Protein Kinase C-β Inhibition: A Promise Not Yet Fulfilled

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Kinases transfer the terminal, “high energy” phosphate group of ATP to a site on a target protein, thereby activating the protein, which may be an enzyme, cell membrane receptor, or ion transport channel. The protein kinase C (PKC) family is a group of such enzymes that require specific activator molecules, including diacylglycerol, whose intracellular concentration increases substantially during hyperglycemia. Studies more than a decade ago identified the association between activation of PKC and increased diacylglycerol levels initiated by hyperglycemia with many vascular abnormalities in retinal, renal, and cardiovascular tissues (1,2). Among the various PKC isoforms, the β isoform activates preferentially in the vasculatures of diabetic animals, including those of the renal glomeruli and retina. Glucose-induced activation of PKC increases production of extracellular matrix and cytokines; enhances contractility, permeability, and vascular cell proliferation; induces the activation of cytosolic phospholipase A2; and inhibits Na⁺-K⁺-ATPase. Activation of the diacylglycerol-PKC pathway (2) may mediate the cellular damage that is induced by the oxidative stress of hyperglycemia.

Since the aforementioned laboratory observations became known, inhibitors of PKC-β isoforms were evaluated to assess their impact on both retinopathy and nephropathy progression. Reviews of clinical outcome trials by various investigators support the notion that systemic inhibitors of the PKC-β isoform were efficacious when used to slow the development of the microangiopathic complications of diabetic retinopathy (3,4).

It is widely known that the presence and the magnitude of diabetic microvascular disease are associated with the presence of diabetic nephropathy in both type 1 and type 2 diabetes (5–8); given this association, it would follow that PKC-β would have a role in mediating concomitant injury in both the retina and the kidney. Note that in most of these studies, renal injury was assessed by magnitude of albuminuria, usually microalbuminuria rather than change in GFR or other renal functional measure. Unfortunately, microalbuminuria is a cardiovascular risk marker and gives information that is more relevant to cardiovascular risk given the mechanism of drug action on the vasculature (9). This also should be the focus of future investigations. In short, use of agents that inhibit PKC-β activity may confer some modest benefits in the vasculature of the eye and the kidney. These benefits have not translated into meaningful outcome differences, but one reason for this may be the intervention at a very early time in progression of nephropathy. Alternatively, this intervention may not offer a significant benefit beyond maximal inhibition of the renin-angiotensin-aldosterone system and BP and glucose control. All of these issues...
should be addressed in a large, meaningfully powered outcome trial.

**Disclosures**

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**References**


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See the related article, “Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease”, on pages 631–636.