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Review – Sexual Medicine

Update on Phosphodiesterase (PDE) Isoenzymes as Pharmacologic Targets in Urology: Present and Future

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Abstract

Objectives & Methods: Diseases of the human urinary tract represent common morbidities characterized by a high prevalence in the population of most westernized countries. The existence of a significant number of affected patients and the recent increase in scientific attention has resulted in various experimental and clinical efforts in order to evaluate the mechanisms controlling the function of urinary tract organs. This review attempts to describe the physiology and pharmacology of phosphodiesterase (PDE) isoenzymes with special regard to their (potential) use in disorders of the human urogenital tract.

Results: The promising clinical data for the orally active phosphodiesterase (PDE) inhibitors sildenafil, vardenafil and tadalafil, used in the treatment of male erectile dysfunction (MED), has boosted research activities on the significance of the cyclic GMP- and cyclic AMP pathway in other genitourinary tract tissues, such as the bladder, prostate, ureter, urethra, as well as female genital tissues. Based on the more extensive understanding of the pathways controlling the function of the male and female urogenital tract, orally administered phosphodiesterase inhibitors are considered a logical and straightforward approach for treating urological diseases. Due to the unending charge to conceive advanced first-line treatments, new therapeutic options taking into consideration the cyclic nucleotide signaling have been introduced or might be launched in the near future. Upcoming strategies will not only focus on the nitric oxide (NO)/cGMP cascade but also on compounds modulating signal transduction mediated by cyclic adenosine monophosphate, as well as combined agents in order to affect multiple peripheral intracellular targets.

Conclusions: The article highlights cGMP- and cAMP-pathways, PDE subtypes and their present or putative future clinical significance in urological practice.
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1. Introduction

The cyclic nucleotide monophosphates (cNMPs) cAMP and cGMP are important intracellular regulators of several processes, including smooth muscle motility, electrolyte homeostasis, neuroendocrine signals and retinal phototransduction [1,2]. Nitric oxide (NO) is a crucial mediator of smooth muscle relaxation of the corpus cavernosum. It is also suggested to be involved in the regulation of smooth muscle tonus of the outflow region, prostate, clitoris and vagina, and to modify neurotransmission in the urogenital region [3–5]. NO interacts with the soluble guanylate cyclase (sGC) in the cell cytoplasm and increases the rate of conversion of GTP into cGMP. The structurally related particulate GC (pGC) extends in an extracellular domain to which natriuretic peptides bind and subsequently can accumulate intracellular cGMP [2]. The molecular mechanism underlying, for example, the control of smooth muscle contractility by cAMP is similar, and includes interactions with cyclic nucleotide-regulated protein kinases, ion channels and PDEs. cNMPs are synthesized following a physiologic signal (e.g., the release of NO from nonadrenergic, noncholinergic nerve terminals or activation of specific G-protein-coupled receptors on the outer cell surface) from the corresponding nucleoside triphosphate by the activity of adenylyl and guanylyl cyclases. This increase in cAMP or cGMP triggers a signal transduction cascade that encompasses the activation of cyclic nucleotide-dependent protein kinases A and G, subsequent phosphorylation of the actin-myosin system, as well as Ca^{2+} channels and adenosine triphosphate-driven Ca^{2+} pumps located in the outer cell membrane or the membrane of the sarcoplasmatic reticulum. This cascade leads to a reduction in cytosolic Ca^{2+} and, finally, to smooth muscle relaxation. cNMPs are degraded by PDEs, a heterogenous group of hydrolytic enzymes. It is because of their central role in smooth muscle tone regulation that PDEs have become an attractive target for drug development. PDEs are classified according to their preference or affinity for cAMP and/or cGMP, kinetic parameters of cNMP hydrolysis, relative sensitivity to inhibition by various compounds, allosteric regulation by other molecules and chromatographic behaviour on anion exchange columns (Fig. 1).

Eleven families of PDE isoenzymes can be distinguished: Ca^{2+}/calmodulin-stimulated PDE (phosphodiesterase type 1 [PDE1]), cGMP-stimulated PDE (PDE2), cGMP-inhibited PDE (PDE3), cAMP-specific PDE (PDE4), cGMP-specific PDE (PDE5) and the cGMP-binding, cGMP-specific PDE of mammalian rods and cones (PDE6). While PDE7 (cAMP-high affinity) and PDE8 (3-isobutyl-1-methylxanthine [IBMX]-insensitive) have preferred selectivity for cAMP, PDE9 exclusively degrades cGMP. PDE 10 and 11 can inactivate both cAMP and cGMP [6–11]. Some of these isoenzyme families contain more than one gene (isogenes), and some genes are alternatively spliced so that, to date, more than 50 isoenzymes or variants have been described [12–15]. Some PDE genes are also variably transcribed in different tissues. For example, PDE2 is predominantly found in vascular smooth muscle. Expression of PDE5 in the corpus cavernosum and the cGMP-mediated relaxation of the cavernous smooth muscle during sexual stimuli have made inhibition of this enzyme a clinical benefit in the management of erectile dysfunction (ED). Phosphodiesterase 7 is abundant in skeletal muscle and is also present in human kidney, brain, and pancreas. Although expressed in other tissues, high levels of PDE8, PDE10 and PDE11 are found in the testis, and PDE9 is expressed in intestinal smooth muscle, skeletal muscle and brain [13,15]. To date, 6 of these 11 isoenzymes (PDE 1, 2, 3, 4, 5 and 11) have been proven to be of pharmacologic importance. Since 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 PDE families or more than one variant of an individual family, there are numerous examples in which an individual PDE is predominantly found in a specific localization (Table 1).

