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Tadalafil for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: Pathophysiology and Mechanism(s) of Action

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Background: The PDE5 inhibitor tadalafil is under investigation for the treatment of lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). Several clinical studies of tadalafil and other PDE5 inhibitors have reported significant symptom reduction but limited urinary flow rate improvement. This manuscript reviews the published literature describing the pathophysiology of male LUTS, with an emphasis on mechanisms that may be modulated or improved by phosphodiesterase type 5 (PDE5) inhibition. **Methods:** Literature (through March 2010) was obtained via Medline searches and from the individual reviewers files. Articles were selected for review based on describing in vitro, preclinical, or clinical studies of pathological processes contributing to LUTS, or possible effects of PDE5 inhibition in the lower urinary tract. **Results:** Major mechanisms contributing to LUTS include: reduced nitric oxide/cyclic guanosine monophosphate signaling; increased RhoA kinase pathway activity; autonomic overactivity; increased bladder afferent activity; and pelvic ischemia. Tadalafil and other PDE5 inhibitors have demonstrated beneficial effects on smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion that may impact LUTS in men. **Conclusions:** The pathophysiology of male LUTS is complex and not completely understood. LUTS may occur independently of BPH or secondary to BPH but in both cases involve obstructive or irritative mechanisms with substantial pathophysiological overlap. While the precise mechanism remains unclear, inhibition of PDE5 seems to have an effect on several pathways that may impact LUTS. *Neurourol. Urodynam. 30:292–301, 2011.* © 2011 Wiley-Liss, Inc.

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INTRODUCTION

Lower urinary tract symptoms (LUTS) in men become increasingly common with age, reaching a prevalence of 45% or greater for moderate-to-severe LUTS in men over 70 years of age.[1] Symptoms may belong to one of three domains: voiding (obstructive) symptoms (slow stream, splitting/spraying of stream, intermittency, hesitancy, straining, and terminal dribble); storage (irritative) symptoms (frequency, nocturia, urgency, and incontinence); and postmicturition symptoms (feeling of incomplete emptying and postmicturition dribble).[2] The presence of LUTS in men has traditionally been thought to be related to the growth of the prostate, with subsequent urethral compression and obstruction, and secondary bladder irritability; for this reason they are commonly referred to as LUTS secondary to benign prostatic hyperplasia (BPH), or BPH LUTS. However, emerging data increasingly suggest that the etiology of LUTS is highly complex and likely multifactorial. This is highlighted by observations that many men with BPH do not develop LUTS while other men with bothersome urinary symptoms do not have BPH or outlet obstruction.[3] Additionally, voiding and storage LUTS are not gender specific,[4] suggesting potential etiologies for LUTS that are not related to the prostate. Voiding LUTS (in men) are generally caused by outlet obstruction and have been attributed to two components, the physical mass of the enlarged prostate gland (the static component), and the tone

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of the smooth muscle of the prostatic stroma (the dynamic component); the combined effect is referred to as benign prostatic obstruction (BPO). Thus, it is reasonable to expect a relation between voiding LUTS and prostate size, and population-based studies have indeed demonstrated modest correlations between benign prostatic enlargement, BPO, and LUTS.[5] However, even for voiding LUTS, evidence for a direct link is far from convincing, and it is now recognized that such symptoms do not reliably reflect the underlying vesicourethral pathology.[6] Storage LUTS, on the other hand, have been associated with bladder dysfunction, and are often seen secondary to BPO. Storage symptoms, including overactive bladder (OAB), have a close association with underlying detrusor overactivity (DO). Several factors probably contribute to the genesis of DO and associated storage LUTS; these clearly include myogenic and neurogenic factors, but a contribution of the urothelium is also likely.[7,8] Precise mechanisms aside, the balance of experimental evidence increasingly suggests that the bladder has to be considered *the* central organ in the pathogenesis of storage LUTS, not only in women, but also in men. Current evidence thus seems to favor the view that the spectrum of voiding and storage LUTS reflect disorders across the whole of the lower urinary tract and that "LUTS are a non-sex-specific, non-organ-specific group of symptoms, which are sometimes age-related and progressive."[9]

The current standard of care for bothersome BPH LUTS is therapy with an α1-adrenergic blocker (α-blocker), or, in men with an enlarged prostate, a 5α-reductase inhibitor therapy.[10] Although effective, these drugs may be associated with unwanted side effects, including dizziness, hypotension, and sexual dysfunction, which may be exacerbated by combination therapy.[11] Since a link between BPH LUTS and erectile dysfunction (ED) is well supported by studies of their epidemiology, pathophysiology, and treatment,[1,12,13] phosphodiesterase type 5 (PDE5) inhibitors such as tadalafil, sildenafil, and vardenafil have been explored for treating BPH LUTS.[14–16] To date, however, only three clinical studies with primary endpoints focusing on urinary symptoms have been registered in the U.S. for sildenafil and vardenafil combined, with none ongoing as of May 2010 (http://www.clinicaltrials.gov, last accessed May 10, 2010); in contrast, six such studies have been completed for tadalafil, and several other placebo-controlled clinical studies were ongoing. Tadalafil (Cialis®) is currently approved for as-needed and once-daily use in men with ED, and its half-life of 17.5 hours may be beneficial when considering treatment regimens for chronic LUTS. This review thus addresses many findings common to PDE5 inhibitors in general, but focuses in particular on tadalafil as it appears to be the only PDE5 inhibitor under active development as a treatment for LUTS.

In a recent dose-finding study in >1,000 men with moderate to severe BPH LUTS, tadalafil was associated with significant improvements in multiple measures of LUTS and related quality of life compared with placebo.[17] However, those improvements occurred without a significant increase in overall peak urinary flow (Q_{max}), although the tadalafil treatment groups of 2.5, 5, 10, and 20 mg did separate numerically from placebo with percentage changes of 15%, 16%, 17%, and 22%, versus 12%, respectively.[18] Improvements in the different measures of LUTS were maintained in a 1-year, uncontrolled, follow-up study.[19]

When 200 men with moderate to severe BPH LUTS with or without bladder outlet obstruction (BOO) were assessed in an invasive and non-invasive urodynamic study,[20] tadalafil once daily showed no negative impact on bladder function as measured by detrusor pressure at maximum urinary flow rate or any other urodynamic parameter assessed.

Studies of treatment with sildenafil and vardenafil have also found improvements in LUTS in the absence of significant changes in Q_{max}.[14,15] Although the clinical importance of the relatively limited improvements in flow rates observed with α_1-adrenoceptor (AR) blocker or 5α-reductase inhibitor therapy for LUTS[10] remains a subject of debate, the mechanisms by which PDE5 inhibitors might influence LUTS, and the relationship between improvements in LUTS and erectile function, are under investigation. The purpose of this article is to examine the available literature (through March 2010) describing clinical and preclinical studies related to mechanisms that may explain the mode of action of PDE5 inhibitors, with a particular focus on tadalafil, in treating LUTS secondary to clinical manifestations consistent with BPH.

