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PDE5 Expression and Function in the Lower Urinary Tract: A Critical Review

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INTRODUCTION

PDE5 is one of eleven families of phosphodiesterases (PDEs) that hydrolyze cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) to their respective linear 5'-nucleoside monophosphates. By controlling cAMP and cGMP concentrations, PDEs play critical roles in numerous physiological and pathological processes. In humans PDE5 exists as three isoforms, PDE5A1, A2, and A3, which are translated from three alternatively spliced mRNAs, and which in turn are transcribed from two alternative promoters of a single gene PDE5A. The three isoforms differ only in the amino terminal, and except for PDE5A3 being smooth muscle-specific, they have no known functional differences.

Like most other PDEs, PDE5 is involved in many physiological and pathological processes. It is best known, however, for its role in terminating cGMP signaling in smooth muscle of various organs, particularly, the penis. In this regard, the launch of sildenafil (Viagra), a PDE5 inhibitor (PDE5I), for the treatment of erectile dysfunction (ED) helped drive PDE5 to the forefront of biomedical research. Now that PDE5's role in erectile function/dysfunction is a given, there has been an increase of interest in expanding its research into other tissues, in the hope that PDE5Is can also treat these tissues' associated diseases. In particular, it seems fitting for urological researchers to shift their attention to diseases such as overactive bladder (OAB), urinary incontinence and benign prostate hyperplasia (BPH). However, while clinical studies seem to indicate PDE5Is' therapeutic benefits, there are conflicting data concerning PDE5 expression and function in these lower urinary tract

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(LUT) tissues. As such, this review 1 article is intended to present all available data that are relevant to PDE5 expression and function in the bladder, prostate, and urethra.

BLADDER: CLINICAL STUDIES

The clinical relevance of bladder PDE5 expression largely concerns two disease entities, namely benign prostate hyperplasia (BPH)-associated bladder outlet obstruction (BOO) and overactive bladder (OAB). For BPH-BOO several clinical studies have concluded that PDE5Is were beneficial for reducing lower urinary tract symptoms (LUTS) [1–8] although a negative outcome was also obtained [9]. However, as BPH-BOO involves both the prostate and bladder, it remains undetermined whether the prostate, the bladder, or both, is the target of PDE5 inhibition. Specifically, studies that demonstrated PDE5Is' beneficial effects almost all showed improvements in both the obstructive and irritative types of LUTS [2–7]. Since the obstructive and the irritative types of LUTS are concerned with different tissue sites (e.g., bladder neck vs. bladder body), the abovementioned clinical data make it difficult to identify a definitive site of action for PDE5Is. Moreover, these studies were also unable to show objective improvement as determined by noninvasive urodynamic testing [2–7]. Nevertheless, in October 2011 the Food and Drug Administration approved tadalafil for the treatment of BPH symptoms. On the other hand, in regard to OAB as a treatment target of PDE5Is, there has been only one clinical study, in which vardenafil was found to significantly improve urodynamic parameters in male patients with spinal cord injury and detrusor overactivity [10].

BLADDER: ANIMAL AND ORGAN BATH STUDIES

In a 1996 tissue bath study PDE5 inhibitor zaprinast was found to have minor effects on human bladder smooth muscle tone [11]. In 1997 zaprinast was reported to have no effect on the contractile response of guinea-pig bladder strips to electric field stimulation, ATP, or KCL, but zaprinast was able to suppress the contractile response to carbachol, a cholinomimetic compound [12]. In two separate studies zaprinast was found to have no effect on the bladder of urethane-anesthetized rats [13] or the phasic activity of isolated guinea-pig bladder [14]. The latter study however found that another PDE5I, dipyridamole, produced a transient rise in frequency, followed by an inhibition of phasic activity [14]. In more recent studies, PDE5Is vardenafil, sildenafil, tadalafil, and udenafil were all found able to relax precontracted bladder strips although the required concentrations were in the micromolar range, which is much higher than their pharmacologically effective ranges [15–19]. In addition, tadalafil (30–60 nM) was able to potentiate sodium nitroprusside (SNP)-induced relaxation of human bladder neck strips [20].

In animal studies, chronic treatment with a large dose (10 mg/kg) of vardenafil was also able to significantly reduce non-voiding contractions in a BOO rat model [16], and udenafil (1 mg/kg) was able to prolong the intermicturition interval in anesthetized rats as determined by cystometry [19].