2. Male erectile dysfunction

The discovery of the importance for relaxation of human cavernous tissue of the NO and cGMP pathway is a landmark for the development of the ''modern'' pharmacology of ED [16,17]. It has led to the identification of certain drugs that can elevate intracellular levels of cGMP. Among these agents are the NO donors sodium nitroprusside, nitroglycerine and linsidomine (SIN-1), and selective inhibitors of PDE5 [18,19]. Further reports of PDE5 as one crucial regulator of the intracellular amount of cGMP in the human corpus cavernosum, and findings that sildenafil improved erectile responses in men with ED by inhibiting PDE5 [20,21], led to a major breakthrough in the pharmacologic management of ED, and prompted the development of additional orally active PDE5 inhibitors, such as vardenafil, tadalafil, TA 1790 and DA 8159, for this therapeutic purpose. All PDE inhibitors are nonhydrolysable
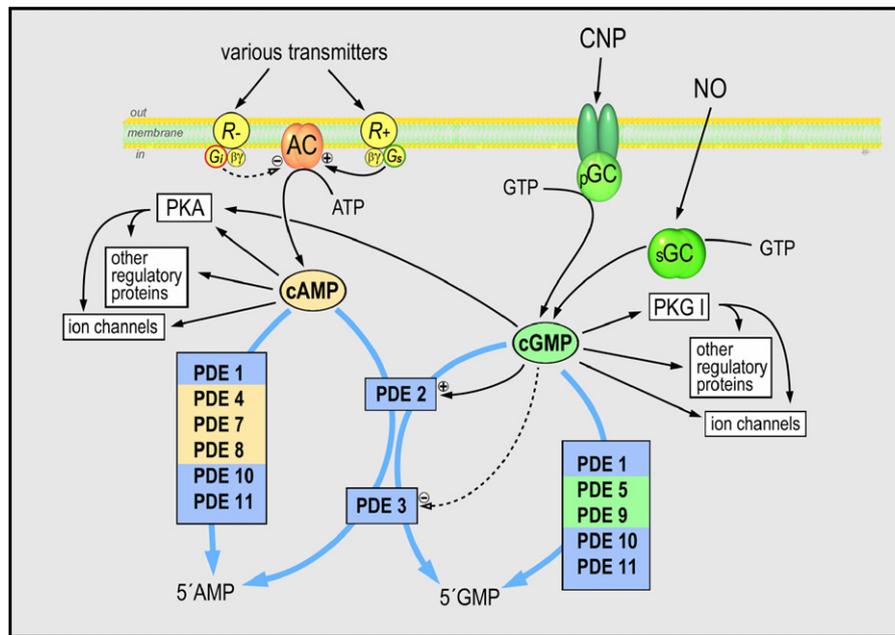
Fig. 1 – Schematic illustration of the pathways involved in regulation of signals mediated by adenosine and guanosine cyclic monophosphates (cAMP and cGMP) in the urogenital tract. The activity of adenylate cyclase (AC), which synthesizes cAMP, is classically modified by numerous transmitter systems (e.g., amines, peptides, purines, and arachidonic acid metabolites), which interact with G-protein-coupled cell-surface receptors. Nitric oxide (NO) interacts with the soluble guanylate cyclase (sGC) in the cell cytoplasm and increases the rate of conversion of GTP into cGMP. The pGC extends in an extracellular domain to which C-like natriuretic peptides bind to and induce the accumulation of intracellular cGMP. The molecular mechanism underlying the control of smooth muscle contractility by cAMP and cGMP include interactions with cyclic nucleotide-regulated protein kinases, ion channels and PDEs. The intracellular levels of cyclic nucleotides are regulated by PDEs, which catalyse the hydrolysis of the $3'5'$-cyclic monophosphates to $5'$-monophosphates. At least 11 families of PDE isoenzymes can be distinguished, and the various PDE isoenzymes exhibit variable affinities to cAMP or cGMP, and the activity of some of the PDEs can also be modified by the cyclic nucleotides. Gi or Gs = inhibitory or stimulatory G-proteins, respectively, with subunits (β and γ); PKA = protein kinase A; PKGI = protein kinase G I; R– or R+ = receptors that are negatively or positively coupled, respectively, to the AC.

analogues to cGMP that counteract the degradation of this cyclic nucleotide by completive binding to the catalytic site of PDE5. Hereby, enhancement of NO-initiated relaxations of cavernous erectile tissue can be obtained [22,23]. To date, the abundant expression of PDE5 protein in the human corpus cavernosum versus other tissues is considered the main reason for the clinical efficacy of PDE5 inhibitors in the treatment of ED. In turn, this elevated expression of PDE5 in the penis might be responsible for the low efficacy of NO donor drugs, which have not yet been introduced successfully to the pharmaceutical market [24].

