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Phosphodiesterase-5 Inhibitors: Potential Nephroprotective Agents

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List of Abbreviations

AKI: Acute Kidney Injury; BNP: Brain Natriuretic Peptide; cGMP: Cyclic Guanosine Monophosphate; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; KIM-1: Kidney Injury Molecule 1; iNOS: Inducible NO Synthase; PUUO: Partial Unilateral Ureteral Obstruction; I/R: Ischemia-Reperfusion; MB: Mitochondrial Biogenesis; NGAL: Neutrophil Gelatinase Associated Lipocaline; NO: Nitric Oxide; PDE5: Phosphodiesterase 5; TGF-β: Transforming Growth Factor Beta

Introduction

Sildenafil, the oldest approved Phosphodiesterase 5 (PDE5) inhibitor, was originally developed for the treatment of angina pectoris [1,2]. However, due to common side effects of enhancing penile erection among volunteers who participated in the initial clinical trials, the focus of research was shifted toward its potential beneficial effects on erectile dysfunction. Since then, besides Sildenafil (Viagra) two other PDE5 inhibitors, namely Vardenafil (Levitra) and Tadalafil (Cialis) have been approved for the treatment of this common sexual disorder. Subsequently, these agents were found to reduce pulmonary-artery pressure and improve exercise capacity, World Health Organization functional class, and hemodynamics in patients with symptomatic pulmonary arterial hypertension [3,4], leading to the approval of Sildenafil for this indication. These effects are largely attributed to the ability of PDE5 inhibitors to relax the arterial wall leading to decreased pulmonary arterial resistance and pressure. Because PDE5 is expressed in arterial wall smooth muscle of the lungs and penis [5], PDE5 inhibitors act selectively in these organs without causing major systemic vasodilation. Besides these two organs, PDE5 is expressed in the renal tissue as was evident by PCR, northern blot and immunohistochemical analysis [6]. Actually, three isoforms of PDE5 have been identified in humans and dogs: PDE5A1, PDE5A2, and PDE5A3. PDE5 which localized to the glomeruli, mesangial cells, cortical tubules, and inner medullary collecting duct plays a critical role in the regulation of renal hemodynamics and kidney excretory function [7]. Support for the physiological importance of PDE5 at the renal level, was recently derived from NO-stimulated cGMP-forming Guanylyl Cyclase Knockout Mice (NO-GC1 KO). The relaxation of renal vasculature as determined in isolated perfused kidneys was reduced in these mice. 2-Kidney-1-Clip-Operation (2K1C) operated Wild Type (WT) mice showed a reduction of cGMP-dependent relaxation of renal vessels, which was not found in the NO-GC1 KOs. The reduced relaxation in operated WT mice was restored by sildenafil indicating that enhanced PDE5-catalyzed cGMP degradation most likely accounts for the attenuated vascular responsiveness [8].

At the cellular level, PDE5 inhibitors protect cyclic Guanosine Monophosphate (cGMP) from degradation by cGMP-specific Phosphodiesterase Type 5 (PDE5) in the target organs. cGMP is derived from either Nitric Oxide (NO) or natriuretic peptides action on soluble or particulate guanylate cyclase, respectively [2], resulting in increased cytosolic levels of cGMP, a well-known potent vasodilator.

In the last few years, research focus has shifted to the field of cardioprotective and subsequently nephroprotective properties of PDE5 inhibitors. Concerning cardioprotection, it was elegantly summarized by Reffelmann and Kloner [2], therefore the current communication will concisely focus on recent studies that support potential nephroprotective profiles of PDE5 inhibitors in both experimental and clinical research. Yet, due to the similarity between the mechanisms underlying cardiac and renal ischemic damage, the present review recognises the great advances in the cardioprotective properties of PDE5 inhibitors, which might be extrapolated to the nephroprotective profile of the these agents. Therefore, a brief referral to the cardioprotective actions of PDE5 inhibitors is brought hereby.

Pre-clinical Research

Besides their vasodilatory action, PDE5 inhibitors possess anti-apoptotic and anti-oxidant properties [9], making them a promising therapy for Ischemia-Reperfusion (I/R) injury of various organs. At the cardiac level, pre-treatment with either Sildenafil or Tadalafil reduced infarct size by 68% and 25% in rabbit and rat models of myocardial infarction, respectively [10,11]. These beneficial cardioprotective effects were attributed to the ability of Sildenafil to open mitochondrial K (ATP) channels in the myocardium [10]. In this context, opening of K (ATP) channels is regarded as an essential step in signalling ischemic preconditioning [12]. Similarly, Vardenafil restored mitochondrial membrane potential in a model of ischemia of isolated rat heart [13]. It should be emphasized that mitochondrial dysfunction is largely recognized as a key mediator of variety of diseases including cardiac, neuronal and renal acute and chronic damage [14-16]. In line with this concept, several studies have demonstrated that restoration of mitochondrial function after ischemic insults may be a key target to the recovery of inflicted organs [15,16]. Recently, Whitaker et al. [16] have demonstrated that cGMP-selective PDE inhibitors stimulate Mitochondrial Biogenesis (MB) both *in vitro* and *in vivo*. Since, ischemic cardiac and renal injuries share the same cellular mechanisms, namely oxidative stress, apoptosis, and fibrosis, PDE5 inhibitors may also possess nephroprotective effects in renal ischemic injury.

