REVIEW

Effect of phosphodiesterase inhibitors in the bladder

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Abstract Many aging men will experience lower urinary tract symptoms (LUTS). Phosphodiesterase type 5 (PDE5) inhibitors have shown promise in treating LUTS in these patients. PDE5 inhibitors mediate their effects through several pathways including cAMP, NO/cGMP, K-channel modulated pathways, and the L-cysteine/H_2S pathway. PDE5 inhibitors exert their effect in muscle cells, nerve fibers, and interstitial cells (ICs). The use of PDE5 inhibitors led to improvement in LUTS. This included urodynamic parameters. PDE5 inhibitors may play a significant role in LUTS due to their effect on the bladder rather than the prostate.

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1. Introduction

Lower urinary tract symptoms (LUTS), which may include storage symptoms (urinary urgency, nocturia), or voiding symptoms (urinary hesitancy, weak stream, straining, and prolonged voiding), can have a significant negative impact on quality of life (QoL) [1,2]. An estimated 45.2% of the worldwide population is affected by atleast one urinary symptom [3]. Out of 19,165 individuals surveyed in a cross-sectional, population-based, multinational study conducted by Irwin and colleagues [4], 64.3% reported atleast one urinary symptom, with nocturia being the most prevalent (men, 48.6%; women, 54.5%). Similarly, in a national study conducted by Herschorn and colleagues [5] in Canada on 1000 respondents, approximately half of the individuals (43% of men and 57% of women) reported one or more urinary symptoms, with nocturia being the most common

symptom (36%). A worldwide model estimates that by 2018, an estimated 2.3 billion individuals will be affected by atleast one urinary complaint (18.4% increase), with the greatest increase expected in the developing regions [3]. Several medications are used to treat urinary symptoms, including alpha blockers, anti-muscarinics, and phosphodiesterase type 5 (PDE5) inhibitors. Although the use of PDE5 inhibitors has been shown to improve LUTS, the clinical mechanism of action of PDE5, if any, remains unclear. We present data on the role of PDE5 in the bladder.

2. Evidence acquisition

A systematic literature search in PubMed was performed between 1994 and 2014. The following terms were used: PDE5 inhibitors, tadalafil, vardenafil, sildenafil. Relevant citations from articles selected under the previously stated

terms were also inducted in the study. Both clinical and basic science studies were included. Each article's title and abstract were reviewed for their appropriateness and relevance to the role of PDE5 inhibitors and their effect on the bladder. Relevant articles were fully reviewed to assess the design of the study and the amount of evidence, and included in the final data acquisition.

3. Evidence synthesis

3.1. PDEs in the bladder

PDE5 plays a role in the smooth muscle cells (SMCs) of the bladder, and the endothelium of blood vessels [6]. PDE5 has been shown to have the highest expression in the muscular cells in the lower urinary tract [7]. Study of Truss et al. [8] was the first to demonstrate the presence of PDE 1, 2, 3, 4 and 5 isoenzymes in the human detrusor. PDE5 affects cGMP which alters the intracellular calcium concentration [Ca], which is the primary regulator of smooth muscle contractility [9].

3.2. *Ex-vivo* studies

Fibbi and colleagues [7] demonstrated that PDE5 had the highest expression in the bladder as compared to the urethra and prostate, and the greatest expression in the muscular cells in the lower urinary tract. In their study conducted on lower urinary tract tissues and SMCs cultured from the urethra, prostate and bladder, the bladder neck demonstrated very high PDE5 levels in the endothelial cells of the blood vessels and in the SMCs of the muscular wall and blood vessels. With the administration of vardenafil, sodium nitroprusside (SNP)-induced growth inhibition in all three tissue preparations was enhanced, with the maximum anti-proliferative effects in the bladder neck ($p < 0.01$ *vs.* urethra and prostate) [7].

PDE inhibitors mediate their effects via several secondary signaling pathways. Oger and colleagues [10] demonstrated that relaxation of the urinary bladder smooth muscle (UBSM) by sildenafil involved the cAMP, cGMP and potassium-channel modulated pathways, with contribution from nitric oxide (NO) not being significant. Human bladder dome samples were taken from 20 patients, who had no previous history of bladder dysfunction and were undergoing cystectomy for bladder cancer. Sildenafil was added to human bladder strips, which were pre-contracted with carbachol, inducing a significant ($p < 0.001$) concentration dependent relaxation. Administration of SNAP (NO donor) did not have a significant relaxant effect and did not increase the effects of sildenafil on the bladder. Administration of a guanylate cyclase inhibitor (ODQ), adenylate cyclase inhibitor (MDL-12,330A), and K^+-channel blockers, however, significantly ($p < 0.001$) reduced sildenafil-induced relaxation in carbachol pre-contracted detrusor strips.