2.1. Sildenafil

Sildenafil (VIAGRA) was introduced into the pharmaceutical market in 1998 and has since revolutionized the pharmacologic management of ED. The inhibition constant (Ki) of PDE5 for sildenafil in cultured human corpus cavernosum smooth muscle cells has been reported as 2–4 nM, and PDE5 assays of sildenafil's effect on cGMP hydrolysis have shown inhibitory concentration of 50% (IC_{50}) values of 1–6.6 nM [25,26]. Binding of cGMP to allosteric binding sites of the PDE5 for cGMP has been proposed to increase the hydrolytic action of the enzyme and is also suggested to affect the dissociation of sildenafil from the catalytic site [27]. The efficacy of sildenafil has been evaluated in various clinical trials involving more than 6000 male subjects with different causes of impotence: psychogenic, with no identifiable organic cause, as well as patients with diabetes, and histories of spinal cord injury and pelvic surgery. A review of 11 double-blind and placebo-controlled studies (12 weeks of flexible-dose treatment) of more than 2500 patients showed significantly improved erectile function for sildenafil (25–100 mg), compared with placebo. This improvement was regardless of age, ethnic origin, etiology,

Table 1 – Human phosphodiesterase isoenzyme families; their major substrates, specific and (nonspecific) inhibitors, and potential target organs in the male and female urogenital tract

PDE isoenzyme	Major substrate(s)	Inhibitors (selective)	Urogenital target tissue (disorder)
PDE1	cAMP/cGMP	Vinpocetine 8-methoxymethyl-IBMX	Urinary bladder (OA, LCB)
PDE2	cAMP	EHNA	
PDE3	cAMP	Amrinone Cilostamide Enoximone Milrinone Ouazinone (Ro 13-6438) Siguazodan Trequinsin (HL 725) Zardaverine	HCC (ED) Urinary bladder (OA, LCB)
PDE4	cAMP	Etazolate Ro 20-1724 Roflumilast Rolipram Zardaverine ZK 803616	Clitoris (FSD) HCC (ED) Prostate (BPS, PCa) Ureter (USD) Vagina (FSD)
PDE5	cGMP	CP 461 DA 8159 E 4021 Exisulind Sildenafil NCX 911 (sildenafil nitrate) TA 1709 Tadalafil Vardenafil Zaprinast (M&B 22948)	Clitoris (FSD) HCC (ED) Prostate (BPS, PCa) Ureter (USD) Urinary bladder (OA; LCB) Vagina (FSD)
PDE6	cGMP	Papaverine Sildenafil Zaprinast Dipyridamole	
PDE7	cAMP	Papaverine Dipyridamole	
PDE8	cAMP	Papaverine Dipyridamole	
PDE9	cGMP	Papaverine Dipyridamole Zaprinast (M&B 22948)	
PDE10	cAMP/cGMP	Papaverine Dipyridamole	Vagina (FSD)
PDE11	cAMP/cGMP	Dipyridamole Tadalafil Zaprinast (M&B 22948)	Clitoris (FSD) Prostate (BPS, PCa)

BPS = benign prostatic syndrome; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; ED = erectile dysfunction; EHNA = 9-erythro-2-(hydroxyl-3-nonyl)adenine; FSD = female sexual dysfunction; HCC = human corpus cavernosum; IBMX = 3-isobutyl-1-methylxanthine; LCB = low-compliance bladder; OA = overactive bladder; PCa = prostate carcinoma; PDE = phosphodiesterase; USD = urinary stone disease.

severity, or duration of ED, or occurrence of assorted comorbidities [28]. In all trials, men receiving sildenafil reported erections sufficient for sexual intercourse more often than did those who received placebo [29]. Sildenafil is rapidly absorbed, and maximum plasma concentrations were observed within 60 minutes after a single dose; the half-life of the drug amounts to 4 hours. The response rates were calculated at 84% in patients with a psychogenic cause of ED to only 43–52% in patients in whom either the central or local production of NO is impaired (e.g., because of diabetes or damages to pelvic neural innervation). These observations highlight the fact that the action of sildenafil and other PDE5 inhibitors requires unimpaired neuronal input into the corpus cavernosum as well as intact cavernous endothelial structures. The most common side-effects reported with the use of sildenafil were headache (18%), flushing (11%), dyspepsia (7%), nasal congestion (5%) and visual disturbances (blue vision, 2%) [30]. These side-effects are related to the fact that PDE5 is not only present in the corpus

cavernosum penis but also in other tissues [31]. Moreover, sildenafil is known to inhibit PDE6, which is the predominant isoenzyme in the mechanism of visual perception in the retina. Evaluation of the safety of sildenafil by analysis of results from double-blind and placebo-controlled studies, as well as data from long-term open-label studies, did not reveal any increase in serious cardiovascular episodes or in mortality rates when compared with expected values for the general population [32]. Because of its mechanism of action (enhancement of cGMP), the use of sildenafil (and other PDE5 inhibitors) is contraindicated in ED patients taking nitrates, because the combination synergistically potentiates vasodilation and may cause severe hypotension.

