Diabetic nephropathy: Treatment with phosphodiesterase type 5 inhibitors

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Abstract

The importance of nitric oxide (NO) in vascular physiology is irrefutable; it stimulates the intracellular production of cyclic guanosine monophosphate (cGMP), initiating vascular smooth muscle relaxation. This biochemical process increases the diameter of small arteries, regulating blood flow distribution between arterioles and the microvasculature. The kidney is no exception, since NO predominantly dilates the glomerular afferent arterioles. It is now evident that the vascular production of cGMP can be augmented by inhibitors of phosphodiesterase type 5 (PDE 5), the enzyme which breakdowns this cyclic nucleotide. This has clinical relevance, since diabetic nephropathy (DN) a major microvascular complication of diabetes mellitus and the most common cause of end-stage renal disease, increases intraglomerular capillary pressure, leading to glomerular hypertension. PDE 5 inhibitors may have, therefore, the potential to reduce glomerular hypertension. This review describes the use of PDE 5 inhibitors to improve the metabolic, haemodynamic and inflammatory pathways/responses, all of which are dysfunctional in DN.

Core tip: Diabetic nephropathy a leading cause of end-stage renal disease, is characterized by dysfunctional metabolic, haemodynamic and inflammatory pathways leading to glomerular hypertension. These pathways were normalized following treatment with phosphodiesterase type 5 inhibitors, which initiated renal vascular smooth muscle relaxation. This therapeutic option for treating diabetic nephropathy may negate the need for costly renal dialysis or transplantation.

INTRODUCTION

Chronic kidney disease is increasing worldwide at an annual rate of 8%, with the prevalence higher in developing countries[1]. Diabetic nephropathy (DN) is a common underlying cause[1]; indeed in many countries it is the main cause of end-stage renal disease (ESRD) and is associated with a high morbidity and mortality[2-5]. DN develops due to a complex interaction between metabolic and haemodynamic pathophysiological factors, which lead to renal damage[6,7]. It can affect 20%-30% of the diabetic population, who present with an increase in urinary albumin excretion (microalbuminuria) in the earliest stage[4]. This may progress to macroalbuminuria and later renal insufficiency and ESRD. There is also evidence of an increase in systemic and vascular markers of inflammation[8,9] as the size of the kidney progressively increases[10]. Accompanying these changes are abnormalities in the blood biochemical indices of renal function, which precede renal failure[11].

Treatment of DN has focused on the integrated control of dyslipidaemia, glycaemia and blood pressure to reduce microalbuminuria[3,12-14]. Nevertheless, although, current treatment strategies may slow the progression of DN to ESRD, it does not fully arrest this process[9,15]. Inevitably, some patients require renal replacement therapy (RRT), at an average cost of €40000-50000 per patient per year[5]. Not surprisingly, the increasing number of diabetic patients on RRT[9,16], is placing a financial strain on health care systems worldwide[2,17]. It has also been established that the cardiovascular morbidity and mortality is higher in diabetic ESRD patients on dialysis compared to those without diabetes[9]. Slowing the decline of renal function, from DN to ESRD is of paramount importance and hence there is a clear need for new strategies to treat DN.

One feasible option for treating the DN-induced enhancement of intraglomerular pressure[7] and the resultant glomerular hypertension[18] is to alter the renal cyclic guanosine monophosphate (cGMP)-NO pathway. This is because NO dilates vessels in the kidney, including the glomerular afferents[19], by stimulating intracellular production of cGMP[20,21], which in turn initiates renal vascular smooth muscle relaxation. It is now evident that the vascular cGMP-NO pathway can be augmented by inhibitors of phosphodiesterase type 5 (PDE 5), the enzyme which breakdowns cGMP[22]. These inhibitors (sildenafil, tadalafil and vardenafil) allow cGMP to accumulate and are increasingly used to treat penile erectile dysfunction[23-25], as they cause a significant relaxation of the corpus cavernosum[24,26] leading to erection. They may also have a therapeutic role in DN, since PDE 5 expression/activity is abundant in the kidney[27] and may contribute towards glomerular hypertension. In this scenario selective inhibition of PDE 5 enzymatic activity would provide renoprotection.