PDE5 inhibitors modulate nervous signaling involved in bladder contraction [11]. Xin and colleagues [12] demonstrated that PDE inhibitors play an important role in nerve-induced contractions of human UBSM and that K^+-channels mediate those effects. They investigated the role of BK (calcium-activated potassium) channels in UBSM. A non-selective PDE inhibitor, 3-isobutyl-1-methylxanthine (IBMX) was added

to human UBSM-isolated cells, which resulted in an increase in the frequency of spontaneous transient outward currents (STOCs), leading to UBSM cell membrane hyperpolarization ($p < 0.05$). The PDE blockade also resulted in a decrease in the intracellular calcium (Ca) levels and a suppression of the myogenic (spontaneous phasic) and nerve-evoked contractions in human UBSM isolated strips (all $p < 0.05$).

A study focusing on the involvement of the H_2S pathway in the mechanism of action of PDE5 inhibitors concluded that the L-cysteine/H_2S pathway might be one possible pathway through which PDE5 inhibitors exert their effects on the bladder [13]. Fusco and colleagues [13] incorporated sildenafil in their studies, which caused a significant concentration-dependent increase in H_2S production compared to vehicle, along with a relaxation of the bladder dome strips. Similarly, when inhibitors of cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) (convertors of L-cysteine to H_2S) were used, relaxation in bladder strips and rise in H_2S both decreased.

3.3. Animal studies

3.3.1. cAMP/cGMP and PDE5 inhibitors

PDE inhibitors mediate their effects via several secondary signaling pathways, including cAMP and cGMP. Artim and colleagues [14] suggested the presence of small amounts of cGMP in rat bladder strips. SNAP (NO donor) was applied to carbachol pre-contracted strips, resulting in a dose-dependent reduction in the contractions. The application of 8-bromo-cGMP (cGMP analog) also decreased the amplitude and frequency of contractions, demonstrating the involvement of cGMP in the NO pathway. The application of Zaprinast to the bladder strips significantly ($p < 0.005$) reduced the carbachol enhanced spontaneous contraction amplitude, and when applied alone, also elicited a small reduction in SC_{carb} frequency ([11.8 ± 2.3]%, $p < 0.05$).

Another study also concluded that PDE5 inhibitors might not act directly on DSM, but rather result in the accumulation of cGMP in interstitial cells (ICs) [15]. Yanai and colleagues [15] demonstrated that SNP (NO donor) increased the amplitude and frequency of spontaneous phasic contractions in a dose-dependent manner, and when applied in the presence of guanylate cyclase inhibitor (ODQ), still increased the amplitude and frequency of the multibundle DSM spontaneous contractions. 8Br-cGMP however abolished/reduced the amplitude and frequency of spontaneous contractions in multibundle DSM, leading to the conclusion that the NO donors had a cGMP-independent mechanism by which they exerted excitatory effects on DSM spontaneous activity. With the application of sildenafil, the amplitude and frequency of the spontaneous contractions were either abolished or reduced in 65% of multibundle DSM, whereas in single bundle DSM, sildenafil had no effects on both the amplitude and frequency of the spontaneous contractions [15].

However, it is not necessary that a rise in cGMP levels is accompanied by relaxation of the bladder. Fujiwara and colleagues [16] demonstrated that NO donors increased the level of cGMP, but did not induce smooth muscle relaxation. They reported positive cGMP-immunoreactivity in stromal cells and nerve fibers and negative cGMP-immunoreactivity in bladder smooth muscle bundles after exposure to NO donors.

These three studies demonstrated the involvement of cGMP in bladder physiology. While Artim et al. [14] and Yanai et al. [15] described the involvement of cGMP in UBSM contractility, Fujiwara et al. [16] proved that an increase in cGMP does not induce smooth muscle relaxation. Qiu et al. [17] and Werkstrom et al. [18] however completely contradicted these findings, as their results put forth cAMP as the primary mediator of UBSM contractility.

Qiu and colleagues [17] suggested that the cAMP pathway was the primary mediator of smooth muscle relaxation, with a rise in cGMP levels not being sufficient independently, whereas Werkstrom and colleagues [18] proposed that vardenafil-induced relaxation in rat bladder was predominantly mediated by cAMP. They were able to demonstrate that adding vardenafil to carbachol pre-contracted detrusor strips resulted in dose-dependent relaxation of the DSM, with max relaxation reaching $(91 \pm 4)\%$ at 100 mmol/L.

