The Effects of Chronic 5-Alpha-Reductase Inhibitor (Dutasteride) Treatment on Rat Erectile Function

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ABSTRACT

Introduction. Numerous clinical series have reported an association between 5-alpha-reductase inhibitors (5ARIs) and sexual dysfunction, but there are limited preclinical data available.
Aim. To further investigate the mechanisms of erectile dysfunction (ED) related to 5ARI therapy using a rat model.
Main Outcome Measures. Outcome measures include serum dihydrotestosterone (DHT), relaxant and contractile properties of cavernosal muscle, and nitric oxide synthase expression.
Methods. Twenty adult male Sprague-Dawley rats were randomized into control (N = 10) and dutasteride (0.5 mg/rat/day, in drinking water, N = 10) groups. Serum samples were obtained at baseline, from which DHT was measured after 30 days of treatment via radioimmunoassay (Beckman Coulter, Fullerton, CA, USA). Before the terminal blood draw, erectile response was measured using cavernosal nerve stimulation. The relaxant and contractile properties of cavernosal muscle strips were evaluated in tissue baths, and immunohistochemical (IHC) staining for nitric oxide synthase (NOS) and collagen deposition was performed.
Results. Mean serum DHT was suppressed by 86.5% (range 64.2–94.8%) after 30 days of 5ARI treatment and was statistically significant ($P = 0.0024$). In vivo erectile response in the dutasteride treated group decreased significantly compared with control ($P < 0.001$). While electrical field stimulation (EFS)-induced and acetylcholine-induced relaxation was decreased, EFS-induced and phenlyephrine-induced adrenergic contraction was significantly enhanced in the dutasteride group ($P < 0.01$). IHC studies demonstrated increased collagen deposition in the treatment arm as well as altered expression of neuronal NOS (nNOS) and inducible NOS (iNOS).
Conclusions. The 5ARIs, as demonstrated in these rat cavernosal smooth muscle studies, have a detrimental effect on erectile function. Enhanced iNOS expression may protect penile smooth muscle from fibrosis. The effect of 5ARIs on human sexual function warrants further investigation. **Pinsky MR, Gur S, Tracey AJ, Harbin A, and Hellstrom WJG. The effects of chronic 5-alpha-reductase inhibitor (dutasteride) treatment on rat erectile function. J Sex Med 2011;8:3066–3074.**

Key Words. Dutasteride; Erectile Function; 5-Alpha Reductase Inhibitors; Benign Prostatic Hypertrophy; Dihydrotestosterone; Sexual Dysfunction

Introduction

Benign prostatic hyperplasia (BPH) is prevalent among middle-aged and elderly men, affecting as many as 75% of men over 50 years old [1]. The 5-alpha-reductase inhibitors (5ARIs) are frequently used in the treatment of BPH and may cause sexual dysfunction. While the rate of erectile dysfunction (ED) in clinical trials with 5ARIs has been reported to vary from 5% to 9%, it is still a difficult clinical issue that physicians must deal with. ED, or any sexual dysfunction for that matter, can have dramatic effects on a man's quality of life, self-esteem, and ability to maintain intimate relationships [2].

There are two isoforms of 5-alpha reductase: type 1 and type 2. Dutasteride (Avodart, Glaxo Smith Kline, Philadelphia, PA, USA), is one of the two oral 5ARIs in clinical use for the treatment of men with BPH [3,4]. This agent suppresses both

isoenzymes and diminishes circulating dihydrotestosterone (DHT) by more than 90%. In clinical trials, 5ARIs have been associated with an increased incidence of ED, ejaculatory dysfunction (EjD), and decreased libido [2]. The initial clinical report on the potency of dutasteride established adverse sexual side effect rates of 7.3% for ED, 4.2% for diminished libido, and 2.2% for EjD [5].

Nitric oxide (NO) and its synthetic enzyme NO synthase (NOS) are major mediators of erectile function. Androgens increase NOS expression in the penile corpus cavernosum of rats, and DHT is much more effective at increasing NOS expression than testosterone [6]. The deleterious effect of dutasteride on sexual and erectile function is perhaps linked to the reduction in DHT associated with its use, thereby decreasing levels of NO and NOS in the corpus cavernosum.