This review describes the use of PDE 5 inhibitors to improve metabolic and haemodynamic pathophysiological factors, as well as inflammatory pathways, all of which are dysfunctional in DN.

METABOLIC CHANGES

Strict glycaemic control is desirable for DN patients, especially as polyol and hexosamine pathways, the accumulation of [advanced glycation end products (AGEs) formed by glucosylation of proteins, lipids and nucleic acid] and activation of protein kinase C are all thought to play a role in disease progression[7]. However, there is little evidence that PDE 5 inhibition reduces diabetic hyperglycaemia, since sildenafil had no effect in streptozotocin-induced diabetic rats[28] or in a model of non-insulin-dependent diabetes mellitus, the Otsuka Long-Evans Tokushima Fatty (OLETF) rats[29]. Even so, the effect of PDE 5 inhibition on other renal metabolic abnormalities needs to be considered.

Kidney weight, histology and electron microscopy
Kidney size and weight are typically increased in diabetes mellitus, primarily due to glomerular and tubular hypertrophy. An increase in the number of glomerular cells (mainly mesangial and endothelial), in extracellular matrix and in capillary number and size all contribute to this hypertrophy[30]. This increase is also evident when kidney weight is corrected for body surface area[31], or in diabetic rats, when expressed as kidney: body-weight, a ratio lowered following treatment with sildenafil[28]. In terms of renal histology, glomerular lesions characterized by hypertrophy, mesangial matrix expansion and sclerotic lesions were evident in the OLETF rat kidney and were significantly reduced by sildenafil[29], demonstrating drug-induced amelioration of NIDDM nephropathy.

The reduction in kidney weight and improved histology afforded by treatment with sildenafil, suggests that PDE 5 inhibition may prove to be an important and effective therapeutic option for DN-induced hypertrophy. This is supported by the finding that renal morphological changes induced in spontaneously hypertensive rats (SHR) by cyclosporin A, a potent nephrotoxic immunosuppressant were also improved with a PDE 5 inhibitor (FR226807, Fujisawa Pharmaceutical, Japan)[32].

The earliest ultrastructural abnormality in DN relates to the diffuse thickening of the glomerular basement membrane, which increases as the disease advances. As previously mentioned, several biochemical changes contribute to this process, notably an increase in collagen type IV deposition and impairment of excess extracellular matrix degradation, mesangial expansion by extracellular matrix deposition and increased mesangial cellularity. There are also changes in glomerular epithelial cells (podocytes), including a decrease in number and/or density, with a reduced podocyte per glomerulus ratio, podocyte foot process broadening and effacement, glomerulosclerosis and tubulointerstitial fibrosis[18,33]. It would be interesting to establish whether PDE 5 inhibitors can prevent or reverse these DN-induced ultrastructural changes observed under electron microscopy.

Serum creatinine
Creatinine is a by-product of muscle-derived creatine. In the early stages of DN, kidney compensatory mechanisms maintain serum creatinine levels, but as the disease progresses this compensation fails due to the marked and continuous damage to functioning nephrons. It seems, therefore, that the increased serum creatinine seen in DN indicates the severity of the clinical renal damage. Interestingly, in the first study to treat DN with a PDE 5 inhibitor (vardenafil given orally for one month to alloxan-induced diabetic rabbits) the elevated serum creatinine level was restored to normal[34].

The notion that PDE 5 inhibition can ameliorate the progression of renal damage has been examined in other animal models. Sildenafil reduced the elevated serum creatinine concentration in rats following 5/6 nephrectomy[35], while another PDE 5 inhibitor normalized the level in SHR treated with cyclosporin A[32]. These finding demonstrate the beneficial effect PDE 5 inhibitors have on impaired renal function.