As mentioned earlier, vardenafil was found to improve urodynamic parameters in male patients with spinal cord injury [10]. Subsequently, this finding was interpreted as evidence for a direct action of PDE5Is on detrusor smooth muscle, particularly of the dome as this tissue site is more related to storage symptoms [21]. In support of this interpretation, sildenafil was found to exert a relaxant effect on human bladder dome smooth muscle strips [21]. However, unlike the situation with many other smooth muscles, sildenafil-induced relaxation of human bladder dome smooth muscle involved not only cGMP but also cAMP signaling pathway and the activation of potassium channels. Thus, it appears that PDE5 inhibition resulted in crosstalk between cAMP and cGMP signaling pathways [22,23]. Also possible is that it could

be due to decreased specificity of sildenafil for PDE5 in the micromolar range, resulting in spillover and inhibition of cAMP-hydrolyzing PDEs (such as PDE4).

Recent studies have also shown that PDE5 inhibition suppressed the sensory pathway of micturition reflex in female rats [24,25] and decreased bladder afferent nerve activity in female rats with spinal cord injury (complete T7-T8 spinalization) [26]. Thus, PDE5Is may have beneficial effects on OAB by decreasing afferent firing in the bladder, and this provides a mechanistic basis for why vardenafil was able to ameliorate OAB in spinal cord injury patients [10].

In addition to the abovementioned detrusor muscle and afferent nerve as potential targets of PDE5Is, interstitial cells in bladder lamina propria has recently been proposed as a target as well. Interested readers can find details of the reasoning and evidence in the review article by Kanai et al [27].

BLADDER: MOLECULAR STUDIES

In a 1998 study that demonstrated the cloning of human PDE5A1 cDNA, PDE5 mRNA expression was identified in human urinary bladder by Northern blot analysis [28] (Table 1). This was confirmed in a 2000 study by RT-PCR analysis, with additional findings that all three PDE5 isoforms were expressed in human urinary bladder [29]. Furthermore, in a survey of various rat tissues, including urinary bladder, PDE5A1 and A2, but not A3 isoform, were detected by Northern blot and RT-PCR analyses [30]. In 2004 and 2011 PDE5 protein expression was identified in human and rat bladder, respectively, by Western blot analysis [31,32]. In 2007, and in three recent studies PDE5 protein expression was identified in the vascular smooth muscle and endothelium of human bladder by immunohistochemistry [16] and in the detrusor smooth muscle of rat bladder by immunofluorescence [33] and Western blot analysis [32].

PROSTATE: CLINICAL STUDIES

As mentioned under “Bladder: Clinical studies”, several clinical studies have concluded that PDE5Is were beneficial for reducing BPH-associated LUTS [1–8], and tadalafil has been approved for treating these symptoms. However, whether PDEIs act specifically on the prostate in these patients remains undetermined. Tissue bath studies (see below) offer some positive hints, but the requirement for large doses of PDEIs in these experiments precludes a definitive conclusion.

PROSTATE: ANIMAL AND ORGAN BATH STUDIES

In the first of such studies, adrenergic tension in human prostatic strip preparations was reversed by sildenafil [34]. In two more recent studies similar results were also obtained with newer PDE5Is tadalafil, vardenafil, and udenafil [35,36]. However, akin to the situation with urinary bladder (see “Bladder: Animal and tissue bath studies”), the concentrations of PDE5Is used in these studies were in the micromolar range and therefore much higher than the range of their pharmacologically effective concentrations. Even when used to potentiate the relaxation effect of NO or SNP, a concentration of 100 nM was necessary for vardenafil [16], 30–60 nM for tadalafil [20], and 0.1 mM for zaprinast [37]. While this requirement of large doses of PDEIs for organ bath studies has come to be expected [38], a recent study [39] found that, zaprinast, which is 240-fold less potent than sildenafil [40] was able to potentiate the relaxation effect of SNP on rat prostatic strips at a concentration of 20 nM. Whether this finding is accurate or not, the abovementioned studies together suggest that the prostate, like the bladder, is a potential target of PDE5Is. As such, the clinically observed beneficial effects of PDE5Is for BPH-BOO are likely the results of targeting both the bladder and the

prostate, as can be expected from the clinical observation that these drugs exert effects both on obstructive and irritative LUTS.