DISTRIBUTION AND PHYSIOLOGICAL EFFECTS OF THE NO/CGMP PATHWAY AND PHOSPHODIESTERASES IN THE LOWER URINARY TRACT

The presence of the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) (NO/cGMP) signaling pathway and various PDEs in the urogenital tract is well established, having been demonstrated in human prostate, pig, guinea pig, and rat urothelium, and rat and sheep urethra.[12,21–24] Signaling occurs through generation of NO by the constitutive NO-synthase (NOS) enzymes: endothelial (eNOS) and neuronal (nNOS) NOS. Nitric oxide has a short half-life (a few seconds) but readily diffuses through cell membranes and thus may function in either autocrine or paracrine signaling. The release of NO stimulates soluble guanylate cyclase to produce cGMP, which regulates protein phosphorylation (notably cGMP-dependent protein kinase 1 [PKG-1]), ion-channel conductivity, and PDE activity. Signaling is modulated in part through inactivation of cGMP by PDEs. In the prostate and urethra, activation of the NO/cGMP pathway is thought to have an effect on both LUT nerves and smooth muscle, where PKG-1 activation leads to dephosphorylation of myosin light chains, thus initiating smooth muscle relaxation. The role of NO/cGMP in the bladder is less clear but the pathway does not seem to have a primary relaxant role.[22]

Localization of NO/cGMP Activity in the Lower Urinary Tract

In the human prostate, the NO/cGMP signal pathway is considered to have important functional roles,[25–27] and all the key enzymes of the pathway, including eNOS and nNOS, PKG-1, and the cGMP-degrading PDE5 have been shown to be expressed in prostate tissue. Neuronal NOS immunoreactivity is localized in the pig urinary tract to nerve fibers of the urethra and to the trigone region, including the bladder neck, where it co-localizes with acetylcholinesterase, vasoactive intestinal peptide, and neuropeptide Y, suggesting that NO may have a role both as a directly acting transmitter and as a modulator of efferent neurotransmission.[28] The urothelium expresses NOS and releases NO in response to various stimuli, as shown by immunohistochemistry studies in guinea pigs and rats,[29–31] and a network of interstitial cells responsive to NO/cGMP has been demonstrated in the lamina propria, in the urethra of sheep,[32] and in the guinea pig detrusor muscle layer.[33]

The significance of NO and cGMP in the control of urethral relaxation has been well demonstrated.[34] In precontracted rabbit smooth muscle urethral preparations, non-adrenergic, non-cholinergic relaxations induced by electrical field stimulation were reversibly abolished by an NOS inhibitor,

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NG-nitro-L-arginine.[34] In female pig urethral preparations, continuous nerve stimulation increased cGMP levels and this effect was significantly reduced by NG-nitro-L-arginine.[35] A wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles has also been reported,[36] and these have been proposed as targets of cGMP-mediated nitrergic neurotransmission.[32] The cGMP immunoreactivity in urethral and vascular smooth muscles from female pigs and humans has been shown to increase after stimulation with NO.[36]

Although NOS containing nerves are present in the bladder, the role of NO in regulating bladder function outside of the bladder neck remains uncertain. Truss et al.[37] found that human detrusor muscle was relatively unresponsive to the NO-donor sodium nitroprusside (SNP) and to other agents acting via the cGMP system. Fujiwara et al.[38] confirmed this result in the mouse bladder but demonstrated a potential functional role for NO as an excitatory neuromodulator, possibly acting on cGMP-positive structures; that is, nerves and stromal cells. Consistent with an excitatory role in the bladder, Kajioka et al.[39] showed that SNP potentiated cGMP-dependent oscillatory inward currents in a small subset (~7%) of isolated pig detrusor muscle strips. The authors suggested that the NO/cGMP pathway might be involved in regulating tonic bladder contractions and proposed that differences in prevalence and organization of NO-responsive smooth muscle cells (SMCs) might contribute to the variable action of the NO/cGMP pathway on bladder tissue observed in different animal models.

Phosphodiesterases

Phosphodiesterases (PDEs) are enzymes that metabolize the second messenger molecules (cyclic adenosine monophosphate [cAMP] and cGMP). The 21 human PDE genes are divided into 11 families based on their protein sequences, catalytic and regulatory considerations, and sensitivity to inhibitors, as well as their cAMP and/or cGMP affinity. Because the distribution and functional significance of PDE isoenzymes vary in different tissues, isoenzyme-selective inhibitors have the potential to exert specific effects on the target tissue. Although mammalian tissues express several members of the PDE families, or more than one variant of an individual family, there are numerous examples of an individual PDE that is dominant at a specific site (e.g., PDE5 in the penis). This implies that by targeting a specific PDE isoenzyme, it should be possible to obtain at least relative organ selectivity. In the LUT, the different PDEs have a varying distribution.

Phosphodiesterases in the prostate. In the human prostate, mRNA transcripts encoding for at least 15 different isoforms of PDE has been demonstrated using molecular biology, biochemical approaches, or immunohistochemistry.[27] The expression of PDE5 was prominent especially in the transition zone. The hydrolytic activity of PDE5 was present in the cytosolic fraction of prostatic tissue. Uckert et al.[40] previously demonstrated the presence of PDE5 (cGMP-PDE) and PDE11 (a cAMP/cGMP dual substrate PDE) in glandular and stromal subglandular areas of human prostatic tissue. Fibbi et al.[41] recently demonstrated PDE5 expression in vascular smooth muscle and endothelial cells of the human prostate and also showed the enzyme to be strongly localized to smooth muscle of the prostatic urethra.

Phosphodiesterases in the urethra. Nitric oxide has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cGMP.[34,36] Nerve-induced relaxations of rabbit and human female urethral preparations were enhanced at low concentrations of sildenafil, vardenafil, and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE5 inhibitors at high concentrations. Strong PDE5 immunoreactivity was demonstrated not only within the SMCs of the urethral wall in the human prostatic urethra, but also in vascular endothelial cells that expressed cGMP immunoreactivity.[41] Prominent expression of PDE5 protein was also recently noted in the urethral striated muscle and levator muscle of female rats.[42]

Phosphodiesterases in the bladder. cAMP seems to be more important than cGMP for detrusor function; hence the cAMP pathway in this tissue has been the most extensively investigated. Truss et al.[43,44] isolated and performed functional studies demonstrating the presence of five PDE isoenzymes (PDEs 1–5) in human and porcine detrusor. Filippi et al.[45] reported that immunoreactivity for PDE5 in human bladder was found primarily in the endothelial and SMCs of the vasculature and in SMCs of muscle bundles; an effect of PDE5 inhibitors in bladder SMCs was supported by observations of relaxation of carbachol-contracted human bladder strips by each of the PDE5 inhibitors, with the strongest effect seen for vardenafil. Werkstrom et al.[46] studied effects of the PDE5 inhibitor, vardenafil, on contraction and cyclic nucleotide levels in isolated rat detrusor. They found that in preparations with and without mucosa, vardenafil relaxed carbachol-induced contraction and inhibited contractions induced by electrical field stimulation of nerves. Relaxation was accompanied by increases in both cAMP and cGMP content, and it was proposed that vardenafil-induced relaxation of rat detrusor was mediated via cAMP through inhibition of a cGMP-dependent cAMP-PDE. Preparations of the human bladder neck contracted by phenylephrine were also effectively relaxed by sildenafil at high concentrations,[47] suggesting that PDE5 inhibitors may have the potential to relax the outlet region.

Phosphodiesterases in LUT vasculature. The presence of PDE5 has been demonstrated in several parts of the LUT vasculature. Substantial expression of PDE5, as evidenced by immunostaining, was shown in the vascular smooth muscle and endothelial cells of the human prostatic urethra, prostate, and bladder neck.[41,45] Expression of PDE5 in human and pig urethral sections was shown by immunohistochemical staining to be localized to SMCs of the wall of larger arteries and to endothelial cells lining the arterial lumen; in smaller arteries PDE5 was localized only to the endothelium.[36] Thus increases in cGMP via PDE5 inhibition may be important for LUT vasculature relaxation.[22]

PATHOPHYSIOLOGY

The pathophysiology of LUTS in men is complex and most likely involves numerous mechanisms affecting the prostate, urethra, and bladder, as well as the pelvic neuronal and vascular networks supporting the LUT. Below, we review the available data for each of these potential mechanisms; risk factors associated with LUTS (and ED) in epidemiological studies[48–50] are summarized in Table I, while pathophysiological pathways leading to LUTS are shown in Figure 1.

Reduced NO/cGMP Activity

Nitric oxide has a general inhibitory effect on LUT smooth muscle tone; lack of NO could therefore be a contributor to

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TABLE I. Selected Risk Factors for LUTS and/or ED Identified in Epidemiological Studies (48–50) and Possible Pathological Mechanisms

Risk factor/comorbid conditions	Mechanism
Age	Vascular dysfunction Reduced eNOS signaling Increased ROCK signaling
Diabetes, metabolic syndrome, obesity, sedentary lifestyle	ANS overactivity Insulin/IGF growth stimulation Vascular dysfunction
Atherosclerotic cardiovascular disease, hypertension	Vascular dysfunction Reduced eNOS signaling ANS overactivity
Inflammatory conditions	Epithelial/stromal cell secretion of IL-8 and other cytokines

LUTS, lower urinary tract symptoms; ED, erectile dysfunction; eNOS, endothelial nitric oxide synthase; ROCK, RhoA/Rho kinase; ANS, autonomic nervous system; IGF, insulin-like growth factor; IL-8, interleukin-8.

