been made to define the molecular and cellular mechanisms pertaining to changes in penile nerve fibers, trabecular smooth muscle, or connective tissue proteins in response to androgen deficiency and supplementation. In androgen-dependent prostate cancer cells, androgens have been shown to inhibit apoptosis by blocking the activation of caspases, a large family of proteases that play a central role in apoptosis [61]. In other studies using cell lines that express androgen receptor, androgens activate pathways involving phosphatidylinositol 3-kinase and Akt, which can inhibit apoptosis [62]. However, the effect of androgens on these pathways in penile corpus cavernosum have not been examined. A more complete discussion of apoptosis can be found in recent publications [63,64]. In addition to programmed cell death, androgen deficiency may cause changes in smooth muscle cells that pertain to their morphology, orientation, organelle content/function, contacts with connective tissue proteins, and responsiveness to vasoactive substances.

**Role of Androgens in Maintenance of Penile Corpus Cavernosum Fibroelastic Properties**

The extracellular matrix (ECM) is a dynamic cellular scaffold that plays an important role in mod-
ulating tissue physiological function. The ECM regulates cell morphology, movement, growth, differentiation, and survival by regulating cell adhesion, cytoskeletal machinery, and intracellular signaling. The ECM in the corpus cavernosum consists of a network of fibrillar collagen which is intimately connected to the trabecular smooth muscle. Fibrillar collagen types I and III are the major components of the corpus cavernosum collagen matrix [65–67]. Collagen type I represents most of the total collagen protein, while type III collagen is present in lower proportions [65,66]. Collagen types I and III exhibit high tensile strength which plays an important role in the function of the corpus cavernosum during erection and flaccidity [68–70].

Changes in the fibroelastic properties of penile tissue may alter penile compliance and hemodynamics, resulting in erectile dysfunction. Histological studies have shown an association between vasculogenic erectile dysfunction and altered ECM deposition [2,67,71–73]. The severity of erectile dysfunction correlated with a reduced smooth muscle/ECM ratio [73–75]. Furthermore, in animal studies, androgen ablation resulted in a significant reduction of trabecular smooth muscle content and increased connective tissue deposition. These marked structural alterations are associated with loss of erectile function [56,59]. To date, limited studies have investigated the role of androgens in modulating the synthesis, accumulation, and deposition of connective tissue proteins in the penis (e.g., collagens, fibronectin, and elastin). In addition, no data are available on the regulation of growth factors that modulate ECM or metalloproteases by androgens.

The amount, composition, and organization of ECM is maintained or altered by at least three different biochemical processes involving connective tissue proteins (collagens, elastin, fibronectin, etc.): (i) synthesis and post-translational modification; (ii) assembly and cross-linking; and (iii) degradation. ECM deposition is the net result of increased synthesis and reduced degradation (turnover). Gene expression of ECM proteins is regulated by multiple signals including hormones, cytokines, and growth factors. TGF-β1, connective tissue growth factor (CTGF), and vascular endothelial growth factor (VEGF) are thought to play a critical role in ECM remodeling that takes place in normal physiological processes such as embryogenesis, implantation, and wound healing, as well as in fibrosis and scarring by diverse autocrine and paracrine mechanisms in many cell types [76]. A regulatory interplay has been proposed to exist between TGF-β1 and CTGF as well as VEGF and CTGF in remodeling of the ECM [77–83]. Further, cyclic AMP, forskolin, prosta
glandin E2, and tumor necrosis factor alpha have been shown to inhibit the action of CTGF at the transcriptional level [76]. However, to date, no data are available on regulation of these growth factors by androgens in penile tissue.

We postulate that in our androgen-deprived animal model, the changes in penile erectile function may be due to (i) reduced synthesis of paracrine growth factors (e.g., VEGF, fibroblast growth factor, and insulin-like growth factor-I) necessary to maintain the structural and functional integrity of the smooth muscle, endothelium, and nerves; (ii) upregulation of paracrine factors (e.g., CTGF and TGF-β1) which increase expression of connective tissue proteins; and (iii) downregulation of metalloproteinases and upregulation of tissue inhibitors of metalloproteinases, resulting in increased ECM deposition.

Thus, we suggest that androgen deprivation, in the animal model, produces alterations in cellular signaling, structure and function of penile nerves, trabecular smooth muscle, endothelium, and connective tissue. These alterations are manifested as changes in tissue fibroelastic properties that impede expandability of the corpus cavernosum, causing reduced blood inflow and failure of the venoocclusive mechanism, contributing to erectile dysfunction (Figure 4).

**Role of Androgens in Regulating Adipocyte Accumulation in the Subtunical Region of the Corpus Cavernosum**

In addition to the changes in connective tissue and smooth muscle, histological examination of penile tissue sections from orchiectomized animals stained with hematoxylin and eosin or Masson’s trichrome revealed clusters of “empty” cellular structures in the subtunical region of the corpus cavernosum that were distinct from cavernous spaces. These hollow cells resembled adipocytes and were consistently present in tissue from orchiectomized animals but absent in tissue from control animals. Because normal processing of paraffin-embedded tissue with organic solvents results in removal of fat droplets, we fixed penile tissue in glutaraldehyde and postfixed with osmium tetroxide, which binds to unsaturated lipids and results in a brown or gray-black stain. When tissues were embedded in epoxy resin and sectioned, we observed large lipid droplets that
were stained with osmium tetroxide, verifying the subtunical cells were indeed adipocytes (Figure 5). These alterations in cavernosal tissue composition and structure are accompanied by a reduced erectile response to pelvic nerve stimulation. It is interesting to note that because venoocclusion depends on the compression of the subtunical venules to impede blood outflow during sexual stimulation, it is possible that the presence of fat cells in the subtunical region of the corpus cavernosum may contribute to venous leak in the orchiectomized animal [84].