2.2. Vardenafil

Vardenafil (LEVITRA is another PDE5 inhibitor used in the treatment of ED. The drug is 10 times more potent than sildenafil (IC_{50}, 6.6 nM), inhibiting the hydrolysis of cGMP by PDE5 with an IC_{50} of 0.7 nM [33,34]. It is more selective for PDE5 than for PDE1 and PDE6, presenting IC_{50} ratios ($IC_{50}PDEX/IC_{50}PDE5$) of 257 (sildenafil, 60) and 16 (sildenafil, 7.4), respectively [35]. Vardenafil is applied in single doses of 10 mg and 20 mg; the time to maximum plasma concentration was determined at 0.7 hour. Fifty percent of patients achieved erections within 30 minutes after the administration of an oral dose. With regard to its pharmacokinetic profile, the drug is similar to sildenafil. Vardenafil is eliminated from the plasma with a half-life time of 4–5 hours, whereas the responsiveness (time from onset to offset of drug action) after drug dosing exceeds the plasma half-life time [36]. Because of its PDE5 inhibitory activity, vardenafil and sildenafil have a similar profile of adverse events. In contrast to sildenafil, no disturbances in visual perception were noted [37]. Results pooled from seven randomized, placebo-controlled, fixed-dose trials of at least 12-weeks duration including 4286 men with organic, psychogenic or mixed ED showed that 69% of the vardenafil treatment group reported improved erections, compared with 26% of the study population receiving placebo. A 26% increase in the success rate for penetration and a 30% increase in the rate for maintaining an erection during intercourse were reported for vardenafil in comparison with placebo. Although patients receiving 20 mg of vardenafil exhibited better improvement of primary efficacy variables than those men who were allocated to 5 or 10 mg of the drug, the meta-analysis could not conclude any clinically relevant difference

between 10 or 20 mg of vardenafil [38]. In a long-term study (2 years) of the efficacy of vardenafil (10 or 20 mg) in 489 patients, 90–92% of patients reported improved erections, and 92–94% successful intercourse attempts at the end of the treatment period [39]. With regard to the cardiovascular safety of the drug, it has been demonstrated that it did not affect the ability of patients with coronary artery disease to maintain a level of exercise similar to that required for sexual activity [40,41].

2.3. Tadalafil

Tadalafil (Cialis) is another compound from the group of selective PDE5 inhibitors. Its chemical structure differs significantly from sildenafil and vardenafil, with little activity against most of the other PDE isoenzymes: The IC_{50} ratio for PDE1, PDE4, PDE7 and PDE10 is greater than 10,000 and was estimated at 780 for PDE6 [42]. Nevertheless, tadalafil presented a 5-fold higher selectivity for PDE11A (IC_{50} ratio, 7.1) than does sildenafil (IC_{50} ratio, 203) and vardenafil (IC_{50} ratio, 346). Until now, the physiologic impact of PDE11, which is mainly present in human prostate, testes and skeletal muscle, and the inhibition of its activity have not been fully evaluated [43]. Within 25–30 minutes after the intake of 20 mg tadalafil, the majority of men achieved penile rigidity following sexual stimulation. The plasma half-life of tadalafil amounts to 17.5 hours. In placebo-controlled, fixed-dose trials, tadalafil significantly enhanced all efficacy outcomes: Integrated analyses of five randomized double-blind, placebo-controlled trials that enrolled 1112 men with mild to moderate ED of various etiologies and with hypertension, stable coronary artery disease or diabetes showed that tadalafil (2.5–25 mg) improved erections in 42–81% of patients, compared with 35% for placebo. Seventy-three percent to 80% of attempts to have intercourse between 30 minutes to 36 hours after intake of 20 mg of tadalafil were reported to be successful [44]. A multicenter, randomized, double-blind, placebo-controlled study of 348 men with mild to moderate ED of organic, psychogenic or mixed etiology verified efficacy of tadalafil at 24 and 36 hours after dosing. Sixty-one percent and 64% of patients reported successful attempts at intercourse at 24 and 36 hours after intake of tadalafil, respectively (vs 37% and 35% for placebo) [45]. Factors such as the intake of food or alcohol have no relevant effects on the pharmacokinetics of the drug. The most common adverse events were headache (in 23% of the patients; placebo, 17%) and dyspepsia (11% vs 7% for placebo). While, in contrast

to sildenafil and vardenafil, no facial flushing was observed with the use of tadalafil, up to 5% of the patients experienced back pain (placebo, 0%) [46]. It has been speculated that the inhibitory activity of tadalafil towards PDE11A might be responsible for this side-effect [47]. Studies to evaluate the interactions between tadalafil and organic nitrates demonstrated only modest synergistic effects of tadalafil on the nitrate-induced reduction in mean systolic and diastolic blood pressure [48].

