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Prostaglandin I₂ Receptor Agonism for Proteinuria and Diabetes: Good for the Goose and Good for the Gander?

Diabetic kidney disease (DKD) remains the leading cause of end-stage renal disease (ESRD) in the developed world (1). In the U.S., the prevalence of both diabetes and DKD have increased linearly and proportionately, as determined by the serial assessments from National Health and Nutrition Examination Survey (NHANES) data, such that the proportion of DKD in patients with diabetes (assessed by albuminuria or glomerular filtration rate) has remained nearly constant (2,3). Further, although diabetic control, adjudged by glycated hemoglobin levels, has sequentially improved in the last decade (4), the prevalence of patients with DKD listed as a primary cause of ESRD in the U.S. has not declined (1,3). These epidemiologic trends have occurred despite the significantly increased use of antihyperglycemic agents and renin-angiotensin-aldosterone blockers among patients with diabetes (3). These data therefore suggest that, in addition to treating hyperglycemia itself, there is a persistent need for drug discovery to treat DKD and delay ESRD progression using agents that could target the multiple effector pathways involved in DKD, either alone or in combination.

Studies have implicated intracellular hyperglycemia with metabolic byproduct accumulation and consequent oxidative stress–related, proinflammatory, and profibrotic pathway activation as important factors contributing to organ damage in diabetes, including DKD (reviewed in refs. 5,6). However, strategies targeting these cellular processes to benefit DKD have met with limited success in clinical studies (7–9). Alternatively, serendipitous and unrelated renoprotective effects of the different classes of antihyperglycemic agents, distinct from their hypoglycemic effects, are also well described, although the clinical consequences need to be further assessed (10–14).

Recent exciting work has focused on pathways that could be involved in the pathogenesis of hyperglycemia while also having a direct bearing on renal epithelial cell injury in DKD. Nephrin, a transmembrane protein in glomerular podocytes, has recently been identified as playing a role in pancreatic β-cell viability and insulin secretion (15) and is an attractive candidate. Podocytes are important among the primary renal cells involved in injury in DKD, with podocyte injury marked by foot process effacement and ultimately podocyte loss encountered as features of DKD (reviewed in ref. 16). Nephrin is essential to the glomerular filtration barrier forming either a homodimer with itself or a heterodimer with Neph1 at the podocyte slit diaphragm, and phosphorylation of highly conserved tyrosine residues in its intracellular tail is required to initiate signaling events that regulate podocyte actin cytoskeletal dynamics (17) (Fig. 1, bottom panel). In the pancreatic β-cells, nephrin phosphorylation at these same tyrosine residues has been shown to regulate glucose-stimulated insulin secretion (18) (Fig. 1, top panel).

In the current issue of *Diabetes*, Batchu et al. (19) focus on the prostaglandin I₂ (IP) receptor, which is expressed in both podocytes and pancreatic β-cells. The authors hypothesized that IP receptor agonism could have beneficial effects in diabetes and DKD via nephrin phosphorylation in both cell types. The IP receptor signals through cAMP, which in turn activates catalytically inactive protein kinase A (iPKA to PKA). This activation has been shown previously to be important in regulating podocyte differentiation (20). The authors performed a series of experiments using a β-cell line, demonstrating initially that IP receptor agonism increased insulin release via nephrin phosphorylation that was dependent on cAMP/PKA. Improved β-cell viability was also observed with IP receptor agonists in vitro. In vivo, improved glycemic control, increased insulin levels, and enhanced β-cell mass were all observed in streptozotocin (STZ)-induced diabetic mice treated with selexipag (an IP receptor agonist) compared
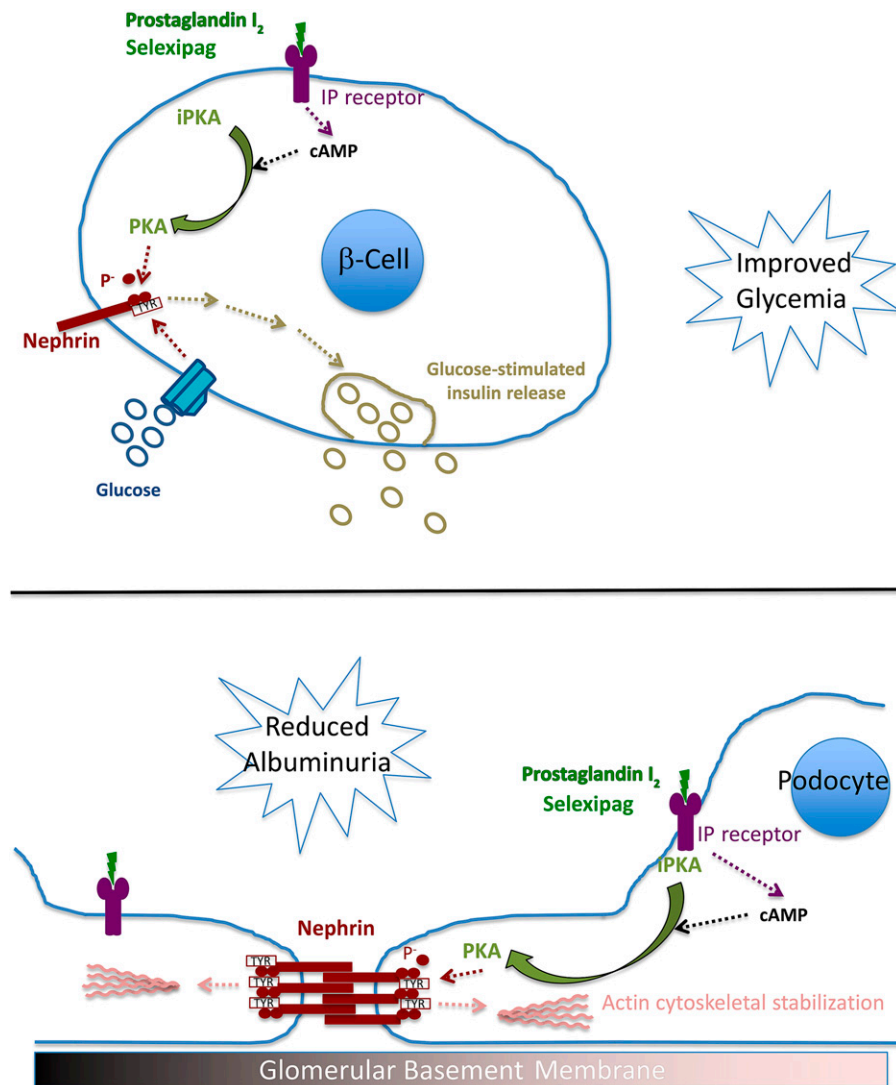
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Figure 1—IP receptor agonism benefits glycemia and albuminuria simultaneously via nephrin phosphorylation. Top panel: Simplified illustration summarizes the findings by Batchu et al. (19). IP receptor agonism via selexipag increases intracellular cAMP, which activates the catalytic activity of PKA, which in turn phosphorylates nephrin at its intracellular tail at specific tyrosine residues. Nephrin phosphorylation improves glucose-stimulated insulin release and glycemia. Bottom panel: In the podocyte, nephrin phosphorylation at these tyrosine residues via cAMP/PKA by IP receptor agonism facilitates actin cytoskeletal stabilization and was found to be beneficial in proteinuria in a mouse model of DKD. It should be noted that glucose itself enhances phosphorylation of nephrin in the β-cell. p-, phosphorylation; TYR, tyrosine residues positioned at 1176/1193.