LUTS. A reduction in the local nitrergic innervation of the prostate in men with BPH and, thus, a decrease in the NO-mediated relaxation of prostatic smooth muscle, could impact the pathophysiology of LUTS.[51] In the detrusor, the role of the NO/cGMP pathway remains to be fully clarified; however, in animal models, inhibition of NO synthesis, scavenging of NO, inhibition of soluble guanylate cyclase, and knock out of PKG-1, the mediator of cGMP actions, all cause increased bladder activity in vivo.[52–55] The NO/cGMP pathway is also known to influence SMC proliferation and excessive SMC proliferation in the prostate and bladder may contribute to LUTS.[56] Additional pathophysiological roles of reduced NO/cGMP activity are discussed below.

Increased Rho-Kinase Activity

Decreased smooth muscle relaxation in the prostate, urethra, bladder neck, and/or penis resulting in increased bladder outlet resistance and impaired erection have been attributed in part to increased activation of the calcium-sensitizing RhoA/Rho kinase (ROCK) pathway, which mediates smooth muscle contraction by modulating the activity of myosin phosphatase.[57–59] Pelvic ischemia and/or atherosclerosis have been associated with upregulation of this ROCK pathway,[12] which is believed to play an important role in regulating urethral and bladder tone and contraction, as well as involuntary bladder contractions associated with increased signaling.[57]

Autonomic Nervous System Overactivity

An important link between autonomic nervous system (ANS) overactivity and LUTS related to BOO is supported by both animal and human data. This impact may be direct, since sympathetic overactivity can cause elevation of smooth muscle tone in the prostate and bladder neck; treatments such as alpha-adrenergic receptor (α_1-AR) blocking agents are routinely used to counteract this effect. The ANS also has an under-appreciated, yet definite role in regulating prostate growth under both normal and abnormal conditions and elevated catecholamines have also been shown to decrease rates of apoptosis of prostatic cells in mice,[60] which suggests a mechanism that could be relevant to BPH.

An epidemiological link between ANS overactivity and LUTS has been demonstrated. Meigs et al.[61] reported that BPH LUTS was frequently associated with factors related to sympathetic activation, specifically heart disease, beta-blocker use, and a sedentary lifestyle. Hammarsten and Hogstedt[62] found that faster-developing BPH was associated with disorders related to sympathetic overactivity, including obesity, increased insulin levels, increased risk of type 2 diabetes, and hypertension. A recent epidemiological study reported an association between voiding LUTS and factors specifically related to elevated blood sugar in metabolic syndrome.[63] These findings are supported by work from Vikram et al.[64] showing that rats fed a high-fat diet (HFD) developed elevated blood sugar and hyperinsulinemia accompanied by significantly increased prostate weight. The β-cell toxin streptozotocin reduced prostate weight of HFD rats to below levels of controls while pioglitozone normalized both insulin levels and prostate weight; the contractile response to α1- and α2-AR agonists also increased significantly in prostatic tissue from HFD compared to control rats. Thus, hyperinsulinemia in rats led to increased cellular proliferation, enhanced α-AR-mediated contraction, and enlargement of the prostate.

Autonomic overactivity (AO) was strongly correlated to LUTS secondary to BPH using direct measurements of sympathetic activity, such as tilt tests, in men with well-characterized LUTS from BPH; these associations remained significant even after adjusting for AO-related factors.[65] Other investigators have verified this relationship using heart rate variability measurements.[66,67]

Previous investigations in rat models[68,69] support a significant role of the ANS in promoting both prostatic hyperplasia and atrophy based on selective neural manipulations (reviewed in Ref. 70). These findings were corroborated by subsequent studies using spontaneously hypertensive rats (SHRs), which were shown to develop increased autonomic activity, prostatic hyperplasia, LUTS, and ED.[71,72] The SHRs had an overabundance of sympathetic fibers innervating the bladder, prostate, and penis.

Enhanced Afferent Nerve Activity

Limited information is available about the impact of afferent nerve activity from the urethra and especially the prostate on LUTS; however, an important role for bladder afferent pathways is recognized. Afferent innervation of the bladder occurs primarily through small myelinated (A-delta, Aδ) and unmyelinated (C-fiber) axons responsive to chemical and mechanical stimuli. Bladder afferent neurons have been shown to synthesize NO and other putative neurotransmitters and alterations in either the degree of afferent innervation or in afferent nerve responsiveness may lead to LUTS.[73]

Neural plasticity in bladder afferent and bladder reflex pathways has been demonstrated following partial urethral obstruction rats. Bladders were enlarged and showed significant increases in the size of bladder afferent and postganglionic efferent neurons.[74] Remodeling of the spinal cord components of the micturition reflex pathway was also evident as bladder afferent terminals expanded in the lateral dorsal horn and in the region of the sacral parasympathetic nucleus. Steers et al. further demonstrated the presence of increased levels of nerve growth factor (NGF) protein in hypertrophic versus normal rat bladders,[75] and then demonstrated that endogenous antibodies to NGF blocked the hypertrophy of both bladder sensory neurons and the increase in afferent projections in the spinal cord.[76]

Increased NGF production in the bladder is due in part to stretch of the bladder secondary to urinary retention.[75] Substantial (40- to 100-fold) increases in levels of urinary NGF have been detected in BOO patients exhibiting OAB

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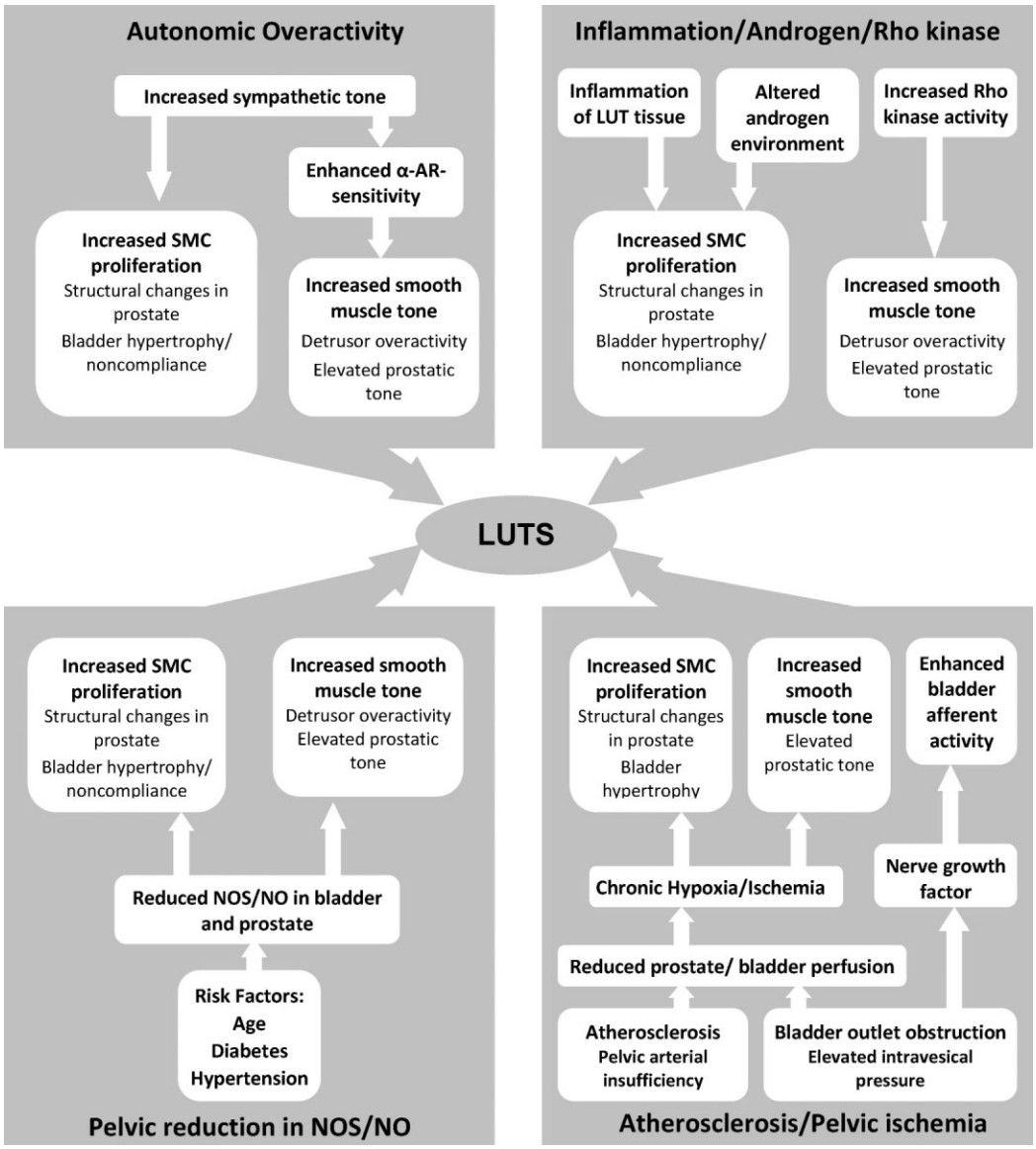


