EDITORIAL
Korean J Intern Med 2012;27:151-153
http://dx.doi.org/10.3904/kjim.2012.27.2.151

pISSN 1226-3303 eISSN 2005-6648
http://www.kjim.or.kr

Effect of Phosphodiesterase Inhibitor on Diabetic Nephropathy

Shin-Wook Kang

Department of Internal Medicine, Brain Korea 21, Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, Korea

See Article on Page 163-170

Diabetic nephropathy, the leading cause of end-stage renal disease worldwide, is characterized pathologically by cellular hypertrophy and increased extracellular matrix accumulation, and clinically by proteinuria. The molecular and cellular mechanisms responsible for these characteristics have not been completely resolved. Although the diabetic milieu, hemodynamic changes, and local growth factors are considered to be mediators in the pathogenesis of diabetic nephropathy, the underlying pathways are not well understood.

Numerous recent studies have demonstrated the infiltration of inflammatory cells within renal glomeruli and the tubulointerstitium in both human diabetic patients and experimental diabetic animals. Monocytes/macrophages are the principle inflammatory cells present in the diabetic kidney, and accumulating evidence suggests that monocytes/macrophages are important in the development and progression of glomerular and tubulointerstitial lesions in diabetic nephropathy [1]. Strict control of blood glucose and blood pressure levels along with the use of renin-angiotensin system blockers has been the gold standard for the management of diabetic patients. The administration of anti-inflammatory agents such as mycophenolate mofetil and retinoic acid was recently found to reduce inflammatory cell infiltration and prevent renal injury in experimental diabetic animals [2]. Irradiation also had a beneficial effect on diabetic nephropathy via an anti-inflammatory mechanism. These findings suggest that an inflammatory process may also contribute to the pathogenesis of diabetic nephropathy and that drugs with anti-inflammatory effects may be useful in preventing nephropathy in diabetic patients.

Pentoxifylline (PTX) is one of a number of anti-inflammatory drugs that have been used for clinical trials in diabetic patients with nephropathy. PTX, a nonselective inhibitor of cyclic-3', 5'-nucleotide phosphodiesterase (PDE), has been shown to improve circulation by altering red blood cell deformability, improving capillary microcirculation, and acting as an adenosine antagonist [3]. Clinically, it has been used mainly to treat patients with peripheral vascular disease. Recently, mounting evidence has demonstrated diverse anti-inflammatory, antiproliferative, and antifibrotic functions for PTX. It has been shown to inhibit not only the transcription of tumor necrosis factor-α (TNF-α) and transforming growth factor-β1 genes but also the proliferation of lymphocytes, fibroblasts, and mesangial cells, leading to reduced extracellular matrix synthesis. In addition, proteinuria, glomerular sclerosis, interstitial inflammation, and apoptosis were ameliorated by PTX administration in animals with various kidney diseases, including anti-Thy1 nephritis, remnant kidney, crescentic glomerulonephritis, adriamycin-induced ne-

Received: April 12, 2012
Accepted: April 23, 2012

Correspondence to Shin-Wook Kang, M.D.
Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-749, Korea
Tel: 82-2-2228-1959, Fax: 82-2-393-6884, E-mail: kswkidney@yuhs.ac

phropathy, and diabetic nephropathy [4]. Considering these experimental findings and the potential of PTX to decrease intraglomerular pressure, PTX has been of interest as a therapeutic agent in patients with various kidney diseases. Previous studies have demonstrated that PTX significantly decreased serum and urinary TNF-α levels in diabetic patients with nephropathy. Moreover, PTX treatment significantly attenuated the increase in urinary monocyte chemoattractant protein-1 concentrations, which was associated with a significant decrease in urinary protein excretion, in patients with proteinuric primary glomerular diseases [5]. The renoprotective and anti-proteinuric effects of PTX have been considered to be attributed to its ability to downregulate the production of proinflammatory cytokines.

In the manuscript titled "Phosphodiesterase inhibitor improves renal tubulointerstitial hypoxia of diabetic rat kidney," Sun et al. [6] investigated the effect of PTX in diabetic nephropathy from a different point of view. Based on the concept that chronic hypoxia, which is attributed to structural abnormalities and functional disorders of the renal vasculature, may play a role in the development of tubulointerstitial fibrosis and atrophy in diabetic nephropathy, the authors hypothesized that PTX, a PDE inhibitor, could improve renal tubular hypoxia and the consequent renal injury in streptozotocin (STZ)-induced diabetic rats. The results of their study showed that the increase in protein-to-creatinine ratios in 8-week diabetic rats was significantly abrogated by PTX treatment. PTX also significantly ameliorated the increases in renal cortical expression of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor mRNA in 8-week diabetic rats. In normal rat kidney cells, in contrast, HIF-1α expression induced by $CoCl_2$ (to create hypoxia *in vitro*) or by high glucose was not altered by PTX. The authors suggested that the underlying mechanism of the beneficial impact of PTX in diabetic nephropathy may be related to improved renal blood flow partly via the attenuation of peritubular endothelial dysfunction, rather than a direct effect on renal tubular cells.