with vehicle-treated STZ animals. Here the authors made a key observation that albuminuria decreased with selexipag treatment even while glycemia was transiently worsening, leading the authors to infer a glycemia-independent benefit of selexipag on albuminuria. Similarly, IP receptor agonism was observed to increase nephrin phosphorylation in a cAMP/PKA-dependent manner in cultured podocytes. To aggravate the renal phenotype in vivo, the authors induced diabetes via STZ in DKD-susceptible eNOS knockout mice and showed improved albuminuria without a concomitant glycemic benefit with selexipag treatment. These data suggest that IP receptor agonism may have beneficial effects on hyperglycemia in diabetes as well as albuminuria in DKD through facilitating nephrin phosphorylation.

Although this study arises from a crucial line of reasoning and explores a novel pathway, some limitations must be noted. First, the benefit of selexipag on glycemia was at best moderate in this study: in the eNOS knockout mice, there was insignificant glycemic improvement with STZ. Next, whether the reduction in albuminuria is entirely independent from glycemia cannot be confirmed from these experiments, as in both instances there was some, albeit minor, glycemic benefit. Recent clinical data from a study of type 1 diabetes has suggested that early improvement in glycemia can have significant and lasting benefit in albuminuria (21). Hence, to truly establish an independent beneficial effect on proteinuria, a nondiabetic model of proteinuria would need to be examined. It must be noted

here that although STZ is a well-known model of insulin-dependent diabetes, a direct toxicity of STZ in the kidney has also been reported (22). Therefore, whether these benefits will remain the same in type 2 diabetes models will need to be further examined. Finally, although a reduction in albuminuria was observed in these mice with selexipag, aside from the enhanced nephrin phosphorylation seen in the podocytes of these mice, no differences in renal histology by light or electron microscopy (including differences in podocyte foot process effacement or podocyte numbers) could be identified. These data may again suggest a relatively modest renal protective effect of selexipag, especially when encountering more severe glomerular injury in diabetes. On the other hand, these data also raise avenues for further investigation regarding the exact mechanism of benefit of IP receptor agonism in proteinuria including potential hemodynamic effects, as IP receptor agonism is known to activate multiple downstream pathways. In addition, whether activation of the cAMP/PKA pathway by other G_s protein–coupled receptor agonists will mimic the effects of IP receptor agonism also remains undetermined.

Notwithstanding these issues, selexipag is an U.S. Food and Drug Administration (FDA)-approved drug for use in pulmonary hypertension with a good safety profile when used for this indication (23) and therefore has the potential to translate rapidly to human DKD studies.

In summary, these studies provide initial evidence on the use of IP receptor agonists as potential drugs to improve both hyperglycemia and proteinuria in DKD. Future studies should address the limitations outlined above and attempt to isolate their antihyperglycemic effects from their antiproteinuric effects and better delineate their roles in both diabetes and DKD. Ultimately, a drug that benefits both diabetes and DKD could be a vital discovery.

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