Although a number of clinical trials have linked 5ARIs and sexual dysfunction [7,8], there has been little investigation into the mechanisms of the sexual side effects related to the use of these medications. Given the lack of available preclinical data, the goal of this study was to investigate the mechanisms of these recognized side effects by assessing different parameters of erectile function in 5ARI-treated rats. Further elucidation of the processes involved may develop new strategies for the prevention and treatment of ED in clinical practice.

Materials and Methods

Animals and Treatment

A total of 20 adult male Sprague-Dawley rats were divided equally into two groups. Group 1 rats (control, N = 10) were given normal drinking water. Group 2 rats were administered dutasteride (0.5 mg/rat/day, in drinking water, N = 10) for 4 weeks. All experiments were conducted under the standard procedure guidelines of The Tulane University Internal Animal Care and Use Committee.

Serum DHT Measurement

Blood samples were obtained from each rat before and after 4 weeks of treatment. These samples were used to recover and measure DHT by radioimmunoassay (DSL-9600 Active DHT, Beckman Coulter, Fullerton, CA, USA).

In Vivo Evaluation of Erectile Function

The rats were anesthetized with sodium pentobarbital (50 mg/kg), the trachea was cannulated to maintain a patent airway, and the carotid artery was cannulated for measurement of mean arterial pressure (MAP, mm Hg) using a transducer attached to a data acquisition system (Biopac MP 100 System, Santa Barbara, CA, USA). A pressure transducer was also used to continuously measure intracavernosal pressure (ICP) via PE-50 tubing inserted into the right crura of the penis. The right major pelvic ganglion and cavernosal nerve were identified, and a stainless steel bipolar hook stimulating electrode was placed around the cavernosal nerve posterolateral to the prostate. MAP and ICP were continuously measured, and the cavernosal nerve was stimulated at a voltage of 5 Hz with a 30-second pulse width using a square wave stimulator (Grass Instruments, Quincy, MA, USA).

Measurement of Isometric Tension in Corpus Cavernosum Smooth Muscle (CCSM) Strips

After appropriate anesthesia, the penis was removed and placed in a Krebs-bicarbonate solution (containing in mM: NaCl: 118.1, KCl: 4.7, KH_2PO_4: 1.0, $MgSO_4$: 1.0, $NaHCO_3$: 25.0, $CaCl_2$: 2.5, and glucose: 11.1 pH) and subsequently exposed to a 95% O_2/5% CO_2 gas mixture. The CCSM tissue strips (1 × 1 × 6 mm) were dissected off and mounted under 1 g of resting tension in 20 mL organ bath chambers. The CCSM strips in the tissue bath were attached to an electrode holder on one end, through a wire to a force transducer on the other end, and were allowed to equilibrate for 60 minutes at 37°C.

In the first series of experiments, electrical field stimulation (EFS) was delivered as a train of square-wave pulses (pulse width 0.5 ms, intensity 20 V) at frequencies of 1–20 Hz across paired platinum electrodes placed on either side of the tissue strips. For EFS response curves, the CCSM strips were preincubated for 30 minutes with guanethidine (5 μM) to eliminate noradrenergic influences, and atropine (1 μM) to prevent cholinergic responses. After phenylephrine (Phe) precontraction under these conditions, EFS produced only relaxation responses mediated by non-adrenergic, non-cholinergic (NANC) fibers.

In the second series of experiments, relaxation induced with acetylcholine (ACh, 10^{-8}–10^{-3} M), sodium nitroprusside (SNP; 10^{-8}–10^{-3} M), and sildenafil (10^{-8}–10^{-3} M) were evaluated after precontraction with Phe (10 μM). In addition, cumulative dose-response curves for contractions induced by Phe (10^{-8}–10^{-3} M) were evaluated.

In the third series of experiments, EFS was conducted at 70 V, 1 ms pulse width, and trains of stimuli lasting 10 seconds at varying frequencies