The maintenance of both normal renal blood perfusion and oxygenation is critical for controlling renal function. Oxygen tension (pO_2) is low in the renal medulla because of countercurrent oxygen diffusion between the descending and ascending vasa recta and the high rate of ion transport activity in the thick ascending limb of the loop of Henle. Therefore, the renal medulla is especially susceptible to further decreases in pO_2. Renal hypoxia has been implicated in the pathogenesis of ischemic nephropathy, and recent studies have suggested that it may participate in the development and progression of diabetic nephropathy via at least two major mechanisms: functional hypoxia, which may occur as a result of increased oxygen consumption to support sodium reabsorption during the early hyperfiltration stage of diabetic nephropathy, and oxidative stress-associated hypoxia, which is dominant in later stages of diabetic nephropathy. In addition, diabetes is commonly associated with decreased bioavailability of nitric oxide (NO), a potent regulator of vascular tone and oxygen utilization, and reduced renomedullary oxygen availability. Palm et al. [7] recently clarified the interrelationship between reduced NO bioavailability and hypoxia in the renal medulla in 2-week STZ-induced diabetic rats. In that study, L-arginine, but not α-tocopherol, significantly abrogated the decrease in renomedullary NO levels in diabetic rats. In contrast, reduced medullary pO_2 in diabetic rats was ameliorated by either acute arginine administration or long-term antioxidant treatment, irrespective of comparable intrarenal microcirculation in control rats. These findings established a link between NO synthase substrate availability and the changes in medullary pO_2 accompanying diabetes. Similarly, blood oxygen level-dependent magnetic resonance imaging revealed hypoxic changes in the renal medulla as early as 2 days after STZ-induction of diabetes, while there was no significant difference in renal medullary blood flow between diabetic and control rats [8]. Given these findings and the fact that NO, which is synthesized from L-arginine and exerts its action in part via cGMP, which is rapidly hydrolyzed and degraded by PDE, inhibitors of PDE may have beneficial effects on the kidney.

In fact, a previous study by Han et al. [9] of the current paper found that the administration of PTX inhibited the renal inflammatory reaction at 4 weeks and prevented proteinuria at 8 weeks in STZ-induced diabetic rats, suggesting that prolonged administration of PTX enhanced its protective effects. However, the current study focused on the effect of PTX on renal hypoxia. Collectively, it is surmised that PTX, a PDE inhibitor, can attenuate renal hypoxia in diabetic rats by restoring the decreased NO bioavailability, with or without changes in renal medullary blood flow. Nevertheless, the results of a recent meta-analysis on the effect of PTX on proteinuria in diabetic patients were disappointing [10], as PTX appeared to have

effects similar to those of captopril in terms of reducing proteinuria. A secondary analysis showed that patients with microalbuminuria had no significant decrease in urinary protein excretion upon PTX treatment, whereas PTX significantly reduced the amount of proteinuria in patients with overt proteinuria. Additional large, high-quality studies are required to elucidate the beneficial renoprotective effect and underlying mechanism of PTX in patients with diabetic nephropathy.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Chow F, Ozols E, Nikolic-Paterson DJ, Atkins RC, Tesch GH. Macrophages in mouse type 2 diabetic nephropathy: correlation with diabetic state and progressive renal injury. Kidney Int 2004;65:116-128.
2. Utimura R, Fujihara CK, Mattar AL, Malheiros DM, Noronha IL, Zatz R. Mycophenolate mofetil prevents the development of glomerular injury in experimental diabetes. Kidney Int 2003;63:209-216.
3. Ehrly AM. Improvement of the flow properties of blood: a new therapeutical approach in occlusive arterial disease. Angiology 1976;27:188-196.
4. Badri S, Dashti-Khavidaki S, Lessan-Pezeshki M, Abdollahi M. A review of the potential benefits of pentoxifylline in diabetic and non-diabetic proteinuria. J Pharm Pharm Sci 2011;14:128-137.
5. Chen YM, Lin SL, Chiang WC, Wu KD, Tsai TJ. Pentoxifylline ameliorates proteinuria through suppression of renal monocyte chemoattractant protein-1 in patients with proteinuric primary glomerular diseases. Kidney Int 2006;69:1410-1415.
6. Sun HK, Lee YM, Han KH, Kim HS, Ahn SH, Han SY. Phosphodiesterase inhibitor improves renal tubulointerstitial hypoxia of the diabetic rat kidney. Korean J Intern Med 2012;27:163-170.
7. Palm F, Friederich M, Carlsson PO, Hansell P, Teerlink T, Liss P. Reduced nitric oxide in diabetic kidneys due to increased hepatic arginine metabolism: implications for renomedullary oxygen availability. Am J Physiol Renal Physiol 2008;294:F30-F37.
8. dos Santos EA, Li LP, Ji L, Prasad PV. Early changes with diabetes in renal medullary hemodynamics as evaluated by fiberoptic probes and BOLD magnetic resonance imaging. Invest Radiol 2007;42:157-162.
9. Han KH, Han SY, Kim HS, Kang YS, Cha DR. Prolonged administration enhances the renoprotective effect of pentoxifylline via anti-inflammatory activity in streptozotocin-induced diabetic nephropathy. Inflammation 2010;33:137-143.
10. McCormick BB, Sydor A, Akbari A, Fergusson D, Doucette S, Knoll G. The effect of pentoxifylline on proteinuria in diabetic kidney disease: a meta-analysis. Am J Kidney Dis 2008;52:454-463.