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COMMENTARY

Dual protein kinase C alpha and beta inhibitors and diabetic kidney disease: a revisited therapeutic target for future clinical trials

Diabetic kidney disease is the primary cause of chronic kidney disease worldwide, which can progress to end-stage renal disease that requires chronic dialysis therapy or renal transplantation[1]. An improved therapeutic strategy to combat diabetic kidney disease might include blocking the mechanisms by which diabetes leads to renal injury; for example, activation of protein kinase C (PKC).

The PKC family comprises a group of related serine/threonine kinases that are ubiquitously expressed and participate in a variety of intracellular signaling pathways. The PKC family is divided into classical (α, β I, β II, γ), novel (δ, ε, η, θ) and atypical (ζ, ι/λ) isoforms on the basis of the biochemical properties of the isoforms[2]. In diabetics, PKC activity is upregulated in vascular tissue including the retina and the renal glomeruli. Of the 10 PKC isoforms, the α, β I, β II, δ, and ζ isoforms have been reported to be activated in glomeruli and renal cells exposed to high concentrations of glucose[3]. In previous preclinical studies, we showed the beneficial effects of oral treatment with the selective PKCβ inhibitor, ruboxistaurin, on diabetic kidney and eye diseases. Treatment with ruboxistaurin improved albuminuria, glomerular filtration rate and retinal circulation in diabetic rats when administered orally for 2–8 weeks. In a longer study in the *db*/*db* mouse, treatment with ruboxistaurin ameliorated albuminuria and mesangial expansion by reducing the expression of transforming growth factor (TGF)-β, fibronectin and type IV collagen[4]. Subsequently, in a study in diabetic transgenic Ren-2 rats, inhibition of PKCβ with ruboxistaurin resulted in amelioration of albuminuria, structural injury and TGF-β expression, despite continued hyperglycemia and hypertension. In short-term clinical trials, ruboxistaurin was shown to be effective in the treatment of diabetic kidney disease and advanced retinopathy, consistent with preclinical studies. However, the results of long-term clinical studies in patients with diabetic eye disease have been disappointing, despite some modest effect on albuminuria[5], and further clinical trials of ruboxistaurin or other PKC β inhibitors are therefore warranted.

Although a number of researchers have implicated PKCβ activation in the development and progression of diabetic kidney disease, other studies have implicated PKCα as a major underlying mechanism of diabetes-induced albuminuria. Specifically for streptozotocin (STZ)-induced diabetes, Kang *et al.*[6] showed activation of PKCα and ε isoforms in the kidney without significant increase in PKCβ isoforms, in contrast to our findings. Using PKCα and β knockout mice, Haller *et al.*[7] showed that PKCβ activation was involved in transforming growth factor (TGF)-β_1-mediated renal hypertrophy and extracellular matrix expansion, whereas PKCα activation mediated the expression of perlecan, vascular endothelial growth factor (VEGF) and nephrin, resulting in albuminuria. Similarly, King *et al.*[8] presented a longer study in diabetic PKCβ knockout mice carried out over 24 weeks that showed reduced glomerular and renal hypertrophy, although only a modest reduction in albuminuria was observed.

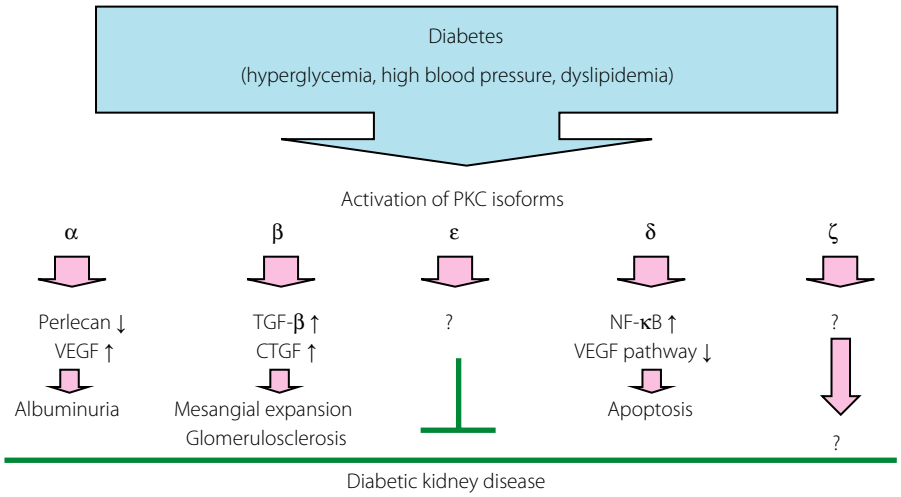

Figure 1 | Diabetes induces activation of protein kinase C (PKC) isoforms (α, β, ε, δ and ζ) in renal tissue through hyperglycemia, high blood pressure and dyslipidemia, resulting in development and progression of diabetic kidney disease. PKCε activation in diabetes might protect against renal injury. The precise role of PKCζ activation in the kidney remains unknown. CTGF, connective tissue growth factor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

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A recent report in *Diabetes* clearly showed that deletion of both PKCα and β isoforms inhibits the development of diabetic kidney disease in STZ-induced diabetic mice, although albuminuria was not completely prevented as compared with exclusively PKCα knockout diabetic mice[9]. As further evidence for these findings, pharmacological inhibition of PKCα and β with CGP41252, an agent utilized as the classical PKC inhibitor in several cancer trials, ameliorated albuminuria, but failed to significantly reduce renal hypertrophy in the STZ-induced 129/SV and the *db*/*db* mice. Interpretation of these findings implicated CGP41252 as a broad-PKC inhibitor as opposed to a specific inhibitor of PKCα and β. Such an agent might inhibit novel PKC isoforms, such as PKCε. Deletion of the PKCε signaling pathway induces glomerulosclerosis and tubulointerstitial fibrosis *in vivo*, suggesting a protective role against diabetic kidney disease[10].

Diabetic kidney disease continues to be a major complication of type 1 and type 2 diabetes, and represents the major cause of end-stage renal disease globally. There is an urgent need for new therapeutic drugs, although intensified blood glucose and blood pressure control with inhibition of the renin–angiotensin system are critical for reducing albuminuria, and preserving or slowing decline of renal function in diabetics. However, this new study highlights the need for further development of isoform-specific PKC inhibitors specifically targeting both PKCα and β action without inhibition of other PKC isoforms (Figure 1). Discovery of such inhibitors could have potential use in the future treatment of diabetic kidney disease.

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