Fig. 1. Potential pathways leading to LUTS in men. Structural changes in the prostate and elevated prostatic tone may lead directly to the obstruction of urinary flow, classically considered to be symptomatic of BPH LUTS. Note that outlet obstruction may lead to enhanced afferent activity and thus to storage LUTS. Additional indirect interactions (i.e., a role for inflammation in pelvic ischemia) are discussed in the text.

symptoms compared to controls and even compared to patients with BOO but without OAB symptoms;[77] urinary NGF levels returned to near normal following successful medical treatment with a combination of an α1-AR blocker and a 5α-reductase inhibitor. Patch clamp recordings from bladder sensory neurons in rats with BOO showed increased amplitude and altered kinetics of tetrodotoxin-sensitive Na+ currents, resulting in lowered firing thresholds.[78]

Atherosclerosis and Ischemia of the Lower Urinary Tract

A strong association has been demonstrated between BPH, LUTS, and risk factors for atherosclerosis such as hypertension, diabetes, and heart disease.[49,62] Atherosclerosis is strongly associated with ED,[79,80] and reduced perfusion of the prostate and bladder has been shown in association with LUTS in men.[81] The association between vascular disease, prostatic perfusion, and LUTS has been assessed through Doppler ultrasound techniques in humans. Berger et al.[82] found significantly reduced perfusion of the LUT in men at high risk for LUTS. In men with diabetes or peripheral arterial occlusive disease, perfusion in the transition zone of the prostate was significantly reduced and LUTS was significantly worse, compared to healthy controls.

The link between atherosclerosis and/or pelvic ischemia and LUTS has been demonstrated with cellular and animal models of LUTS and is supported by clinical data as well. One factor contributing to vascular dysfunction in the LUT may be age-related reductions in eNOS signaling (reviewed in Ref. 13), which might contribute to the strong association observed between aging and LUTS. Another proposed mechanism to describe the link between cardiovascular dysfunction and

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LUTS is that ischemia in the LUT leads to activation of the hypoxia inducible factor (HIF) pathway, leading to reduced cellular apoptosis and overexpression of various growth factors in the prostatic capsule and stroma.[83] Human prostate cell lines subjected to hypoxic conditions demonstrate rapid increases in HIF-1α activity, followed by induction of numerous factors known to stimulate endothelial and SMC growth, such as vascular endothelial growth factor (VEGF), transforming growth factor-β and interleukin-8 (IL-8).[84] Du et al.[85] identified frequent (n = 19/28, 68%) positive immunostaining for HIF-1α in prostate tissue from men with BPH; in contrast, no HIF-1α immunostaining was detected in tissue from 13 healthy controls. Intriguingly, Lekas et al. showed that finasteride treatment reduced levels of HIF-1α (−71%) and VEGF (−60%) in resected prostate tissue, and also reduced microvessel density and bleeding during surgery, when administered for a mean of 23 weeks prior to surgery. The magnitude of the reductions was strongly associated with duration of finasteride dosing, with the effect first becoming significant after 10 weeks of treatment, prior to any improvements in international prostate symptom score (IPSS).[86] Thus, 5α-reductase inhibitors could reduce prostate size in part through decreasing levels of HIF-1α and other hypoxia-related growth factors, which may otherwise contribute to hyperplastic growth of prostatic tissue. Further research is clearly needed to elucidate the mechanisms involved. Notably, in a rabbit model, chronic prostatic ischemia also increased contractile responses of prostatic tissue to electrical field stimulation and phenylephrine,[87] suggesting that a more direct impact on prostate tone could also contribute to LUTS, secondary to pelvic ischemia.

In a rabbit model of pelvic atherosclerosis, Azadzoi et al.[88] found that blood flow in the bladder wall was significantly reduced compared to sham-operated controls, and that this was accompanied by severe bladder fibrosis and reduced compliance. Acute oxidative stress, bladder hypoxia, and concomitant pelvic neurodegeneration were demonstrated in this model.[89] Reactive oxygen species, which have been associated with ischemia in numerous settings including models of BOO, have been shown to cause DO in a rat model.[90] This appears to occur via activation of capsaicin-sensitive C-fiber afferent pathways, suggesting that ischemia of the LUT could contribute directly to afferent overactivity in the bladder.

Pinggera et al. reported significantly lower maximum filling capacity and reduced change in perfusion during bladder filling in 19 men with LUTS compared to 4 healthy, age-matched controls. Following 5 weeks of alpha-blocker therapy, bladder capacity increased substantially, and the change in perfusion during filling reached essentially normal levels, along with substantial improvements in LUTS.[91] A similar finding was seen in a rat model of BOO, where treatment with the same α_1-AR significantly improved blood flow and voided volume and reduced urinary frequency to approximately the levels seen in sham-operated mice.[92] Perfusion of the bladder may be significantly lower in men with OAB that persisted after transurethral resection of the prostate (TURP) compared to men in whom OAB resolved after TURP.[93] Notably, in a study in 17 men, Kershen et al.[94] also demonstrated a significant correlation between decreased bladder blood flow and reduced bladder compliance.

Inflammation

Chronic inflammation is well recognized as a risk factor for cardiovascular and other diseases that are associated with BPH LUTS. While the source of the inflammation remains debated,[95] a potential role for inflammation, and subsequent growth factor and cytokine secretion, in prostatic SMC growth is likely.[96] Indeed, Nickel[97] found evidence of a relationship between the degree of LUTS and the degree of chronic inflammation, and Robert et al.[98] demonstrated a strong correlation between histological inflammation and increased IPSS and prostate volume. Furthermore, in the Medical Therapy of Prostatic Symptoms (MTOPS) trial, chronic inflammatory infiltrates were found at increased frequency in baseline biopsy samples from men who experienced subsequent symptom worsening, acute urinary retention ($P < 0.05$), and later need for surgery,[99] suggesting a potentially important role in BPH progression. IL-8 has been proposed as a key mediator of inflammatory effects on prostatic endothelial and stromal cell proliferation.[100]

Androgen

An effect of androgen milieu on corpus cavernosum tissue and on PDE5 expression and/or activity in human and experimental animal corpus cavernosum has been extensively demonstrated.[101,102] Rat bladder PDE5 expression and activity has also been shown to be positively affected by testosterone replacement in castrated animals.[45] However, to date virtually all studies of PDE5 inhibitor treatment for LUTS in humans have been conducted in the male population and more studies are needed to clarify whether or not sex steroid milieu might affect clinical results on PDE5 inhibition for LUTS. Androgen milieu does have at very least a permissive role in the development of BPH[103] and this is confirmed by the efficacy of long-term medical treatment with 5α-reductase inhibitors in treating obstructive LUTS.

IS THERE A MECHANISTIC RATIONALE FOR TREATING MALE LUTS WITH A PDE5 INHIBITOR?