3.3.2. Urothelium and PDE5 inhibitors

The urothelium, also known as the uro-epithelium, is the innermost layer of the bladder [19]. It is involved in bladder contraction and may be one possible site of action of the PDE5 inhibitors. Animal studies conducted by Gillespie et al. [20—22] have shown that the NO/cGMP pathway is present in the urothelium and may play a role in the maintenance of detrusor tone. Nerves present in bladder interstitial cells produce cGMP which facilitates relaxation. Therefore, PDE inhibitors may influence bladder function at the level of the urothelium by inhibiting cGMP degradation.

3.3.3. Nerve fibers and PDE5 inhibitors

Behr-Roussel and associates [23] were the first to demonstrate that vardenafil reduces both non-voiding contractions and bladder afferent nerve firing in unanesthetized, decerebrate, spinal cord injured (SCI) rats. Fifteen female Sprague—Dawley rats with SCI were studied to assess the use of vardenafil for reduction in bladder afferent nerve firing and improvement in urodynamic parameters. After an injection of vardenafil, there was a significant ($p < 0.001$) reduction in the amplitude and frequency of non-voiding contractions as compared to saline, along with a rapid and significant ($p < 0.001$) drop in the mean spike rate of bladder afferent nerve firing.

Tadalafil was also able to inhibit the activity of both mechanosensitive afferent nerve fibers in two experiments performed by Minagawa and colleagues [11]. In the first of two experiments, single afferent activity (SAA) of both single afferent fibers decreased significantly in a dose-dependent manner after tadalafil administration. In the second experiment, acrolein instillation did not significantly change the SAA when pretreatment was carried out with tadalafil. The suggestion that PDE5 inhibitors reduce LUTS by acting in the neural pathways controlling the bladder and not in the detrusor smooth muscle was further reinforced by Artim and colleagues [24] in their study on the rat urinary bladder.

In an animal model of neurogenic bladder, Mirzaii-Dizgah and Salmanyan [25] assessed 40 male rats divided into five equal groups. SCI was induced in all but the sham group, and renal system and motor functions were evaluated 28 days following injury. Rats were given statins, PDE5 inhibitors (sildenafil and tadalafil), or saline. PDE5 inhibitors improved motor function, but did not impact renal function.

3.3.4. Bladder oxygenation and PDE5 inhibitors

The role of PDE5 inhibitors in bladder oxygenation was investigated by Morelli and colleagues [26], who demonstrated that vardenafil significantly reduced bladder hypoxia using an animal model of naturally occurring overactive bladder. The effects of vardenafil administration on bladder oxygenation in spontaneously hypertensive rats (SHRs) were investigated by the administration of a single dose of vardenafil (10 mg/kg) to SHRs 90 min before they were sacrificed. It was observed that vardenafil not only relaxed the muscular wall, but also improved urinary vesicle blood perfusion. Similar results were obtained in a study conducted by Nomiya and colleagues [27], who administered tadalafil to rats that had induced chronic bladder ischemia. Apart from preventing neo-intimal formation and luminal occlusion, tadalafil significantly improved all functional and morphological parameters and eventually decreased bladder overactivity.

3.4. Human studies

Open-label studies were performed in men to demonstrate the efficacy of PDE5 inhibitors for the treatment of LUTS. Sairam and colleagues [28] reported the results of their open-label study, which evaluated the possible relationship between erectile dysfunction (ED) and LUTS. They demonstrated that treatment of ED with sildenafil improved LUTS, and proposed that the NO/sildenafil pathway could be involved in smooth muscle relaxation in the lower urinary tract. A total of 112 men were enrolled in the study. Participants were treated with oral sildenafil and were assessed after 1 and 3 months using international prostate symptom score (IPSS) and QoL questionnaires. LUTS were classified as mild, moderate, or severe. After 3 months of treatment, all LUTS that were initially classified as severe in intensity became moderate, 60% of LUTS that were moderate in intensity became mild, and 18% of LUTS that were mild became moderate. The QoL had also improved. A similar result was obtained by Mulhall and colleagues [29] in their open-label study to assess the effect of Viagra on LUTS. They demonstrated that sildenafil had a positive effect of LUTS, suggesting that sildenafil mediates its effects through bladder neck/prostatic smooth muscle relaxation. A total of 48 men were enrolled in the study, all of whom had an initial IPSS score of greater than 10. A 100 mg dose of sildenafil was administered to all the patients, with a mean number of uses of 2.0 ± 0.6 per week. IPSS questionnaire was filled atleast 3 months after the commencement of sildenafil and was then compared to the pre-treatment IPSS questionnaire. There was a mean improvement of 4.6 points ($p = 0.013$) in IPSS and a mean improvement of 1.4 points ($p = 0.025$) in QoL score. Of the 48 participants, 60% displayed improvement in IPSS score, 35% had atleast a 4-point improvement in IPSS score, and 1% had IPSS score <7 by the end of the treatment. Both of these open-label studies assessed the efficacy of PDE5 inhibitors in the bladder, paving the way for the subsequent

randomized, placebo-controlled, double-blind trials that provided further evidence to corroborate these claims.