2.4. PDE inhibitors in the treatment of ED: beyond PDE5?

Prior to the generally accepted clinical use of PDE5 inhibitors for the management of ED, compounds proceeding through cAMP-dependent mechanisms were widely used in ED self-injecting regimes. Related drugs include prostaglandin E1 (PGE1), vasoactive intestinal polypeptide, and forskolin, a diterpene stimulating adenylyl cyclase (AC) [49–51]. By binding to specific G-protein–coupled receptors in the membrane of smooth muscle cells, prostaglandins or peptidergic ligands can activate AC with increased intracellular production of cAMP. cAMP preferably acts on the cAMP-dependent protein kinase, which antagonises the cellular contractile mechanism via modulation of the activities of other proteins (e.g., Ca^{2+} channels). The intracellular level of cAMP in human erectile tissue is mainly regulated by the cAMP-degrading PDE3 and 4. Although activation of the AC/cAMP–signaling system is established as an effective relaxation-producing pathway in human cavernous tissue, only a few studies have been conducted to characterize regulatory proteins of the AC/cAMP axis. Evidence for the presence of PDE 3 and 4 in human erectile tissue has been shown. Messenger RNA (mRNA) encoding for PDE3A, PDE4A-D, PDE7A and PDE8A, all of which are known to hydrolyse cAMP, was shown by means of reverse transcription polymerase chain reaction and Northern blot analysis [52,53]. Results obtained in vitro suggest that PDE3 and PDE4 might be the predominant isoenzymes in the human corpus cavernosum [54,55]. Interestingly, it has been shown that the relaxation of alpha$_1$-adrenoceptor (a$_1$-AR)-mediated tension of isolated human corpus cavernosum induced by sildenafil and tadalafil was reversed by the protein kinase A inhibitor Rp-8-CPT-cAMPS, suggesting an involvement of cAMP-mediated mechanisms in the action of PDE5 inhibitors. A significant role of PDE4 and cAMP in the control of human erectile tissues is further supported by the finding that immunoreactions specific for PDE4 and PDE4A were detected in

cavernous endothelial and neuronal structures [56]. On the basis of these observations, an important complementary role might be considered for the AC/cAMP/PKA pathway in the regulation of cavernous smooth muscle tone. This observation provides a rationale to further investigate the effects of selective PDE4 inhibitors, as well as compounds inhibiting both PDE5 and PDE4, in models for erectile function and dysfunction [57,58].

3. Premature ejaculation

Besides erectile dysfunction, premature ejaculation (PE) is another very common sexual disorder among males. PE might be primary or secondary to other underlying diseases. The pharmacotherapy of PE has been primarily focused on behavioural therapy, topical anaesthetics, tricyclic antidepressants and selective serotonin reuptake inhibitors. Nevertheless, an approved treatment is not yet available. Therefore, the community of pharmacologists and physicians is aiming to set up new pathophysiologic models describing the mechanisms of PE, which take into account sympathetic, motor pudendal and suprasacral disturbances, as well as alterations on the level of serotonin receptor expression, all of which might well affect normal seminal vesicle (SV) and ductus deferens (DD) smooth muscle function [59]. Some pioneer work conducted by Machtens et al. [60–62] and Heuer et al. [63] suggested a significance of the NO-cGMP pathway in the control of the function of human SV. They reported the inhibition of SV contractile activity by various NO donor drugs and demonstrated by means of immunocytochemistry the occurrence of endothelial nitric oxide synthase in endothelial cells lining SV glandular spaces. In addition, they found immunosignals specific for neuronal nitric oxide synthase in subepithelial glandular structures and nerve fibers. Their conclusion that SV smooth muscle function is regulated by the NO-cGMP cascade is supported by results from recent clinical trials [64,65] suggesting a potential usefulness of the PDE5 inhibitor sildenafil in the treatment of PE. It is assumed that the capability of sildenafil to retard male ejaculation may include the modulation of the contractile response of the DD and SV. However, until now, only a little is known about the distribution of PDE isoenzymes in the human SV and DD, and the functional effects of PDE inhibitors on the contractile activity and cyclic nucleotide turnover in the said tissues. The results of experiments from our laboratory demonstrated

that PDE inhibitors could reverse the contractility induced by norepinephrine of isolated human SV tissue and increase levels of cyclic nucleotides [66]. Thus, the available data also indicate that there is clinical, physiologic and pharmacologic evidence to explain the efficacy of PDE5 inhibitors in PE; however, much experimental work is needed to establish a comprehensive conceptual pharmacologic framework for the future drug therapy of PE using PDE inhibitors or NO donor drugs.

4. Diseases of the prostate: benign prostatic syndrome and prostate cancer

The so-called benign prostatic syndrome (BPS) represents a major health care problem in westernized countries. BPS comprises obstructive and irritative symptoms (lower urinary tract symptomatology [LUTS]), as well as benign prostatic enlargement (BPE) with variable degrees of bladder outlet obstruction [67,68]. It is estimated that approximately 50% of men older than 50 years have moderate to severe symptoms arising from LUTS and that 25% of these seek medical attention for relief of clinical BPE [69]. Major symptoms may include urinary frequency, nocturia and slow stream. Untreated BPE can lead to urinary retention, urinary tract infections and, in rare cases, renal insufficiency.

The current pharmacologic management of LUTS and BPE involves alpha$_1$-adrenergic blockers, such as alfuzosin, doxazosin and tamsulosin, to diminish urethral resistance by reducing the a_1-AR-mediated tension of smooth muscle fibres located in the transitional zone and periurethral region [70]. Intervention in the hormonal control of prostate growth by using inhibitors of 5-alpha-reductase activity is another approach to ease symptoms [71,72]. However, nearly 20% of all patients presenting with LUTS/BPE have to undergo surgery to achieve effective relief of symptoms [73]. To date, various attempts involving different drugs, such as aromatase inhibitors, derivatives of the polyenantibiotic partricin, potassium channel openers and antagonists of the peptide endothelin 1, have been made to inhibit the proliferation of prostatic stromal tissue or to reverse the tone of prostatic smooth musculature [74–77].