While the pathophysiology of LUTS is complex and influenced by multiple factors, increasing the activity of the NO/cGMP/PKG pathway through inhibition of the PDE5 isoenzymes may influence various pathological mechanisms contributing to LUTS and, therefore, may provide an innovative approach to the treatment of men with LUTS.

Upregulating NO/cGMP Activity

In vitro studies have demonstrated the ability of PDE5 inhibition to partially reverse norepinephrine- and endothelin-1-induced contraction of human prostatic tissue strips,[27,104] supporting the hypothesis that the upregulation of intracellular smooth muscle cGMP by PDE5 inhibition is likely to decrease smooth muscle tension in the prostatic stroma and capsule.[21,27,105] Similar findings have been reported with vardenafil treatment of strips from human prostatic stroma, capsule, and bladder neck.[45] Additionally, NO/cGMP signaling has shown an antiproliferative effect in cultured human prostatic and bladder SMCs,[45,56] which suggests that a PDE5 inhibitor, by increasing intracellular cGMP, might attenuate cellular proliferation associated with prostate enlargement or bladder hypertrophy. When BPH was induced in rats by steroid hormones (testosterone plus 17b-estradiol), concomitant administration of a PDE5 inhibitor for 8 weeks significantly attenuated increases in intraurethral pressure in a dose-dependent manner.[106]

Filippi and coworkers examined carbachol precontracted human bladder neck muscle strips and found that while the

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NO donor SNP partially relaxed the human preparations, relaxation was significantly increased following preincubation with vardenafil. They also found that PDE5 inhibitors antagonize cGMP conversion to metabolites in human bladder neck homogenates.[45]

Down-Regulating Rho-kinase Activity

Morelli and coworkers treated SHRs, which had decreased intercontraction intervals and bladder capacity, with vardenafil for 2 weeks. They found that vardenafil reversed deterioration of urodynamic measures and prevented RhoA activation, decreased ROCK activity; and increased cGMP levels in vivo (rat) and in vitro in human bladder muscle cells.[57] Kedia and coworkers assessed the effect of PDE5 inhibitors and other compounds acting on the NO/cAMP/cGMP pathway on endothelin-1-induced contraction of human prostatic tissue, which is mediated by the ROCK pathway. Among PDE5 inhibitors, the rank order of activity was tadalafil $>>$ sildenafil $\sim$ vardenafil; notably, only tadalafil, the adenylyl cyclase activator forskolin, and the PDE4 inhibitor rolipram achieved $>50\%$ relaxation of the precontracted strips.[104]

Modulation of ANS Overactivity and Bladder and Prostate Afferent Nerve Activity

It is not completely clear what role PDE5 isoenzymes play in ANS overactivity in the LUT;[107] nonetheless, LUTS caused by ANS overactivity seem to be reduced with PDE5 inhibitor treatment.[65] NO has an inhibitory effect on ion channels in afferent neurons and on afferent nerve activity; furthermore, the inhibition of Ca^{2+} channels in bladder afferent neurons by NO has been shown to be mediated by cGMP.[108] Thus, it is possible that the reduction of storage LUTS by PDE5 inhibitors is due in part to an enhancement of NO inhibition of afferent nerve activity. In addition, phasic contractions in isolated neonatal rat bladder strips, which are intrinsically hyperactive, were inhibited by an NO donor via a cGMP related mechanism. Inhibition of PDE5 with zaprinast reduced the amplitude and frequency of phasic contractions and increased the degree of inhibition produced by a NO donor,[109] suggesting a possible direct role for PDE5 inhibitors in modulating bladder overactivity in some animal models.

When Filippi and coworkers partially ligated the urethra in female rats they induced pronounced bladder hypertrophy and bladder non-voiding contractions (NVCs), similar to DO in humans. The NVCs were significantly decreased following 5 weeks of treatment with either vardenafil or tamsulosin (versus placebo).[45] Beamon et al.[110] assessed mice with surgically induced BOO and found increases in bladder overactivity, bladder mass, detrusor muscle hypertrophy, and fibrosis that were significantly attenuated with 6 weeks of sildenafil treatment. Bladder capacity and detrusor pressure increased but were not significantly affected by sildenafil. In men with spinal cord injury receiving oxybutinin, administration of a single dose of vardenafil 20 mg significantly decreased the maximum detrusor pressure and improved maximum cystometric capacity and DO volume.[111]

Increasing Pelvic Blood Perfusion and Reducing Lower Urinary Tract Chronic Ischemia

Various studies have provided evidence to suggest that increased vascular perfusion of the lower urinary tract is likely to have a therapeutic effect on LUTS.[81,91,112,113] One possibility is that improved overall endothelial function could improve LUT perfusion. Rosano et al. assessed the effect of tadalafil 20 mg every other day for 4 weeks on endothelial function in 32 men at high risk for endothelial dysfunction. Compared to controls, men receiving tadalafil showed significant improvement in flow-mediated dilation of brachial artery, reduced levels of endothelin-1, and increased levels of plasma nitrite−nitrates. Notably, increases in flow-mediated dilation and decreases in endothelin-1 levels were strongly correlated ($r^2 = 0.82$, $P < 0.0001$), and improvements were maintained at least 2 weeks after the end of tadalafil dosing.[114]

Reduction in LUTS could also be a consequence of increased perfusion specific to the prostate or bladder neck.[115,116] Using a rabbit model of chronic prostate ischemia, Azadzoi et al.[117] demonstrated that sildenafil significantly increased cGMP levels in ischemic and control LUT tissues and decreased sensitivity of contractions to electrical stimulus. In 12 men awaiting surgery for BPH, Bertolotto et al.[118] demonstrated increased prostatic blood perfusion using contrast-enhanced ultrasound following tadalafil administration. In a study of the effects of PDE5 inhibitors in pulmonary arterial hypertension, pretreatment with tadalafil, but not sildenafil or vardenafil, significantly inhibited the extended phase of hypoxia-induced pulmonary artery ring constriction; tadalafil also significantly reduced hypoxia-induced increases in TNF-α and IL-1β mRNA expression measured in the pulmonary artery rings after homogenization.[119] Notably, SHRs show hypoxia of bladder tissue with elevated expression of endothelin-1B and VEGF; these were rapidly reduced to the levels seen in controls with the administration of vardenafil.[120] Given that endothelin-1 plays a role in regulating SMC proliferation, reduced endothelin-1 levels could directly impact bladder and prostatic SMC outgrowth, as well as serving as a marker of improved overall oxygenation.

Reducing Inflammation

Roumeguere et al. recently assessed the impact of sildenafil, vardenafil, or tadalafil on IL-8 production from cultured endothelial cells in response to myeloperoxidase-modified low-density lipoprotein and TNF-α. Following stimulation, they found attenuation of IL-8 secretion to control levels with tadalafil but not with sildenafil or vardenafil.[121] Tadalafil also abrogated hypoxia-induced upregulation of TNF-α and IL-1β expression in isolated rat pulmonary arteries, an effect that was not likely to be caused by effects directly relating to relaxation of the pulmonary artery because sildenafil and vardenafil caused comparable arterial relaxation (absent hypoxia) without reducing expression of these proinflammatory cytokines.[119] In addition, Ahluwalia et al.[122] have demonstrated a central role for soluble guanylate cyclase, and hence cGMP, in the NO mediated inhibition of leukocyte rolling and adhesion. Given the prominent expression of PDE5 in vascular endothelium throughout the LUT, a role for PDE5 inhibition in reducing both atherosclerotic damage and overall inflammation as a result of reducing leukocyte recruitment can be envisaged.