HAEMODYNAMIC FACTORS

Glomerular filtration rate/creatinine clearance

Glomerular filtration rate (GFR) and creatinine clearance (CrCl), a good index of GFR[36], are routinely used to check kidney function. Specifically, they estimate blood flow per minute through the glomeruli, and measure how well the kidneys filter the DN-induced build up of blood creatinine. The early stages of DN are characterized by an increase in glomerular hyperfiltration, which elevates GFR and contributes to renal impairment[37]. However, as the disease progresses, renal function deteriorates and there can be a relentless decline in GFR[16,38,39]. This functional change develops as a consequence of structural abnormalities, including an increase in kidney size[29,31], together with poor metabolic control[40]. Lau et al[34] found CrCl was reduced in diabetic rabbits and restored by vardenafil, suggesting that PDE 5 inhibitors can improve diabetes-induced renal impairment.

Cyclosporin A-induced nephrotoxicity and renal damage caused by 5/6 nephrectomy, provide indirect support for this concept; both are characterized by a decrease in CrCl and improved by treatment with a PDE5 inhibitor[32,35].

The beneficial effect of the PDE 5 inhibitors is likely to be due to NO-cGMP accumulation[20,21] causing dilatation of glomerular afferent blood vessels[19]. In this regard, it is proposed that glomerular hyperfiltration depends upon an increase in NO activity in the early phase of DN[41], whereas in the later phase when the GFR starts to fall, a concomitant reduction in NO activity would lead to glomerular hypertension. The diabetes-induced reduction in NO activity could be due to defective synthesis or quenching through the production of superoxide radicals and AGEs[42,43]. Therefore, the beneficial action of PDE 5 inhibitors is to increase renal NO-cGMP activity and restore GFR/CrCl. An increase in kidney cGMP content, rather than blood pressure reduction, was also thought responsible for the improved renal function in rats with cyclosporin A-induced nephrotoxicity following PDE 5 inhibitor treatment[32].

Hypertension is twice as frequent in diabetic patients and a major reason why most develop cardiovascular disease[44]. It also plays a significant role in the progression of DN[7,45]. Consequently, lowering blood pressure has to be an important consideration in the management of DN. Kuno et al[29] noted that sildenafil treatment for 8 wk significantly reduced systolic and diastolic blood pressure in OLETF rats, providing further evidence of the haemodynamic benefits that can be achieved by treatment with PDE 5 inhibitors.

Urinary albumin excretion and total protein/creatinine ratio

The progressive increase in urinary albumin excretion, commonly termed proteinuria is another clinical hallmark of DN and also a predictor of cardiovascular disease. Such DN-induced increase in proteinuria is part of a series of clinical events, which includes elevated blood pressure and a progressive decline in GFR. Moreover, proteinuria does not diminish as DN progresses. Proteinuria is, therefore, a consequence of the glomerular damage in diabetes mellitus and a cause of further damage, since it leads to inflammation and fibrosis in the renal tubules and a loss of functional nephrons. Urinary albumin excretion and total protein/creatinine ratio can be used to monitor proteinuria[46,47]. Both markers were elevated in six months diabetic rabbits, as well as diabetic and OLETF rats and were normalized by vardenafil and sildenafil treatment[28,29,34]. Sildenafil also reduced the elevated proteinuria in 5/6 nephrectomized rats[35]. Taken together, these findings imply that PDE 5 inhibitors reduce proteinuria and improve the renal status in DN.