Results from experimental studies suggested a potential significance of the NO-cGMP and AC-cAMP pathways in the control of prostate smooth musculature [78–80]. Ückert et al. [81] demonstrated the expression of PDE isoenzymes in the human prostate by means of molecular biology and protein chemistry. They found mRNA transcripts encoding for PDE 1, 2, 4, 5, 7, 8, 9 and 10 in the different anatomic regions of the human prostate and demonstrated hydrolytic activities of PDE isoenzymes 4 and 5 in cytosolic fractions of prostatic tissue. The a_1-AR–mediated tension of prostatic strip preparations was reversed by the AC activator forskolin, the NO donor SNP, and by rolipram and sildenafil, known as inhibitors of PDE 4 and 5, respectively. In another study [82] from the same group, they used immunohistochemical methods and showed the expression of PDE4 (cAMP-PDE) in the fibromuscular stroma and in glandular structures of the transition zone, whereas they observed immunoactivity that indicated PDE5 (cGMP-PDE) mainly in glandular regions. These results, together with molecular biology data [24], support the use of inhibitors of PDE4 and 5 for treating LUTS and urinary obstruction secondary to BPH. Interestingly, the results from a clinical pilot study [83] including male subjects complaining of LUTS indicated a positive impact of sildenafil in these men according to a significant improvement in their IPSS symptom scores. It has been presumed that these effects might be mediated through prostatic smooth muscle relaxation. On the basis of the results of molecular biology analysis, involvement of the dual substrate PDE11, a cAMP/cGMP PDE, in the control of the prostate was also suggested [11]. It was shown by means of immunohistochemistry that PDE11A protein is mainly expressed in glandular epithelial and subepithelial layers [84]. Interestingly, it has been demonstrated that an increase in both intracellular cAMP and cGMP in human prostate cancer cell lines initiates morphologic differentiation, and inhibits the proliferation and invasive potential of the cells [85,86]. The antiproliferative and proapoptotic effects of the PDE5 inhibitors MY 5445, exisulind (sulindac sulfone) and its derivatives CP248 and CP461 were described. The potential use of these compounds as selective apoptotic and antineoplastic drugs in the treatment of localized and advanced prostate cancer was speculated [87,88]. Moreover, it is notable that, to date, the most potent compounds known to inhibit the activity of PDE11 are PDE5 inhibitors. The distribution of PDE5 and 11A in the transition zone of the prostate might give way to the speculation that these isoenzymes are of significance in the control of glandular epithelial tissue proliferation, and it can be speculated as to whether PDE inhibitors have the potential to prevent or reverse the malignant transformation of prostatic intraepithelial cells.

5. Bladder overactivity

Anticholinergic drugs are currently the therapy of choice to treat urgency and urge incontinence [89]. Nevertheless, until now, muscarinic receptor blockers acting exclusively on detrusor smooth muscle are not available. Moreover, the unstable detrusor seems to be regulated in part by noncholinergic mechanisms. These factors may explain the common side-effects and the limited clinical efficacy of anticholinergics. The development of new drugs with novel mechanisms of action for the treatment of the overactive bladder is therefore essential, and the future use of beta$_3$-adrenoceptor agonists, alpha$_1$-adrenoceptor antagonists and potassium channel openers has been discussed [90]. The specific modulation of intracellular second messenger pathways also offers the promising possibility of a selective manipulation of tissue function, especially with regard to the contraction and relaxation of human urinary bladder smooth musculature. Thus, a potential benefit of PDE inhibitors in the treatment of the unstable detrusor was addressed. Using chromatographic methods, Truss et al. [91] were the first to show the presence of the PDE isoenzymes 1 (cAMP/cGMP PDE, Ca^{2+}/calmodulin dependent), 2 (cAMP PDE, cGMP dependent), 3 (cAMP-PDE, cGMP inhibited), 4 (cAMP-PDE) and 5 (cGMP-PDE) in the human detrusor. They also reported the relaxant responses of isolated human detrusor strips contracted by the muscarinic agonist carbachol to the nonspecific PDE inhibitor papaverine and the PDE1 inhibitor vinpocetine. The relaxing effects of the drugs were paralleled by an increase in tissue levels of cAMP and cGMP [92]. They concluded that the cAMP pathway and the Ca^{2+}/calmodulin-dependent PDE1 might be of functional importance in the regulation of human detrusor smooth muscle. In another study, Ückert et al. [93] investigated the functional responses of isolated normal human detrusor to inhibitors of the PDE isoenzymes 2, 3 and 5, including MEP1, trequinsin, E 4021, diethylaminosulfonyl-pyrazolopyrimidine and morpholinosulfonylpyrazolopyrimidine (MSPP). They found that the PDE5 inhibitor MSPP was one of the most efficacious drugs tested with regard to the reversion of tissue tension induced by carbachol and speculated that the application of PDE inhibitors may be feasible to treat urge incontinence. Later, results from a randomized, double-blind, placebo-controlled study [94] to assess the clinical effects of the PDE1 inhibitor vinpocetine in patients with urgency and urge incontinence who failed standard pharmacologic therapy demonstrated that vinpocetine was superior to placebo with regard to the

clinical outcome parameters micturition frequency, bladder volume at first sensation, bladder volume at voiding desire, maximum detrusor pressure and voided volume.