McVary and associates [30] conducted a 12-week, double-blind, placebo controlled study of sildenafil for the treatment of men with both ED and LUTS. One hundred and eighty-five men receiving 50 mg daily of sildenafil reported significant improvements in IPSS when compared to 180 men receiving placebo (-6.32 *vs.* -1.93, $p < 0.0001$) and mean IPSS QoL score *vs.* placebo (-0.97 *vs.* -0.29, $p < 0.0001$). No differences were seen in urinary flow rates (Q_{max}, $p = 0.8$) between the two groups. Roehrborn and colleagues [31] similarly conducted a study in 1058 men with LUTS secondary to benign prostatic hyperplasia (BPH). Following a 4-week placebo run-in period, participants were randomized to receive once daily treatment with placebo or tadalafil (2.5, 5, 10 or 20 mg) for 12 weeks. Significant improvements were observed in IPSS irritative and obstructive subscores for participants taking 5, 10, and 20 mg tadalafil. The 5 mg dose was noted to provide the best risk-benefit profile.

In a double-blind study, Gacci and colleagues [32] assessed the role of vardenafil in continence recovery after bilateral nerve sparing radical prostatectomy (BNS-RP). Thirty-nine men with prostate cancer were enrolled and assigned to vardenafil on demand, vardenafil nightly, or placebo. Urinary bother and urinary function were assessed using the University of California—Los Angeles Prostate Cancer Index questionnaire preoperatively and at 1, 3, 6, 9, 10, and 12 months post-operatively. Significant improvements in urinary bother and urinary function were observed after nightly and on-demand administration of vardenafil at 12 month follow-up when compared to placebo. Daily vardenafil administration yielded better results than on-demand administration in regard to continence rates.

Urodynamic studies are beneficial in monitoring LUTS and the response of LUTS to treatment. In a single center, randomized, double-blind, placebo controlled trial, Gacci and colleagues [33] assessed changes in urodynamic indices following vardenafil administration in 25 patients with SCI. Three urodynamic parameters were assessed: maximum detrusor pressure, maximum cystometric capacity, and detrusor overactivity volume. One urodynamic assessment was performed at baseline and a second one was performed 3 h after the administration of 20 mg vardenafil in 15 cases and placebo in 10 cases. Urodynamic parameters were unchanged for those who received placebo. Vardenafil administration produced significant improvements. Vardenafil reduced maximum detrusor pressure with a mean decrease of 12% ($p < 0.001$), increased mean maximum cystometric capacity by 17% ($p < 0.001$), and increased detrusor overactivity volume by 25% ($p < 0.0001$).

A similar improvement in urodynamic indices was observed by Taie and colleagues [34], who performed a pilot study to assess the impact of single dose oral tadalafil on 20 patients with supra sacral spinal cord injury. After an initial baseline urodynamic assessment, all patients were administered a single dose of 20 mg tadalafil. A second urodynamic test was performed after 1 h and urodynamic indices were then compared. Improvements were observed in bladder compliance, bladder capacity, maximum voiding detrusor pressure, and maximum detrusor filling pressure.

4. Conclusion

The prevalence of LUTS increases with age, and its complex pathophysiology can make treatment difficult. Recently, the bladder has become the target of several studies as the focus of research has shifted from a prostate-centered approach to LUTS treatment. The NO/cGMP and cAMP pathways appear to be involved in the pathophysiology of LUTS. Several theories, however, remain regarding the mechanism of action of PDE inhibitors. Studies have shown the involvement of the cAMP, cGMP, K^+-channel modulated pathways and the ʟ-cysteine/H_2S pathway as possible pathways through which PDE5 inhibitors exert their effects on the bladder. Animal models have also produced conflicting results as to the location of the bladder where the PDE5 inhibitors exert their effects, whether it is the muscle cells, nerve fibers, or interstitial cells. Human trials and urodynamic studies involving the use of PDE5 inhibitors have however provided encouraging results in the treatment of LUTS. Further studies are therefore required to definitively identify the underlying processes associated with the use of PDE5 inhibitors in order to effectively manage conditions related to the lower urinary tract.

Conflicts of interest

The authors declare no conflict of interest.

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