Previous studies in the intact rabbit have noted that administration of the endocrine disruptors, bisphenol A and tetrachlorodibenzodioxin (TCDD), which may act as antiandrogens in the corpus cavernosum, resulted in an abnormal deposition of fat-containing cells in the subtunical region of the corpus cavernosum [85,86]. Organ bath studies using cavernosal tissue from bisphenol A and TCDD-treated animals showed a reduced relaxation response to nitroprusside and acetyl-

![Figure 4](image1.jpg)

**Figure 4** Working model of androgen action in the corpus cavernosum. This framework proposes that androgens are critical for maintaining the structure and function of penile erectile tissue. Thus, androgen deprivation may result in smooth muscle atrophy and apoptosis, altered nerve and endothelial growth, and increased deposition of extracellular matrix (ECM). We suggest that androgens may be required for maintaining an appropriate balance of paracrine and autocrine growth factors (CTGF, VEGF, TGF-β, NO). In addition, androgens may regulate the proteases that are involved in the dynamics of ECM accumulation and deposition (MMPs and TIMPs). Androgen-sensitive changes in the production of growth factors and ECM constituents most likely occur early in relation to changes in cell growth/atrophy/apoptosis and ECM deposition, which occur later in the remodeling process. Thus, androgen deprivation may lead to overexpression of ECM and atrophy of smooth muscle, dysfunction of some or all of the cellular components (nerve, smooth muscle, endothelium), resulting in erectile dysfunction. Furthermore, these adverse changes may be reversible with androgen supplementation.

![Figure 5](image2.jpg)

**Figure 5** Appearance of adipocytes after androgen deprivation. Mature New Zealand white rabbits were left intact or orchiectomized. After 2 weeks, penile cavernosal tissues from intact (A) or orchiectomized (B) animals were fixed, embedded, and sectioned for light microscopy, as described in Figure 2, and stained with hematoxylin and eosin. Tissue samples from orchiectomized animals were also processed in parallel for transmission electron microscopy (C), as described in Figure 3. Arrows in panel B denote “hollow” cellular structures in the subtunical region.
choline. In other studies, neonatal rats exposed to the estrogen receptor agonist, diethylstilbestrol, showed accumulation of fat-containing cells in the penile corpus cavernosum, whereas animals treated with vehicle exhibited no fat-containing cells [87,88]. The authors suggested that estrogen treatment, coupled with low plasma androgen levels, may have contributed to alterations in penile morphology, infertility, and erectile dysfunction [87,88]. Because estrogens are known to act as antiandrogens, these studies point to the potential role of androgens in maintaining penile corpus cavernosum structural integrity.

The mechanism by which androgens regulate growth and differentiation of trabecular smooth muscle cells and/or adipocytes in the penis remains poorly understood. Bhasin et al. [89] proposed that androgens promote the commitment of pluripotent stem cells into a muscle lineage and inhibit their differentiation into an adipocyte lineage. In a recent study, Singh et al. [90] have shown that differentiation of pluripotent cells is androgen-dependent. Both testosterone and DHT decreased the number of adipocytes and downregulated the expression of the adipogenic markers PPAR-γ2 and C/EBPα. However, these mechanisms have yet to be investigated in tissue or cells from the corpus cavernosum. It is possible that pluripotent stem cells are present in the corpus cavernosum and that these cells respond to androgen deprivation by differentiation into an adipogenic lineage.

Another possibility is the dedifferentiation of the corpus cavernosum trabecular smooth muscle cells into other phenotypes. Corradi et al. [91] have shown that inhibition of 5α-reductase activity induces stromal remodeling and smooth muscle dedifferentiation in the prostate, suggesting that 5α-DHT deficiency promotes smooth muscle dedifferentiation. While in several experimental systems vascular smooth muscle was shown to undergo dedifferentiation into other phenotypes [92,93], there are no data in the literature on the dedifferentiation of the trabecular smooth muscle in the corpus cavernosum. Future studies using expression of muscle-specific biochemical markers as well as changes in ultrastructure, as determined by electron microscopy, will be needed to test this possibility in the corpus cavernosum under androgen deprivation and supplementation.

Summary and Perspective

The effects of androgens on erectile physiology are complex. We suggest that in the corpus cavernosum, androgens regulate (i) the expression and/or activity of NOS isoforms, phosphodiesterases, and ion channels; (ii) the growth and state of differentiation of smooth muscle cells; (iii) connective tissue metabolism; and (iv) the differentiation of progenitor stromal cells into myogenic and adipogenic lineages. Much of the data on mechanistic alterations influenced by androgens are necessarily obtained through animal studies. Many of these studies rely on castrated animal models that cause almost immediate and severe androgen depletion vs. the gradual decline that occurs in most men. Interestingly, a recent study demonstrated a dose-dependent effect of testosterone on changes in overall sexual function and self-reported waking erections in men between the ages of 60 and 75 years [94]. While some investigators have used aging animal models in laboratory studies, further investigation of the effects of multiple doses of androgens (ranging from subphysiological to physiological) is required. In summary, androgen deficiency is likely to affect multiple cellular components and molecular pathways to adversely change the structural and functional integrity of penile corpus cavernosum.

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