Modulating the activity of PDEs might represent a novel approach, possibly avoiding the limitations of anticholinergic therapy in patients with lower urinary tract dysfunction. Future studies will delineate as to whether PDE inhibitors, such as the PDE1 inhibitor vinpocetine or selective PDE5 inhibitors, may have significance in the treatment of detrusor instabilities and urge incontinence.

6. Urinary stone disease

Urinary stone disease is an indication in which pharmacologic relaxation of ureteral smooth muscle would present an attractive therapeutic alternative. In the case of an uncomplicated renal or ureteral concrement, the intravenous administration of analgesics is the most effective way to relieve pain [95]. With respect to the potential beneficial effect of ureteral relaxation on stone passage, spasmolytic agents, such as phentolamine and orciprenaline, have been shown to dilate the ureteral lumen at the position of an artificial concretion, thus enabling increased fluid flow. Many drugs have been used in ureteral colic management, but a drug that can relieve pain and facilitate stone passage with minimal side effects is not yet available. Taher et al. [96] reported the presence of the PDE isoenzymes 1, 2, 4 and 5 in cytosolic supernatants prepared from human ureteral tissue and demonstrated the ability of the PDE3 inhibitor quazinone, PDE4 inhibitor rolipram, and dual PDE5/PDE1 inhibitor zaprinast to relax the tension induced by KCl of circular ureteral segments in vitro. Kühn et al. [97] confirmed the relaxing properties of inhibitors of PDE4 (rolipram) and 5 (E 4021, MSPP) on ureter smooth musculature, and showed that the relaxing properties of the drugs were paralleled by their ability to elevate intracellular levels of cAMP and cGMP, respectively. In a rabbit model, Becker et al. [98] examined the in vivo potential of rolipram in comparison with papaverine, theophylline and scopolamine to induce ureteral relaxation. They found that only rolipram induced pronounced relaxation of the rabbit ureter in vivo with no effects on the systemic circulation, whereas the injection of scopolamine, papaverine and theophylline exerted either no or only short-lasting relaxation of the ureter but significantly lowered systemic blood pressure. Three characteristics of a PDE4 inhibitor should be beneficial in the treatment of ureteral

colics: (1) Relaxation of the ureteral muscle at the site of the calculi should relieve colic pain and facilitate stone passage. (2) PDE4 inhibitors are supposed to induce minimal systemic side-effects at the dosage needed. (3) Improved isoenzyme selectivity of third-generation PDE inhibitors will help to focus drug effects on the target tissue. For clinical application, the use of PDE4 inhibitors seems promising because of the anti-inflammatory effect as well as the favourable effect/side-effects ratio.

7. Female sexual dysfunction

Female sexual dysfunction (FSD) is evolving as a new and exciting topic in urology. FSD is supposed to be age related and highly prevalent, affecting approximately 30–50% of women in westernized countries [99,100]. Because of the development of successful treatments for male ED, FSD is now also receiving increased awareness among clinicians and pharmacologists. Although FSD is a condition involving anatomic, physiologic, psychologic and medical components, it is without doubt that the normal function of anatomic key structures of the female genital tract, such as the clitoris and vagina, is essential to experience sexual excitement, arousal and orgasm. With sensory and visual sexual stimulation, an increase in genital blood flow and the relaxation of the smooth musculature of the vagina and clitoris occur, which result in an increase in vaginal lubrication and luminal diameter, as well as an engorgement of the erectile tissue of the corpus cavernosum clitoris [101,102]. These events are considered prerequisites to enable the penetration of the penis during sexual intercourse and allow perception of noncoital and coital stimulation leading to arousal and orgasm. Nevertheless, the mediators and mechanisms contributing to this process are only poorly understood. Numerous studies have described the importance of cNMP, especially the cGMP signaling cascade, in the induction of penile erection, and there is increasing knowledge on the significance of cNMP-mediated transmission in the control of the function of human female genital organs: It was deduced from the results of earlier studies that the NO-cGMP pathway may also play a role in the mechanism of female sexual arousal and that the response to sexual stimulation in women is mediated by the same biologic pathways as those in males. This deduction is supported by the finding that both the endothelial and neuronal isoforms of nitric oxide synthase (NOS) are largely distributed in the human clitoris [103]. The presence of PDE5 in the human clitoris was shown by means of ion exchange chromatography and immunohistochemistry [104,105]. Moreover, immunosignals related to PDE2, 4 and 4A were shown in subepithelial blood vessels; the fibromuscular stroma, sinusoidal endothelial and subendothelial layers; and in nerve fibers, respectively, of the clitoris [105,106].