Indeed, our group has evaluated the early nephroprotective effects of Tadalafil, a PDE5 inhibitor, in an experimental model of renal I/R

[17]. For this purpose, Sprague-Dawley rats were divided into two groups: vehicle-treated I/R, and Tadalafil (10 mg/kg po)-treated I/R group. After removal of the right kidney and collection of two baseline urine samples, the left renal artery was clamped for 45 min followed by reperfusion for 60, 120, 180, and 240 min. Vehicle-treated I/R animals exhibited significant reduction in Glomerular Filtration Rate (GFR) throughout the follow-up period. In addition, the ischemic kidney showed remarkable cast formation, necrosis, and congestion, a consistent pattern of acute tubular necrosis. Furthermore, urinary excretion of Neutrophil Gelatinase Associated Lipocaline (NGAL) and Kidney Injury Molecule 1 (KIM-1), two novel biomarkers of kidney injury [18-21], substantially increased following I/R insult. In contrast, Tadalafil treatment resulted in a significant improvement in kidney function and amelioration of the adverse histological alterations of the ischemic kidney. Noteworthy, the urinary excretion of NGAL and KIM-1 markedly decreased in the Tadalafil-treated I/R group. These findings demonstrate that Tadalafil possesses early nephroprotective effects in rat kidneys subjected to I/R insult. This approach may suggest a prophylactic therapy for patients with ischemic AKI.

These results are in agreement with other studies that reported beneficial renal effects of PDE5 inhibitors in the I/R rat model [22,23], after unilateral ureteral obstruction [24], following cardiopulmonary bypass AKI in swine [25], and post-transplant of warm ischemic kidney [26]. While these studies examined the effects of PDE5 inhibitor pre-treatment on renal histology, oxidative stress, and function, our study [17] assessed the effects of PDE5 inhibitors on the more sensitive biomarkers of AKI [18-21], namely NGAL and KIM-1. Concerning the efficacy of the three approved PDE5 inhibitors, it was found that Sildenafil demonstrated slightly higher anti-apoptotic effects in renal tubular tissue compared with Vardenafil and Tadalafil [24]. All the tested PDE5 inhibitors suppressed the activation of the deleterious isoform of NO synthase, Inducible NO Synthase (iNOS) in the renal tissue after Partial Unilateral Ureteral Obstruction (PUUO) model [21]. PUUO is a common urological problem, where it induces progressive apoptosis of both renal tubular and interstitial cells which contributes to renal tissue loss in obstructive uropathy [26]. On the other hand the nephroprotective effects of Sildenafil in postcardiopulmonary bypass AKI in swine was associated with preservation of Endothelial NO Synthase (eNOS) and ATP bioavailability and prevention of endothelial dysfunction, regional hypoxia, inflammation, up-regulation of iNOS and tubular damage [25]. These effects are consistent with the notion that ischemic AKI is characterized by disruption of mitochondrial homeostasis and inhibition of MB, and that restoration of mitochondrial number and function is required for recovery of the injured kidney [16]. Sildenafil has been shown to promote MB in cultured renal proximal tubular cells and in renal tissue derived from experimental folic acid-induced AKI in mice [16]. In addition, the elevated cGMP levels and enhancement of eNOS expression following PDE-5 inhibition is essential for the maintenance of renal perfusion and glomerular filtration [27]. Noteworthy, PDE5 is expressed in both proximal tubules and glomeruli [28]. Likewise, cGMP derived from either NO or PDE5 inhibition regulates glomerular filtration by modulating the reorganization of the glomerular slit diaphragm and cytoskeleton of the podocytes [29,30].

