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REVIEW

Effect of phosphodiesterase inhibitors in the bladder

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Overactive bladder syndrome (OAB);
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NO/cGMP;
cAMP

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.

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

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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.