AREAS FOR FUTURE RESEARCH

Animal and clinical studies have indicated that PDE5 inhibitors may act by multiple mechanisms to suppress LUTS. Based on data linking alterations in bladder innervation with DO, further experiments in animal models of DO are needed to evaluate the influence of PDE5 inhibitors on bladder and prostatic afferent nerve activity. Because increased afferent

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nerve excitability and LUTS have been linked with increased levels of NGF in the LUT, associations between changes in urine NGF levels and changes in irritative bladder symptoms during treatment with PDE5 inhibitors should be assessed during clinical studies. Bladder smooth muscle, which is relatively insensitive to inhibition by the cGMP pathway under normal conditions, may exhibit increased sensitivity to cGMP under pathological conditions. The influence of pathology on the NO/cGMP/PKG signaling pathway and PDE5 activity and on the sensitivity of bladder tissues to PDE5 inhibitors should thus be explored. Inflammatory conditions may impact blood flow through systemic effects on vascular function and may be associated with pathological processes leading to LUTS. Therefore the impact of PDE5 inhibition on inflammatory processes throughout the LUT merits further research, preferably with studies combining functional assessments with evaluations of protein and mRNA expression. The impact of tadalafil or other PDE5 inhibitors on pelvic blood flow could also be further assessed in animal studies such as those reported by Yono et al.[115] They examined the impact of α_1-AR subtypes, prazosin and naftopidil, on pelvic blood flow and NOS levels in SHRs. A placebo-controlled study in men with BPH to analyze and visualize prostate and bladder neck blood perfusion after PDE5 use would help confirm preliminary clinical studies suggesting that PDE5 inhibition increases blood perfusion in the LUT. Such studies could answer several of our gaps in knowledge regarding the relationship between PDE5 isoenzyme activity in pelvic vasculature and blood perfusion of the LUT.

CONCLUSION

The pathophysiology of LUTS is complex and not completely understood. Clinical evidence shows that LUTS may occur independently of BPH or secondary to BPH but in both cases involves direct (related to obstruction) or indirect (related to storage) mechanisms with substantial pathophysiological overlap. Clinical studies of PDE5 inhibitors in men with BPH LUTS have consistently reported clinically meaningful and statistically significant symptom reduction with little or no improvement in peak urinary flow. While the precise mechanisms for improvements remains unclear, inhibition of PDE5 seems to impact several pathways involved in LUTS, with effects that include reduced smooth muscle and endothelial cell proliferation, decreased nerve activity, and increased smooth muscle relaxation and tissue perfusion. Together these effects may explain the positive effects of PDE5 inhibition on LUTS reported to date.

REFERENCES

1. Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: The multinational survey of the aging male (MSAM-7). Eur Urol 2003;44:637–49.
2. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37–49.
3. Chapple CR, Roehrborn CG. A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: Focus on the bladder. Eur Urol 2006;49:651–8.
4. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: Results of the EPIC study. Eur Urol 2006;50:1306–14.
5. Jacobsen SJ, Girman CJ, Lieber MM. Natural history of benign prostatic hyperplasia. Urology 2001;58:5–16.
6. Abdel-Aziz KF, Lemack GE. Overactive bladder in the male patient: Bladder, outlet, or both? Curr Urol Rep 2002;3:445–51.
7. Andersson KE. Storage and voiding symptoms: Pathophysiologic aspects. Urology 2003;62:3–10.
8. Roosen A, Chapple CR, Dmochowski RR, et al. A refocus on the bladder as the originator of storage lower urinary tract symptoms: A systematic review of the latest literature. Eur Urol 2009;56:810–20.
9. Chapple CR, Wein AJ, Abrams P, et al. Lower urinary tract symptoms revisited: A broader clinical perspective. Eur Urol 2008;54:563–9.
10. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chapt_3_appendix.pdf, 2003.
11. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003;349:2387–98.
12. Kohler TS, McVary KT. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. Eur Urol 2009;55:38–48.
13. McVary K. Lower urinary tract symptoms and sexual dysfunction: Epidemiology and pathophysiology. BJU Int 2006;97:23–8.
14. Stief CG, Porst H, Neuser D, et al. A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol 2008; 53:1236–44.
15. McVary KT, Monnig W, Camps JL Jr, et al. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: A randomized, double-blind trial. J Urol 2007;177:1071–7.
16. McVary KT, Roehrborn CG, Kaminetsky JC, et al. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol 2007;177:1401–7.
17. Roehrborn CG, McVary KT, Elion-Mboussa A, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: A dose finding study. J Urol 2008;180:1228–34.
18. Roehrborn CG, Kaminetsky JC, Auerbach SM, et al. Changes in peak urinary flow and voiding efficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. BJU Int 2010; 105:502–7.
19. Donatucci C, Brock G, Goldfischer E, et al. Tadalafil administered once daily for treatment of men with lower urinary tract symptoms secondary to benign prostatic hyperplasia: A 1-year study. BJU Int 2010 (in press).
20. Dmochowski R, Roehrborn C, Klise S, et al. Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: A randomized, placebo controlled 12-week clinical trial. J Urol 2010;183:1092–7.
21. Kedia GT, Uckert S, Jonas U, et al. The nitric oxide pathway in the human prostate: Clinical implications in men with lower urinary tract symptoms. World J Urol 2008;26:603–9.
22. Andersson KE, Uckert S, Stief C, et al. Phosphodiesterases (PDEs) and PDE inhibitors for treatment of LUTS. Neurourol Urodyn 2007;26:928–33.
23. Roumeguere T, Zouaoui Boudjeltia K, Hauzeur C, et al. Is there a rationale for the chronic use of phosphodiesterase-5 inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia? BJU Int 2009;104: 511–7.
24. Tinel H, Stelte-Ludwig B, Hutter J, et al. Pre-clinical evidence for the use of phosphodiesterase-5 inhibitors for treating benign prostatic hyperplasia and lower urinary tract symptoms. BJU Int 2006;98:1259–63.
25. Hedlund P, Ekstrom P, Larsson B, et al. Heme oxygenase and NO-synthase in the human prostate–relation to adrenergic, cholinergic and peptide-containing nerves. J Auton Nerv Syst 1997;63:115–26.
26. Bloch W, Klotz T, Loch C, et al. Distribution of nitric oxide synthase implies a regulation of circulation, smooth muscle tone, and secretory function in the human prostate by nitric oxide. Prostate 1997;33:1–8.
27. Uckert S, Kuthe A, Jonas U, et al. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol 2001;166:2484–90.
28. Persson K, Alm P, Johansson K, et al. Co-existence of nitrergic, peptidergic and acetylcholine esterase-positive nerves in the pig lower urinary tract. J Auton Nerv Syst 1995;52:225–36.
29. Gillespie JI, Markerink-van Ittersum M, de Vente J. Expression of neuronal nitric oxide synthase (nNOS) and nitric-oxide-induced changes in cGMP in the urothelial layer of the guinea pig bladder. Cell Tissue Res 2005;321: 341–51.
30. Gillespie JI, Markerink-van Ittersum M, de Vente J. Endogenous nitric oxide/cGMP signalling in the guinea pig bladder: Evidence for distinct populations of sub-urothelial interstitial cells. Cell Tissue Res 2006;325:325–32.
31. Birder LA, Apodaca G, de Groat WC, et al. Adrenergic- and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. Am J Physiol 1998;275:F226–9.
32. Garcia-Pascual A, Sancho M, Costa G, et al. Interstitial cells of Cajal in the urethra are cGMP-mediated targets of nitrergic neurotransmission. Am J Physiol Renal Physiol 2008;295:F971–83.
33. de Jongh R, van Koeveringe GA, van Kerrebroeck PE, et al. Alterations to network of NO/cGMP-responsive interstitial cells induced by outlet obstruction in guinea-pig bladder. Cell Tissue Res 2007;330:147–60.