The beneficial nephropotective effects of PDE5 inhibitors are not restricted to AKI. It was shown that Sildenafil treatment prevented hypertension and deterioration of renal function, reduced histologic damage, inflammation and apoptosis, delayed the onset of proteinuria, and preserved renal capillary integrity in an experimental model of Chronic Kidney Diseases (CKD) induced by 5/6 nephrectomy [31]. However, the beneficial anti-proteinuria impact of Sildenafil was lost when therapy began 4 weeks after the induction of the disease; suggesting that efficacy is reduced if pathological changes are already established. Similarly, Vardenafil ameliorated renal damage in type 1 diabetic rats via restoration of cGMP levels in podocytes [32]. The nephroprotective effects of Vardenafil were evident by the reduction of renal Transforming Growth Factor Beta (TGF-β) and the restoration of nephrin and podocin expression accompanied by reduced proteinuria. The nephroprotective effects of PDE5 inhibitors in models of CKD are not solely due to blood pressure lowering action [33], since they possess a potent anti-proliferative effect, preventing mesangial cell proliferation and extracellular matrix expansion [34,35]. Similarly, PDE5 inhibition induce anti-apoptotic effects, [31,36] anti-oxidative stress [37] and anti-inflammation [38] on renal cells in CKD models [33].

Clinical Research

Acute kidney injury is a common clinical problem affecting 2–7% of hospitalized patients including 5–10% of critically ill subjects [39-41]. Despite the advances in critical care medicine, AKI still poses an important clinical challenge associated with high morbidity and mortality. This is attributed to delay in diagnosis of AKI on the one hand and largely to lack of efficient treatment on the other. In this regard, several strategies have been proposed to deal with this disease. These include antioxidants and antioxidant enzyme mimetics, erythropoietin, peroxisome-proliferator-activated receptor agonists, inhibitors of poly (ADP-ribose) polymerase, carbon monoxide-releasing molecules, statins, adenosine, and acetylcysteine [39-42]. Unfortunately, the therapeutic efficacy of these approaches is inconsistent and in most cases disappointing. Compared with the many advances in the use of PDE5 inhibitors in clinical cardiac settings, to the best of our knowledge these agents were not tested in AKI clinical situations. Specifically, PDE5 inhibition resulted in important cardioprotective effects as was evident by reduction of infarct size, cardiac hypertrophy, lung edema and improved cardiac function in experimental models of heart failure or myocardial injury [2,13,43,44]. Clinical studies have also demonstrated beneficial effects of Sildenafil and Vardenafil on endothelial function [45], where chronic therapy with these agents improves endothelial function in patients with chronic heart failure. Similarly, chronic Sildenafil therapy significantly improved heart rate recovery, an important prognostic marker, in patients with heart failure [46]. In line with these findings, Guazzi et al. [47] have demonstrated that Sildenafil improves left ventricle ejection fraction, diastolic function and clinical status, suggesting a role for PDE5 inhibition in heart failure therapy. Beneficial effects of Sildenafil have been documented in patients with severe pulmonary hypertension who underwent cardiac valve replacement surgery [48]. Unfortunately, neither this study nor other relevant clinical trials reported the impact of PDE5 inhibition on kidney function, where AKI is prevalent in patients who undergo this type of cardiac surgery. It is tempting to assume that PDE5 inhibitors will improve kidney function in various renal insults including AKI and cardio-renal syndrome as was shown in experimental studies. Concerning the latter, it was shown that Sildenafil mimics the hemodynamic effects of Brain Natriuretic Peptide (BNP) in dogs with heart failure induced by rapid pacing [49]. Additional encouraging hints came from clinical trials where treatment of type-2 diabetic patients with Sildenafil for one month reduced albuminuria [50].

Lasaponara et al. [51] have tested the safety of PDE5 inhibitors in patients with erectile dysfunction and severe renal disease or those who have received renal transplants. Both sildenafil and vardenafil were found to be efficacious and well tolerated for the treatment of erectile dysfunction in patients receiving renal dialysis or transplant. At the renal level, kidney function in graft recipients was not adversely affected by sildenafil administration. The glomerular filtration rate and filtration fraction of renal grafts were significantly increased in 10 patients who received a single 100-mg dose of sildenafil. Moreover, lithium clearance was also significantly increased in sildenafil-treated patients. Significant decreases were also observed in renal vascular resistance and mean arterial pressure. Serum creatinine increased slightly from baseline in 50 transplant recipients given sildenafil 25, 50, or 100mg as needed for 12 weeks in an open-label study. However, no effect on creatinine level was found in a second open-label study of 65 younger transplant recipients who received sildenafil 50 or 100mg for an unspecified time period or in a randomized, controlled, crossover trial of sildenafil 25, 50, or 100mg for 8 weeks. No negative effects of sildenafil on CLcr occurred in 20 patients who received sildenafil 50mg for 4 weeks [51]. Blood urea nitrogen was also not significantly changed in transplant recipients who received sildenafil 50mg. Blood chemistry and hemoglobin were also unchanged with sildenafil treatment.