Inflammation and fibrosis

Diabetes-induced kidney fibrosis results from prolonged renal injury initiated by excessive extracellular matrix deposition. Inflammation is central to the development and progression of this complication. It is characterized by glomerular and tubulointerstital migration of activated inflammatory cells (neutrophils, macrophages, T lymphocytes, and mast cells) and fibroblasts in the kidney, regardless of the initial insult. At the injury site, inflammatory cells synthesize reactive oxygen species plus fibrogenic cytokines and growth factors, which exacerbate the renal damage. This leads to excessive and poorly ordered matrix deposition and fibrosis; in turn this affects normal-tissue architecture and ultimately can disable proper functioning of the kidney[9,48]. Jeong et al[28] found that sildenafil treatment significantly attenuated the diabetes-induced increase in renal cortex 8-OHdG content and its elevated excretion (measures of oxidative stress and DNA damage), probably by inhibiting the accumulation of oxidized DNA in the kidney. DN-induced macrophage infiltration into the glomeruli and tubulointerstitium of diabetic rats, an indication of inflammation, was also ameliorated by sildenafil. It seems likely that controlling excessive inflammation and generation of reactive oxygen species with PDE 5 inhibitors will have therapeutic potential in inhibiting diabetes-induced kidney fibrosis. Interestingly, drugs with antiinflammatory activity have been found to slow or reverse DN[9].

Angiotensin II

Angiotensin II (Ang II), is an octapeptide trophic hormone and a powerful vasoconstrictor widely recognised as a regulator of blood pressure, fluid and electrolyte homeostasis[7]. It has a central role in the pathogenesis of DN where increased Ang II levels cause a preferential constriction of the efferent glomerular arterioles, an increased glomerular permeability to proteins and enhanced formation of AGEs[33]. It regulates, therefore, systemic and glomerular haemodynamics, as well as glomerular hypertrophy and sclerosis[7]. In mesangial cells it triggers the production and release of cytokines, chemokines and growth factors, with the net effect of mediating and/or amplifying renal damage[18]. The physiological actions of Ang II in the kidney are due to activation of angiotensin II receptor type 1

(AT1) receptors. These receptors are mainly expressed in smooth muscle cells where they induce vasoconstriction, proliferation and inflammation[21].

The regulation of Ang Ⅱ is governed by interplay with NO[21]. NO antagonizes the vasoconstrictive and pro-atherosclerotic effect of Ang Ⅱ, as well as directly modulating angiotensin-converting enzyme (ACE) activity. Conversely, Ang Ⅱ decreases NO bioavailability by promoting oxidative stress[21,49]. Ang Ⅱ has been reported to upregulate super oxide production in endothelial and vascular smooth muscle cells, which is thought to directly contribute to Ang Ⅱ-induced contraction of vascular smooth muscle[50].

It is possible that the beneficial effect of PDE 5 inhibitors in DN is due to their regulatory action on the renal Ang Ⅱ response. There is clinical evidence that inhibition of ACE and AT1 receptor blockade suppress development of DN[51-53]. Whether the beneficial effects of PDE 5 inhibitors in DN also include regulatory actions on the renal Ang Ⅱ response merits future investigation.

CONCLUSION

Over the last few years the cellular and molecular events underlying the renal structural and functional abnormalities of DN have been the subject of intense study. The role played by metabolic and haemodynamic stimuli in disease progression should not be underestimated. It is likely that diabetic hyperglycaemia and oxidative stress increase the formation of AGEs, cytokines and growth factors, which are important in the development of glomerulosclerosis and tubulointerstitial fibrosis, by stimulating the production of extracellular matrix and inhibiting its degradation. Ang Ⅱ also plays an important role in DN, since it increases mesangial proliferation and matrix accumulation and induces proinflammatory and fibrogenic processes. These events lead to the progressive decline of nephron function and their destruction.

The evidence outlined in this review suggests that PDE 5 inhibition may provide an additional therapeutic option to treat this debilitating disorder. Ultimately, it may be necessary to use PDE5 inhibitors in conjunction with other treatment modes; for example, hypoglycaemic drugs and antihypertensives, such as ACE inhibitors and AT1 receptor blockers. In addition, cardiovascular risk factors, such as hyperlipidaemia and smoking should be reduced. These life style changes, supported by appropriate drug therapy, could ultimately reduce the number of patients with DN who require costly renal dialysis or transplantation.

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