With regard to the vagina, immunoreactivities for PDE4 and PDE5 were observed in both vascular and nonvascular smooth muscle [107,108]. NO-immunoreactive nerves were found around vascular structures of the vagina, forming a dense subepithelial network (unpublished data). Although early experiences from human studies have so far not been conclusive, they suggest that the PDE5 inhibitor sildenafil may improve arousal responses in pre- and postmenopausal females with FSAD [109–111]. Other studies [112–114] also reported varying effects of PDE5 inhibition on sexual function in women with multiple sclerosis, spinal cord injury or unspecified sexual dysfunction. The overall lower clinical success of the PDE5 inhibitor sildenafil in the treatment of FSD might be due to the fact that, in the female genital tissues, clitoris and vagina, the expression of PDE5 is much lower than in the male penile erectile tissue [24,106]. Nevertheless, it has been shown that the use of additional diagnostic procedures, such as photoplethysmographic assessment of vaginal pulse amplitudes, may help to identify women responding to PDE5 inhibition [115]. Taken together, morphologic and preclinical findings are in favor of a role for PDE5 in the regulation of female genital vascular responses. Although the early experiences from clinical studies have so far not been conclusive, they suggest that the inhibition of PDE5—or other PDE isoenzymes—may be of benefit for selected subjects with FSD.

8. Gene-based strategies targeting PDE isoenzymes

Instead of abandoning the activity of a PDE isoenzyme by using selective inhibitors, downregulation of the expression of a respective PDE protein has also been discussed. This approach is an attractive alternative, since no cross-reactions with PDEs in the same or other tissues are expected to occur because of the unique sequences of exons and mRNA specific for PDE isoforms [116]. It is known that twice as much mRNA encoding for PDE5A is expressed in the human corpus cavernosum than in intestine, detrusor, brain or cardiovascular tissue [30]. The identification, cloning and investigation of the expression of PDE5 isoforms suggested that the

PDE5A3 variant is restricted to smooth muscle or cardiac tissue [117]. It was shown that the transfection of human corpus cavernosum smooth muscle cells with a specific PDE5 gene antisense oligonucleotide induced accumulation of cGMP in the cells, indicating that this approach may provide groundwork for gene therapy in the treatment of ED [118]. Nevertheless, to date, the only experimental models for genetic modulation in the field of urology are related to NOS, K$^+$ channels, protein kinase G and heme oxygenase in the penile tissue of rats and transgenic mice [119]. Further investigations of gene expression, protein localization and functional activities of PDEs in urogenital tissues may disclose interesting molecular targets for therapeutic intervention and may also identify disease-related alterations in the distribution of genetic material in a respective organ.

9. Conclusion

On the basis of the knowledge of the physiologic mechanisms regulating the male and female urogenital tract, the use of selective PDE inhibitors has been suggested a logical approach for the treatment of various urologic diseases. The increased scientific awareness in this field and the unending charge to conceive first-line treatments demonstrating advanced and superior efficacy to that of previous options offer a promising future for the use of PDE inhibitors in the therapy of diseases of the urinary tract and reproductive tissues. While some approaches should involve the NO-cGMP cascade, other strategies should also take into account the modulation of cAMP pathways, as well as the combination of active agents to affect multiple peripheral intracellular targets (e.g., a drug combining PDE5 inhibitory and NO-releasing properties). It is assumed that PDE inhibitors will be efficacious in terms of promoting normal organ function and will exert limited systemic adverse events.

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Editorial Comment

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The efficacy of cell to cell communication in the uro-genital system, as well as in other human tissues, is strictly dependent on a timely appropriate, discrete chemical and physical signalling, which is thereby transformed in appropriate cellular behaviour. Cyclic nucleotide monophosphates (cNMPs) are one of the best characterized signal transducers tightly regulated in both their formation and degradation. The phosphodiesterase enzymes (PDEs) play a crucial role in cNMPs degradation, and therefore in terminating otherwise overwhelming signals. PDEs, however, cannot be considered merely precious housekeepers, because they are actively involved in determining the final cellular response, in a tissue-specific way. The paper by Ückert and coworkers overviews their relevance in urogenital pharmacology, summarizing results obtained so far by inhibiting their activity, and, more interesting, broadcasting possible future goals with chemical or even genetic manipulation. PDEs are drug targets for the treatment of various medical conditions, including urogenital diseases. The best example of the extraordinary potential of PDEs manipulation is derived from clinical and experimental studies on PDE5, a cGMP-specific hydrolytic enzyme. Due to an androgen-dependent PDE5 over-expression in the penis [1,2], the employment of NO donors, which increase cGMP levels, does not result in relevant clinical benefit for the treatment of erectile dysfunction (ED), because newly formed cGMP is readily degraded. Conversely, silencing PDE5 degradation by genetic [3] or chemical (PDE5 inhibitors, PDE5i) manipulation results in a dramatic improvement in penile erection. As far as PDE5i is concerned, their combined specificity and the enrichment in the therapeutic target (PDE5) guaranties a timely and spatially limited effect and, therefore, their clinical success. Because other uro-genital tissues express a relative PDE5 abundance, as vas deferens [4], prostate and bladder [1], it is possible to envisage new potential benefit for PDE5i employment in premature ejaculation, benign prostate hyperplasia and overactive bladder. All these aspects are excellently covered by Ückert and coworkers in the present review.

References

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