PROSTATE: MOLECULAR STUDIES

In a 1998 study that demonstrated the cloning of human PDE5A1 cDNA, PDE5 mRNA expression was identified in human prostate by Northern blot analysis [28] (Table 2). This was confirmed in a 1999 study by RT-PCR analysis, with additional findings that PDE5A1 and A2 isoforms were both expressed in the prostate [41]. In year 2000 expression of all three PDE5 isoforms in human prostate as analyzed by RT-PCR was reported [29]. Furthermore, in a 2003 study PDE5A1 and A2, but not A3 isoform, were detected by Northern blot and RT-PCR analyses in rat prostate [30]. In human prostate tissue, the cGMP-hydrolyzing activity of PDE5 was identified in the cytosolic but not the particulate (membrane-bound) fraction, and in prostatic strip preparations the adrenergic tension was reversed by about 30% and 20%, respectively, by zaprinast and sildenafil at the highest concentration of 100 μM [34]. However, experimental data concerning the localization and level of PDE5 expression in the prostate have been subject of considerable inter-experimental variations (Table 2). In a 2004 study PDE5 expression level in the prostate was shown by Western blot analysis to be the highest among several human tissues including the urinary bladder and corpus cavernosum, and this was accompanied by real-time PCR analysis also showing high-level PDE5 mRNA expression in the prostate [31]. In 2005 PDE5 mRNA and protein in the prostate were found to be expressed at less than half the levels as in corpus cavernosum [42]. In 2010 somewhat high-level PDE5 mRNA in the prostate was again reported [38], but in 2011 reverted to low-level [43]. The latest data are in agreement with a 2006 and a 2011 study by two different research groups. Specifically, in the 2006 study PDE5 mRNA expression in the prostate was found to be among the lowest, especially when compared to the bladder (6-fold difference) [15], and in the 2011 study the prostate was found to be among the lowest in PDE5 protein expression [32]. However, in a 2012 paper PDE5 expression in the prostate based on Western blot analysis was described as abundant although PDE5 immunoreactivity was described as scanty and localized to the fibromuscular stroma [39]. In contrast, a 2006 study found immunoreactivity in the entire glandular region of human prostate [44]. However, this epithelial staining has been disputed by the abovementioned 2010 and 2011 studies, in which PDE5 was found in vascular smooth muscle and endothelium but not in the glandular epithelium [38,43]. In fairness though, the localization of PDE5 in the vasculature was done without co-staining for smooth muscle or endothelial markers. Yet, while also showing no staining in the epithelium, another study found that PDE5 was localized to the stroma with no mention of the vascular tissues [45]. This study nevertheless is the only one that used PDE5 peptide blocking to show PDE5 staining specificity and thus appears to be more convincing. In any event, what's most surprising is that none of these studies has indicated whether PDE5 is expressed in the prostate smooth muscle. This of course contrasts sharply with studies that clearly showed smooth muscle-specific PDE5 expression in smooth muscle-containing organs such as the bladder, penis, etc. [16,33,46]. As to why this ambiguity persists and why large data variations occurred, there is no clear answer, although some suggestions will be provided in "Concluding remarks".

URETHRA: CLINICAL STUDIES

The foremost concern for the urethra as a treatment target is how to make it more able to contract, as in the situation with stress urinary incontinence [47]. As such, the urethra, unlike the bladder or the prostate, is not an "attractive" treatment target for PDE5Is. Still, a clinical trial for "Fowler's Syndrome" or "obstructed voiding or retention associated with the primary disorder of sphincter relaxation" has been conducted with disappointing outcomes [48].

URETHRA: ANIMAL AND ORGAN BATH STUDIES

Zaprinast has been found to potentiate nitrergic relaxation of sheep urethral smooth muscle strips [37]. A similar effect of zaprinast was also observed in urethane-anesthetized rats, but surprisingly this effect appeared to involve an increase in urethral striated muscle tone [13]. Whether this striated muscle involvement is related to the recently demonstrated PDE5 expression in urethral striated muscle [33] needs to be investigated further. In 2006, vardenafil, sildenafil, and tadalafil were found able to relax precontracted rat and pig urethral strips, respectively [15,49]. In 2010, a newer PDE5I, udenafil, has also been found to relax prostatic urethral smooth muscle, and this was interpreted as a basis for using udenafil to treat BPH/LUTS [19].

URETHRA: MOLECULAR STUDIES

PDE5 isoforms were identified in human and rat urethra by RT-PCR in 2000 and 2003, respectively [29,30] (Table 3). In 2006 PDE5 expression was identified in human and pig urethral smooth muscle by immunofluorescence analysis [49]. In 2010 and 2011 PDE5 expression was identified in human urethra by real-time PCR and immunohistochemistry [38,43].

The abovementioned studies examined PDE5 expression in the urethra without specifying whether the tissue was smooth muscle or striated muscle. It turned out that the striated muscle not only express PDE5 but also the level was 6 times higher than in the smooth muscle [33]. In addition, the adjoining levator muscle, which is also striated and important for urethral closure, also expresses PDE5 at a high level [33]. On the other hand, striated muscle in the limbs does not express PDE5 [30,33]. While the unusual PDE5 expression in the striated urethral and levator ani muscles is apparently related to their sharing a common embryonic origin (splanchnic mesoderm) with the urethral smooth muscle 50, its functional significance is presently unknown.