15206777, 2011, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nau.20999 by Egyptian National Sci. Network (Enstine), Wiley Online Library on [06/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

34. Andersson KE, Garcia Pascual A, Persson K, et al. Electrically-induced, nerve-mediated relaxation of rabbit urethra involves nitric oxide. J Urol 1992; 147:253–9.
35. Werkstrom V, Persson K, Ny L, et al. Factors involved in the relaxation of female pig urethra evoked by electrical field stimulation. Br J Pharmacol 1995;116:1599–604.
36. Werkstrom V, Svensson A, Andersson KE, et al. Phosphodiesterase 5 in the female pig and human urethra: Morphological and functional aspects. BJU Int 2006;98:414–23.
37. Truss MC, Uckert S, Stief CG, et al. Cyclic nucleotide phosphodiesterase (PDE) isoenzymes in the human detrusor smooth muscle. II. Effect of various PDE inhibitors on smooth muscle tone and cyclic nucleotide levels in vitro. Urol Res 1996;24:129–34.
38. Fujiwara M, Andersson K, Persson K. Nitric oxide-induced cGMP accumulation in the mouse bladder is not related to smooth muscle relaxation. Eur J Pharmacol 2000;401:241–50.
39. Kajioka S, Nakayama S, Seki N, et al. Oscillatory membrane currents paradoxically induced via NO-activated pathways in detrusor cells. Cell Calcium 2008;44:202–9.
40. Uckert S, Oelke M, Stief CG, et al. Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE) isoenzymes in the human prostate. Eur Urol 2006;49:740–5.
41. Fibbi B, Morelli A, Vignozzi L, et al. Characterization of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. J Sex Med 2010;7:59–69.
42. Lin G, Hunag YC, Wang G, et al. Prominent expression of phosphodiesterase 5 in the striated muscle of rate urethra and levator ani. J Urol 2010;184: 769–74.
43. Truss MC, Stief CG, Uckert S, et al. Initial clinical experience with the selective phosphodiesterase-I isoenzyme inhibitor vinpocetine in the treatment of urge incontinence and low compliance bladder. World J Urol 2000;18:439–43.
44. Truss MC, Stief CG, Uckert S, et al. Phosphodiesterase 1 inhibition in the treatment of lower urinary tract dysfunction: From bench to bedside. World J Urol 2001;19:344–50.
45. Filippi S, Morelli A, Sandner P, et al. Characterization and functional role of androgen-dependent PDE5 activity in the bladder. Endocrinology 2007;148: 1019–29.
46. Werkstrom V, Hedlund P, Lee T, et al. Vardenafil-induced relaxation and cyclic nucleotide levels in normal and obstructed rat urinary bladder. BJU Int 2009;104:1740–5.
47. Bittencourt JA, Tano T, Gajar SA, et al. Relaxant effects of sildenafil on the human isolated bladder neck. Urology 2009;73:427–30.
48. Cinar A, Hall SA, Link CL, et al. Cluster analysis and lower urinary tract symptoms in men: Findings from the Boston Area Community Health Survey. BJU Int 2008;101:1247–56.
49. Coyne KS, Kaplan SA, Chapple CR, et al. Risk factors and comorbid conditions associated with lower urinary tract symptoms: EpiLUTS. BJU Int 2009;103: 24–32.
50. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: Prospective results from the Massachusetts male aging study. Prev Med 2000;30:328–38.
51. Klotz T, Mathers MJ, Bloch W, et al. Nitric oxide based influence of nitrates on micturition in patients with benign prostatic hyperplasia. Int Urol Nephrol 1999;31:335–41.
52. Persson K, Igawa Y, Mattiasson A, et al. Inhibition of the arginine/nitric oxide pathway causes bladder hyperactivity in the rat. Acta Physiol Scand 1992; 144:107–8.
53. Pandita RK, Mizusawa H, Andersson KE. Intravesical oxyhemoglobin initiates bladder overactivity in conscious, normal rats. J Urol 2000;164: 545–50.
54. Persson K, Pandita RK, Aszodi A, et al. Functional characteristics of urinary tract smooth muscles in mice lacking cGMP protein kinase type I. Am J Physiol Regul Integr Comp Physiol 2000;279:R1112–20.
55. Soler R, Fullhase C, Lu B, et al. Bladder dysfunction in a new mutant mouse model with increased superoxide—Lack of nitric oxide? J Urol 2010;183: 780–5.
56. Guh JH, Hwang TL, Ko FN, et al. Antiproliferative effect in human prostatic smooth muscle cells by nitric oxide donor. Mol Pharmacol 1998;53: 467–74.
57. Morelli A, Filippi S, Sandner P, et al. Vardenafil modulates bladder contractility through cGMP-mediated inhibition of RhoA/Rho kinase signaling pathway in spontaneously hypertensive rats. J Sex Med 2009;6:1594–608.
58. Bing W, Chang S, Hypolite JA, et al. Obstruction-induced changes in urinary bladder smooth muscle contractility: A role for Rho kinase. Am J Physiol Renal Physiol 2003;285:F990–7.
59. Chitaley K, Wingard CJ, Clinton Webb R, et al. Antagonism of Rho-kinase stimulates rat penile erection via a nitric oxide-independent pathway. Nat Med 2001;7:119–22.
60. Marinese D, Patel R, Walden PD. Mechanistic investigation of the adrenergic induction of ventral prostate hyperplasia in mice. Prostate 2003;54: 230–7.
61. Meigs JB, Mohr B, Barry MJ, et al. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. J Clin Epidemiol 2001;54:935–44.
62. Hammarsten J, Hogstedt B. Clinical, anthropometric, metabolic and insulin profile of men with fast annual growth rates of benign prostatic hyperplasia. Blood Press 1999;8:29–36.
63. Kupelian V, McVary KT, Kaplan SA, et al. Association of lower urinary tract symptoms and the metabolic syndrome: Results from the Boston Area Community Health Survey. J Urol 2009;182:616–24.
64. Vikram A, Jena GB, Ramarao P. Increased cell proliferation and contractility of prostate in insulin resistant rats: Linking hyperinsulinemia with benign prostate hyperplasia. Prostate 2010;70:79–89.
65. McVary KT, Rademaker A, Lloyd GL, et al. Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol 2005;174:1327–433.
66. Thor PJ, Mazur M, Furgala A, et al. The autonomic nervous system function in benign prostatic hyperplasia. Folia Med Cracov 2006;47:79–86.
67. Ullrich PM, Lutgendorf SK, Kreder KJ. Physiologic reactivity to a laboratory stress task among men with benign prostatic hyperplasia. Urology 2007;70: 487–91.
68. McVary KT, Razzaq A, Lee C, et al. Growth of the rat prostate gland is facilitated by the autonomic nervous system. Biol Reprod 1994;51:99–107.
69. Wang JM, McKenna KE, McVary KT, et al. Requirement of innervation for maintenance of structural and functional integrity in the rat prostate. Biol Reprod 1991;44:1171–6.
70. McVary KT, McKenna KE, Lee C. Prostate innervation. Prostate Suppl 1998;8:2–13.
71. Golomb E, Rosenzweig N, Eilam R, et al. Spontaneous hyperplasia of the ventral lobe of the prostate in aging genetically hypertensive rats. J Androl 2000;21:58–64.
72. Persson K, Pandita RK, Spitsbergen JM, et al. Spinal and peripheral mechanisms contributing to hyperactive voiding in spontaneously hypertensive rats. Am J Physiol 1998;275:R1366–73.
73. de Groat WC, Yoshimura N. Afferent nerve regulation of bladder function in health and disease. Handb Exp Pharmacol 2009;194:91–138.
74. Steers WD, Ciambotti J, Etzel B, et al. Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction. J Comp Neurol 1991;310:401–10.
75. Steers WD, Kolbeck S, Creedon D, et al. Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function. J Clin Invest 1991;88:1709–15.
76. Steers WD, Creedon DJ, Tuttle JB. Immunity to nerve growth factor prevents afferent plasticity following urinary bladder hypertrophy. J Urol 1996;155: 379–85.
77. Liu HT, Kuo HC. Urinary nerve growth factor levels are increased in patients with bladder outlet obstruction with overactive bladder symptoms and reduced after successful medical treatment. Urology 2008;72:104–8.
78. Steers WD, Tuttle JB. Mechanisms of disease: The role of nerve growth factor in the pathophysiology of bladder disorders. Nat Clin Pract Urol 2006;3: 101–10.
79. Kostis JB, Jackson G, Rosen R, et al. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol 2005;96:85M–93M.
80. Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease: Matching the right target with the right test in the right patient. Eur Urol 2006;50:721–31.
81. Berger AP, Deibl M, Leonhartsberger N, et al. Vascular damage as a risk factor for benign prostatic hyperplasia and erectile dysfunction. BJU Int 2005;96: 1073–8.
82. Berger AP, Bartsch G, Deibl M, et al. Atherosclerosis as a risk factor for benign prostatic hyperplasia. BJU Int 2006;98:1038–42.
83. Ghafar MA, Puchner PJ, Anastasiadis AG, et al. Does the prostatic vascular system contribute to the development of benign prostatic hyperplasia? Curr Urol Rep 2002;3:292–6.
84. Berger AP, Kofler K, Bektic J, et al. Increased growth factor production in a human prostatic stromal cell culture model caused by hypoxia. Prostate 2003;57:57–65.
85. Du Z, Fujiyama C, Chen Y, et al. Expression of hypoxia-inducible factor 1alpha in human normal, benign, and malignant prostate tissue. Chin Med J (Engl) 2003;116:1936–9.
86. Lekas AG, Lazaris AC, Chrisofos M, et al. Finasteride effects on hypoxia and angiogenetic markers in benign prostatic hyperplasia. Urology 2006;68: 436–41.
87. Azadzoi KM, Tarcan T, Kozlowski R, et al. Overactivity and structural changes in the chronically ischemic bladder. J Urol 1999;162:1768–78.
88. Azadzoi KM, Tarcan T, Siroky MB, et al. Atherosclerosis-induced chronic ischemia causes bladder fibrosis and non-compliance in the rabbit. J Urol 1999;161:1626–35.
89. Azadzoi KM, Yalla SV, Siroky MB. Oxidative stress and neurodegeneration in the ischemic overactive bladder. J Urol 2007;178:710–5.
90. Masuda H, Kihara K, Saito K, et al. Reactive oxygen species mediate detrusor overactivity via sensitization of afferent pathway in the bladder of anaesthetized rats. BJU Int 2008;101:775–80.