The variability in the extent of the beneficial renal and extra-renal effects of the various PDE5 inhibitors in both experimental and clinical studies may stem from their selectivity to the different PDE isoforms. In this context, tadalafil is extremely selective for PDE5, but also potently inhibits PDE11, an enzyme with unknown physiological function [52]. As PDE1 is expressed in the brain, myocardium, and vascular smooth muscle cells, non selectivity with respect to this enzyme (selectivity: tadalafil>vardenafil>sildenafil) may result in vasodilation and tachycardia. Inhibition of PDE6 (selectivity: tadalafil>vardenafil congruent with sildenafil), which is expressed only in retina and functions in visual transduction, can transiently disturb vision. PDE5 inhibitors may also indirectly inhibit PDE3 by increasing cyclic guanosine monophospate levels, thereby elevating heart rate and vasodilation while inhibiting platelet aggregation [52]. Another important aspect is the dose at which PDE5 inhibitors were tested. In the experimental studies the applied doses were higher than the clinically effective doses, raising concerns over their inhibitory effects on other PDEs isoforms. In addition, in the clinical studies a wide range of doses were applied. This aspect once again calls for a highly selective PDE5 inhibitor, which upon dose escalation will still be free from non-selective and undesired adverse effects. Such an agent will be the ideal drug candidate for nephroprotection.

Conclusions and Perspectives

The initial application of PDE5 inhibitor for erectile dysfunction has evolved to other clinical settings including heart failure, pulmonary hypertension and kidney dysfunction. These therapeutic approaches are not surprising in light of the discovery that PDE5 is expressed in a number of tissues such as lung, heart and kidney. While the cardioprotective effects of PDE5 inhibitors are supported by both experimental and to a lesser extent clinical studies, the nephroprotective effects of these agents in AKI and CKD are still emerging with limited animal studies and only one clinical trial [50]. Thus, carefully controlled large clinical studies are needed before extrapolating the encouraging experimental findings to clinical indications. Additional issue of debate involves the mechanisms underlying the cardio- and nephroprotective effects of PDE5 inhibitors. It is widely accepted that these agents exert their beneficial renal and cardiac effects via systemic and regional hemodynamics. However, since Sildenafil significantly reduced necrosis and apoptosis of cultured myocytes exposed to ischemia and of renal cells, a direct effect independent of their vascular action may contribute to the cardio- and nephroprotective effects of PDE5 inhibitors [9]. Thus, it seems that PDE5 inhibitors exert their beneficial effects via multiple mechanisms which involve both hemodynamic and molecular signalling pathways, including NO and cGMP and their downstream cascade [13]. A plausible mechanism for the improvement of cardiac and renal function by PDE5 inhibition is proposed in Figure 1. Moreover, although PDE5 inhibitors have an excellent safety record, they may provoke minor side-effects, such as dyspepsia, headache, and myalgia.

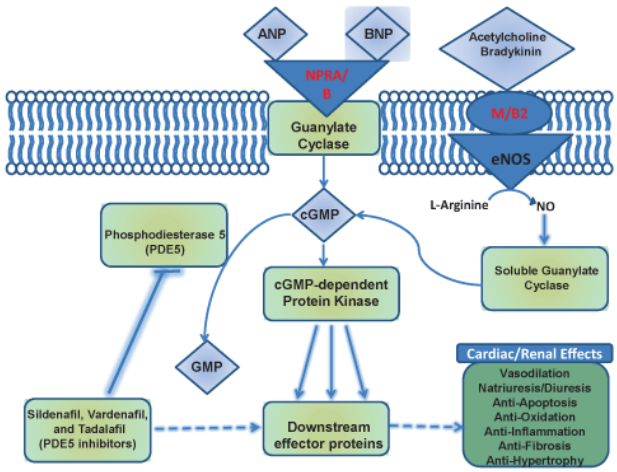

Figure 1: Schematic description of the intracellular mechanism of action of natriuretic peptides and nitric oxide and their functions in target organs.
These agents increase intracellular cGMP, which causes vasodilation, diuresis, natriuresis, and other beneficial renal and cardiac effects. PDE5 degrades cGMP, thus abolishing the beneficial effects of natriuretic peptides and other substances that act via NO generation, such as bradykinin and acetycholine. PDE5 inhibitors, protect against cGMP degradation by PDE5, thus augmenting the beneficial actions of natriuretic peptides, bradykinin, and acetylcholine. ANP: Atrial Natriuretic Peptide; BNP: Brain Natriuretic Peptide; B2: Bradykinin Receptor Type 2; cGMP: Cyclic Guanosine Monophosphate; eNOS: Endothelial Nitric Oxide Synthase; M: Muscarinic Receptor; NO: Nitric Oxide; NRPA,B: Natriuretic Peptide Receptors A,B respectively; PDE5: Phosphodiesterase 5.

In conclusion, despite the encouraging results from animal studies, till now there is insufficient evidence to support the renoprotective effects of PDE5 inhibitors in humans. Of relevance could be patients who undergo interventional procedures associated with increased risk for AKI including radiocontrast-induced nephropathy, kidney transplants, cardiopulmonary bypass surgery and critically ill patients.

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