DISCUSSION

Following the footsteps of the successful deployment of PDE5Is for ED treatment, urological researchers have been investigating whether PDE5Is can treat other urological diseases, particular those associated with the prostate, bladder, and urethra. These efforts obviously require a clear understanding of the expression status of PDE5 in these tissues. However, despite numerous clinical studies that suggest usefulness of PDE5Is for treating LUTS, molecular data concerning the prostate are highly inconsistent (Table 2). While it is not possible to know exactly why and how this occurred, likely reasons are, in this order, (1) different parts of the prostate were used for analysis, (2) differences in antibody specificity, (3) differences in techniques/experimental condition, and (4) species differences. Specifically, in regard to the first possibility, the prostate is known to contain the secretory ducts of seminal vesicles and coagulating glands (in the rat), which might differ from the prostate tissue proper in PDE5 expression. In addition, blood vessels are PDE5-rich; therefore, the degree of their inclusion in a Western blot can make a significant difference. Thus, to mitigate these problems and to make future research more clinically relevant, we suggest the following:

1. Focus more on human tissues because animal data do not always translate into human.
2. The age, disease status, medication history, and ethnicity of the donors from whom the tissues were obtained should be specified.

3. Focus more on immunostaining because (1) Western blotting and RT-PCR are unable to distinguish between different tissue compartments (e.g., vascular versus stromal smooth muscle), (2) not all RNA is translated into functional protein, and (3) when done properly, immunostaining is the only technique that permits both the localization and quantification of protein expression.
4. Currently available PDE5 antibodies should be validated and compared.
5. PDE5 peptide blocking, as performed in a 2010 study [45], should be employed to ensure antibody specificity.
6. PDE5 protein expression in different parts of the prostate should be investigated using dissecting microscopy.
7. Double staining should be performed to convincingly show co-localization. Specifically, claims of PDE5 expression in prostatic vascular smooth muscle and endothelium [38,43] should be validated by co-staining for smooth muscle markers (e.g., smooth muscle actin) and endothelial markers (e.g., CD31), respectively.

CONCLUSIONS

PDE5 expression and function in the lower urinary tract have been investigated at the clinical, animal/organ bath, and molecular levels. The resulting data are by and large consistent for the bladder and the urethra. On the other hand, those for the prostate at the molecular level are highly variable. Thus, a dedicated study on the systematic analysis of PDE5 expression in the prostate is urgently needed.

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Table 1

Studies examining PDE5 expression in the bladder

Publication year/First author	Species	Detection method	Expression level	Expression location	Source of PDE5 Antibody	Tension reversion	Additional notes
1996/Truss[15]	Human	Organ bath	ND	ND	NA	Minor effect by zaprinast	
1997/Longhurst[16]	Guinea pig	Organ bath	ND	ND	NA	Zaprinast suppressed carbachol effect	Zaprinast did not suppress ATP or KCL effect
1998/Stacey[32]	Human	Northern	ND	ND	NA	ND	
2000/Lin[33]	Human	PCR	ND	ND	NA	ND	
2002/Wibberley[17]	rat	Organ bath	ND	ND	NA	Zaprinast had no effect	
2003/Lin[34]	Rat	PCR & Northern	PDE5A2 > PDE5A1	ND	NA	ND	
2004/Gillespie[18]	Guinea pig	Organ bath	ND	ND	NA	Zaprinast had no effect	Dipyridamole had transient effect
2004/Morelli[35]	Human	qPCR & Western	Among the highest	ND	Dr. Giorgi	ND	Same level as CC
2006/Tinel[19]	Rat	qPCR & Organ bath	Among the highest	ND	NA	Vardenafil > Sildenafil > Tadalafil	
2007/Filippi[20]	Human & Rat	qPCR, IHC & Organ bath	Among the highest	Detrusor & vascular smooth muscle & endothelium	Dr. Giorgi	Vardenafil (100nM)	
2008/Yanai[21]	Guinea pig	Organ bath	ND	ND	NA	Sildenafil had partial effect	
2009/Werkstrom[22]	Rat	Organ bath	ND	ND	NA	Vardenafil (100μM)	
2010/Lee[23]	Rabbit	Organ bath	ND	ND	NA	Udenafil (10mM)	
2010/Lin[37]	Rat	IF	High	Detrusor smooth muscle	Dr. Visweswariah	ND	
2011/Muller[36]	Rat	Western	Among the highest	ND	Cell Signaling Technology	ND	
2012/Angula[24]	Human	Organ bath	ND	ND	NA	Tadalafil (30–60nM) potentiated SNP-induced relaxation	

CC: Corpus cavernosum; PCR: Reverse transcription-polymerase chain reaction; qPCR: Quantitative PCR; IF: Immunofluorescence; IHC: Immunohistochemistry; SNP: Sodium nitroprusside; ND: Not determined; NA: Not applicable.