15206777, 2011, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/nau.20999 by Egyptian National Sci. Network (Enstinet), Wiley Online Library on [06/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

91. Pinggera GM, Mitterberger M, Pallwein L, et al. alpha-Blockers improve chronic ischaemia of the lower urinary tract in patients with lower urinary tract symptoms. BJU Int 2008;101:319–24.
92. Okutsu H, Matsumoto S, Hanai T, et al. Effects of tamsulosin on bladder blood flow and bladder function in rats with bladder outlet obstruction. Urology 2010;75:235–40.
93. Mitterberger M, Pallwein L, Gradl J, et al. Persistent detrusor overactivity after transurethral resection of the prostate is associated with reduced perfusion of the urinary bladder. BJU Int 2007;99:831–5.
94. Kershen RT, Azadzoi KM, Siroky MB. Blood flow, pressure and compliance in the male human bladder. J Urol 2002;168:121–5.
95. Kramer G, Mitteregger D, Marberger M. Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? Eur Urol 2007;51:1202–16.
96. Kramer G, Steiner GE, Handisurya A, et al. Increased expression of lymphocyte-derived cytokines in benign hyperplastic prostate tissue, identification of the producing cell types, and effect of differentially expressed cytokines on stromal cell proliferation. Prostate 2002;52:43–58.
97. Nickel JC. Inflammation and benign prostatic hyperplasia. Urol Clin North Am 2008;35:109–115.
98. Robert G, Descazeaud A, Nicolaiew N, et al. Inflammation in benign prostatic hyperplasia: A 282 patients' immunohistochemical analysis. Prostate 2009; 69:1774–80.
99. Roehrborn CG, Kaplan SA, Noble WD, et al. The impact of acute or chronic inflammation in baseline biopsy on the risk of clinical progression of BPH: Results from the MTOPS Study [Abstract 1286]. J Urol 2005;173:390.
100. Fibbi B, Penna G, Morelli A, et al. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. Int J Androl 2009;33:475–8.
101. Corona G, Maggi M. The role of testosterone in erectile dysfunction. Nat Rev Urol 2010;7:46–56.
102. Yang R, Huang YC, Lin G, et al. Lack of direct androgen regulation of PDE5 expression. Biochem Biophys Res Commun 2009;380:758–62.
103. Bartsch G, Rittmaster RS, Klocker H. Dihydrotestosterone and the concept of 5alpha-reductase inhibition in human benign prostatic hyperplasia. World J Urol 2002;19:413–25.
104. Kedia GT, Uckert S, Kedia M, et al. Effects of phosphodiesterase inhibitors on contraction induced by endothelin-1 of isolated human prostatic tissue. Urology 2009;73:1397–401.
105. Uckert S, Sormes M, Kedia G, et al. Effects of phosphodiesterase inhibitors on tension induced by norepinephrine and accumulation of cyclic nucleotides in isolated human prostatic tissue. Urology 2008;71:526–30.
106. Kang KK, Kim JM, Yu JY, et al. Effects of phosphodiesterase type 5 inhibitor on the contractility of prostate tissues and urethral pressure responses in a rat model of benign prostate hyperplasia. Int J Urol 2007; 14:946–51.
107. Kohler TS, McVary KT. The relationship between erectile dysfunction and lower urinary tract symptoms and the role of phosphodiesterase type 5 inhibitors. Eur Urol 2009;55:38–48.
108. Yoshimura N, Seki S, de Groat WC. Nitric oxide modulates Ca(2+) channels in dorsal root ganglion neurons innervating rat urinary bladder. J Neurophysiol 2001;86:304–11.
109. Artim DE, Kullmann FA, Daugherty SL, et al. Activation of the nitric oxide-cGMP pathway reduces phasic contractions in neonatal rat bladder strips via protein kinase G. Am J Physiol Renal Physiol 2009;297:F333–40.
110. Beamon CR, Mazar C, Salkini MW, et al. The effect of sildenafil citrate on bladder outlet obstruction: A mouse model. BJU Int 2009;104:252–6.
111. Gacci M, Del Popolo G, Macchiarella A, et al. Vardenafil improves urodynamic parameters in men with spinal cord injury: Results from a single dose, pilot study. J Urol 2007;178:2040–3.
112. Azadzoi KM. Effect of chronic ischemia on bladder structure and function. Adv Exp Med Biol 2003;539:271–80.
113. Waldkirch E, Uckert S, Yildirim H, et al. Cyclic AMP-specific and cyclic GMP-specific phosphodiesterase isoenzymes in human cavernous arteries—Immunohistochemical distribution and functional significance. World J Urol 2005;23:405–10.
114. Rosano GM, Aversa A, Vitale C, et al. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. Eur Urol 2005;47:214–20.
115. Yono M, Yamamoto Y, Imanishi A, et al. Differential effects of prazosin and naftopidil on pelvic blood flow and nitric oxide synthase levels in spontaneously hypertensive rats. J Recept Signal Transduct Res 2008;28: 403–12.
116. Pinggera GM, Mitterberger M, Steiner E, et al. Association of lower urinary tract symptoms and chronic ischaemia of the lower urinary tract in elderly women and men: Assessment using colour Doppler ultrasonography. BJU Int 2008;102:470–4.
117. Azadzoi KM, Babayan RK, Kozlowski R, et al. Chronic ischemia increases prostatic smooth muscle contraction in the rabbit. J Urol 2003;170: 659–63.
118. Bertolotto M, Trincia E, Zappetti R, et al. Effect of tadalafil on prostate haemodynamics: Preliminary evaluation with contrast-enhanced US. Radiol Med 2009;114:1106–14.
119. Tsai BM, Turrentine MW, Sheridan BC, et al. Differential effects of phosphodiesterase-5 inhibitors on hypoxic pulmonary vasoconstriction and pulmonary artery cytokine expression. Ann Thorac Surg 2006;81: 272–8.
120. Morelli A, Filippi S, Comeglio P, et al. Acute vardenafil administration improves bladder oxygenation in spontaneously hypertensive rats. J Sex Med 2010;7:107–20.
121. Roumeguere T, Zouaoui Boudjeltia K, Babar S, et al. Effects of phosphodiesterase inhibitors on the inflammatory response of endothelial cells stimulated by myeloperoxidase-modified low-density lipoprotein or tumor necrosis factor alpha. Eur Urol 2010;57:522–8.
122. Ahluwalia A, Foster P, Scotland RS, et al. Antiinflammatory activity of soluble guanylate cyclase: cGMP-dependent down-regulation of P-selectin expression and leukocyte recruitment. Proc Natl Acad Sci USA 2004;101:1386–91.

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