Tadalafil Enhances the Inhibitory Effects of Tamsulosin on Neurogenic Contractions of Human Prostate and Bladder Neck

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ABSTRACT

Introduction. Lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH-LUTSs) may be associated with erectile dysfunction (ED). Phosphodiesterase type 5 (PDE5) inhibitors used for treating ED have shown clinical benefit in patients with LUTS but their actions in human LUT tissues are not well defined.
Aim. To determine the effects of the long-acting PDE5 inhibitor, tadalafil, on smooth muscle tone in human prostate and bladder neck as well as to evaluate the influence of tadalafil on the efficacy of the α-adrenergic receptor antagonist, tamsulosin, in inhibiting contractile responses in these tissues.
Methods. Strips of human peripheral prostate (HPP), human internal prostate (HIP), and human bladder neck (HBN) were obtained from organ donors and patients with BPH. The strips were then disposed in organ baths to evaluate nitric oxide/cyclic guanosine monophosphate (cGMP)-mediated relaxation and cGMP kinetics in HPP and HIP, and electrical field stimulation (EFS)-induced neurogenic contractions in HPP and HBN.
Main Outcome Measures. Tadalafil-induced effects on sodium nitroprusside (SNP)-induced relaxation and cGMP accumulation in HPP and HIP and influence of tadalafil and tamsulosin on EFS-induced contractions of HPP and HBN.
Results. SNP-induced relaxation of HPP and HIP was significantly potentiated by tadalafil (30–60 nM). SNP-induced cGMP accumulation in HPP and HIP was enhanced by tadalafil (30–60 nM), but significant difference was only obtained in HPP. EFS-induced contractions sensitive to tetrodotoxin in HPP were significantly inhibited by tadalafil (30 nM) but not by tamsulosin (0.01–100 nM) or vehicle. Further inhibition of neurogenic responses in HPP was achieved by combining tadalafil and tamsulosin treatments. Tamsulosin, but not tadalafil, significantly reduced EFS-induced contractions in HBN, but the coadministration of both therapies resulted in additional inhibition of contractions.
Conclusions. While tadalafil enhances cGMP accumulation and potentiates prostate relaxation, tadalafil combined with tamsulosin results in enhanced inhibition of neurogenic contractions of HPP and HBN. **Angulo J, Cuevas P, Fernández A, La Fuente JM, Allona A, Moncada I, and Sáenz de Tejada I. Tadalafil enhances the inhibitory effects of tamsulosin on neurogenic contractions of human prostate and bladder neck. J Sex Med 2012;9: 2293–2306.**

Key Words. Benign Prostatic Hyperplasia; Erectile Dysfunction; Lower Urinary Tract Symptoms; Phosphodiesterase Type 5 Inhibitors; Tadalafil; Tamsulosin

Introduction

Lower urinary tract symptoms (LUTSs) secondary to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) are prevalent conditions, especially in the aging man, where these bothersome diseases often coincide [1]. Increasing age may help explain why BPH and ED often share common risk factors such as atherosclerosis and reduced oxygenation of the lower urinary tract

[2]. BPH-LUTS is a chronic condition that currently is mitigated by the treatment of daily alpha-blockers, 5-alpha-reductase inhibitors, or the combination of both. While phosphodiesterase type 5 (PDE5) inhibitors have proven their efficacy in the treatment of men with ED, the ongoing research are now investigating the impact of daily treatment on BPH-LUTS. The only PDE5 inhibitor currently approved for once daily treatment of ED is tadalafil with a t1/2 of 17.5 hours. In placebo-controlled clinical studies, enrolling men with BPH-LUTS (International prostate symptom score [IPSS] $\geq$ 13) and bladder outlet obstruction (peak flow 4–15 mL/second) once daily tadalafil resulted in symptom improvement but without a significant change in urinary peak flow [3–5]. Thus, the mechanisms responsible for the clinical effects of tadalafil on LUTS are under debate.

The expression of PDE5 has been confirmed in human prostate [6], urethra [7], and bladder [8], and the PDE5 inhibitor is one of the main enzymes hydrolyzing cyclic guanosine monophosphate (cGMP), which is a key step in nitric oxide (NO)/cGMP pathway regulation [2,9]. Nitrergic innervation has been observed in close relation with stromal smooth muscle cells and glandular structures [10], and nitrergic signaling has been detected in nerve fibers interspersing the transition zone and traversing the fibromuscular stroma as well as in glandular epithelium and subepithelial nerve plexus [11,12]. Positive staining for the endothelial NO synthase (NOS) was found in endothelial cells of small vessels supplying the prostate [12]. Human bladder neck was also found to contain a high density of neurons with positive immunoreactivity for NOS [13].

As NO signaling regulates the smooth muscle tone of the bladder neck, urethra [14], and prostate [12], the aim of this in vitro study was to ascertain the influence of tadalafil alone or in combination with an α_1-adrenergic receptor antagonist on human prostate and bladder neck contractility.

Methods

Human Tissue Harvesting

Specimens were obtained from 17 organ donors at the time of organ collection for transplantation as well as from 30 patients who underwent suprapubic adenomectomy (Millin's approach) for BPH. In this case, a transverse incision in the prostate capsule was made across the anterior surface. A little piece of prostate tissue from this incision (7×5 mm approximately) was carefully excised. One or several strips from peripheral prostate were obtained from this piece for using in organ chamber studies. In this surgical procedure, a little wedge of bladder neck was also resected, which was used to obtain one or several bladder neck strips. Organ donors were free of urological disease. All experimental groups included similar proportion of tissues from organ donors and BPH patients. The study complies with Spanish regulation regarding human tissue collection, conservation, and elimination, and the protocols were approved by the Ethics Committees at the hospitals where the tissues were collected in both Spain and Portugal. Patients provided their informed consent for being included in the study. Mean age of patients was 61.7 $\pm$ 2.5 years (range 21–80 years). Tissues were placed in ice-cold M-400 solution (pH 7.4; 400 mOsm/kg, composition in w/v: 4.19% manitol, 0.2% KH_2PO_4, 0.97% $K_2HPO_4 \cdot 3\ H_2O$, 0.11% KCl, and 0.08% $NaHCO_3$) and transported to the laboratory for utilization within 24 hours.

Preparation of Tissues in Organ Bath

Human prostate specimens were cleaned of fat and connective tissue. Peripheral and internal prostate tissues were separated, containing, respectively, the capsule and external smooth muscle layers of the prostate (peripheral) and glandular structures and internal smooth muscle layers of the prostate (internal prostate). Then, both peripheral and internal prostate contained the anatomical structure known as transition zone but also maintaining capsule and glandular structures, respectively, which were not removed to preserve nerve terminals as much as possible. Tissues were cut into strips for organ bath assays. Human bladder neck specimens were cleaned of fat and connective tissue and cut into strips without compromising the integrity of the urothelial layer. Strips of human prostate and bladder neck were mounted on force transducers in 8 mL organ baths containing physiological salt solution (PSS), which consists of the following composition (mM): NaCl 119, KCl 4.6, $CaCl_2$ 1.5, $MgCl_2$ 1.2, $NaHCO_3$ 24.9, glucose 11, KH_2PO_4 1.2, and ethylenediaminetetraacetic acid (EDTA) 0.027 at 37°C continuously bubbled with 95% O_2/5% CO_2 mixture to maintain a neutral pH of 7.4. Prostate and bladder strips were submitted to a resting tension of 1.5 g and then left for equilibration for 90 minutes with extensive washouts. Tissues were subsequently exposed to 125 mM K^+ (equimolar substitution of NaCl for KCl in PSS) and contractile responses were measured.