Table 2

Studies examining PDE5 expression in the prostate

Publication year/First author	Species	Detection method	Expression level	Expression location	Source of PDE5 Antibody	Tension reversion	Additional notes
1998/Stacey[32]	Human	Northern	ND	ND	NA	ND	
1999/Kotera[45]	Human	PCR	PDE5A2 > PDE5A1	ND	NA	ND	
2000/Lin[33]	Human	PCR	ND	ND	NA	ND	
2001/Uckert[38]	Human	PCR, cGMP hydrolysis & Organ bath	ND	ND	NA	Zaprinast > Sildenafil (0.1–100μM)	Both drugs reversed <30% tension at 100μM
2003/Lin[34]	Rat	PCR & Northern	PDE5A2 > PDE5A1	ND	NA	ND	
2004/Morelli[35]	Human	qPCR & Western	Among the highest	ND	Dr. Giorgi	ND	Same level as CC
2005/Zhang[46]	Rat	qPCR & Western	Medium	ND	Dr. Giorgi	ND	Half level as CC
2006/Uckert[48]	Human	IF	ND	Glandular & subglandular	Dr. Omori	ND	
2006/Tinel[19]	Rat	qPCR & Organ bath	Among the lowest	ND	NA	Vardenafil > Sildenafil > Tadalafil	
2010/Fibbi[42]	Human	qPCR & IHC	Medium	Vascular smooth muscle & endothelium	Dr. Giorgi	ND	
2010/Zenzmaier[49]	Human	IHC	ND	Stroma; not epithelium	Cell Signaling Technology	ND	PDE5 peptide blocked staining
2011/Morelli[47]	Human	qPCR & IHC	Low	Vascular smooth muscle & endothelium	Dr. Giorgi	ND	One-quarter level as CC
2011/Muller[36]	Rat	Western	Extremely low	ND	Cell Signaling Technology	ND	
2012/Zhang[43]	Rat	qPCR, Western, IHC, & Organ bath	Abundant by PCR & Western; scanty by IHC	Fibromuscular stroma	Transduction Laboratories	Zaprinast at 20 nM potentiated SNP effect	

CC: Corpus cavernosum; PCR: Reverse transcription-polymerase chain reaction; qPCR: Quantitative PCR; IF: Immunofluorescence; IHC: Immunohistochemistry; SNP: Sodium nitroprusside; ND: Not determined; NA: Not applicable.

Table 3

Studies examining PDE5 expression in the urethra

Publication year/First author	Species	Detection method	Expression level	Expression location	Source of PDE5 Antibody	Tension reversion	Additional notes
2000/Lin[33]	Human	PCR	ND	ND	NA	ND	
2001/Costa[41]	Sheep	Organ bath	ND	ND	NA	Zaprinast potentiated nitrergic effect	
2002/Wibberley[17]	Rat	Organ bath	ND	ND	NA	Zaprinast potentiated nitrergic effect	Involved striated muscle
2003/Lin[34]	Rat	PCR	PDE5A2 > PDE5A1	ND	NA	ND	
2006/Tinel[19]	Rat	qPCR & Organ bath	Medium	ND	NA	Vardenafil > Sildenafil > Tadalafil	
2006/Werkstrom[53]	Pig	IF & Organ bath	ND	Urethral & vascular smooth muscle & endothelium	FabGennix	Vardenafil & tadalafil (30μM)	
2010/Lee[23]	Rabbit	Organ bath	ND	ND	NA	Udenafil (10mM)	
2010/Lin[37]	Rat	IF & Organ bath	High in striated muscle	Striated > smooth muscle	Dr. Visweswariah	Sildenafil potentiated SNP effect	Levator ani also positive
2010/Fibbi[42]	Human	qPCR & IHC	Medium	Smooth muscle	Dr. Giorgi	ND	
2011/Morelli[47]	Human	qPCR	Medium	ND	NA	ND	

PCR: Reverse transcription-polymerase chain reaction; qPCR: Quantitative PCR; IF: Immunofluorescence; IHC: Immunohistochemistry; SNP: Sodium nitroprusside; ND: Not determined; NA: Not applicable.