Overexpression of Cyclooxygenase-2 Predisposes to Podocyte Injury

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Increased podocyte cyclooxygenase-2 (COX-2) expression is seen in rats after renal ablation and Thy-1 nephritis and in cultured murine podocytes in response to mechanical stress. For investigation of whether COX-2 overexpression plays a role in podocyte injury, transgenic B6/D2 mice in which COX-2 expression was driven by a nephrin promoter were established. Selective upregulation of COX-2 expression in podocytes of transgenic mouse kidneys was confirmed by immunoblotting and immunohistochemistry. Whether upregulation of podocyte-specific COX-2 expression enhanced sensitivity to the development of Adriamycin nephropathy was examined. Adriamycin administration induced dramatically more albuminuria and foot process effacement and reduced glomerular nephrin mRNA and immunoreactivity in transgenic mice compared with wild-type littermates. Adriamycin also markedly increased immunoreactive COX-2 expression in podocytes from transgenic mice compared with the wild-type mice. Reverse transcriptase–PCR indicated that this increase represented a stimulation of endogenous COX-2 mRNA expression rather than COX-2 mRNA driven by the nephrin promoter. Balb/C mice, which are susceptible to renal injury by Adriamycin, also increased podocyte COX-2 expression and reduced nephrin expression in response to administration of the drug. Long-term treatment with the COX-2–specific inhibitor SC58236 ameliorated the albuminuria that was induced by Adriamycin in the transgenic mice. SC58236 also reduced Adriamycin-induced foot process effacement in both the COX-2 transgenic mice and Balb/C mice. Therefore, overexpression of COX-2 may predispose podocytes to further injury.


Podocyte injury is a major cause of progressive glomerular damage (1), but underlying factors of the predisposition of podocytes to injury and the mechanisms that mediate the injury remain unclear. Prostaglandins that are derived from cyclooxygenase-2 (COX-2) that is expressed in mammalian kidney have been identified as important mediators of vascular tone, salt and water balance, and renin release (reviewed in reference [2]). In addition to localized expression of COX-2 in macula densa and medullary interstitial cells, previous studies reported that COX-2 is detectable in the podocytes of human kidney (3). Increased podocyte COX-2 expression in rats has been reported in models of subtotal renal ablation (4–8), Thy-1 nephritis (9), and diabetic nephropathy (10), and selective COX-2 inhibitors have been shown to decrease proteinuria and retard progressive glomerular injury in models of renal ablation (4–7), diabetes (11), and salt-sensitive hypertension (12). A recent in vitro study demonstrated that mechanical stress could induce COX-2 expression in cultured podocytes (13). Although the role of prostanoids in functional and structural responses of podocytes has not been studied intensively, the few studies that have been performed suggest that they play an important functional role (14). The underlying mechanisms of in vivo COX-2 upregulation in podocytes and its potential role in podocyte function in response to injury have not been addressed formally. To investigate whether COX-2 upregulation is a mediator or simply a consequence of podocyte injury, we generated transgenic mice with increased COX-2 in podocytes and studied their response to the nephrotoxin Adriamycin.

Materials and Methods

Materials

The selective COX-2 inhibitor SC58236, which exhibits a COX-2/COX-1 selectivity of 1780-fold (15), was a gift from Pfizer (St. Louis, MO). Rabbit anti–COX-2 and anti–COX-1 antibodies were from CAYman Chemical Co. (Ann Arbor, MI). Goat anti-nephrin, Wilms’ tumor 1 (WT-1) antibody, rabbit anti-CD2AP antibody, and goat anti–β-actin antibodies were from Santa Cruz Biotechnology (Santa Cruz, CA); rabbit anti–zonula occludens 1 (anti–ZO-1) antibody was from Zymed Laboratories (San Francisco, CA); rabbit anti-podocin and podocalyxin antibodies were from Alpha Diagnostics International (San Antonio, TX). Cy3-labeled anti-goat antibody and anti-rabbit antibody were from Jackson ImmunoResearch Laboratories (West Grove, PA). ECL (En-
hanced Chemiluminescence Kit) and ECL Hyperfilm were from Amersham (Arlington Heights, IL). BCA protein assay reagent kit, ImmunoPure ABC peroxidase staining kit, and biotin-labeled mouse anti-rabbit or rabbit anti-goat IgG (H+L) antibodies were from Pierce (Rockford, IL). Adriamycin was from Bedford Laboratories (Belford, OH). Abuwell and creatinine kits were from Exocell (Philadelphia, PA). Other reagents were purchased from Sigma Chemical Co. (St. Louis, MO).

**Animal Model and Genotype**

All animal study protocols were reviewed and approved by the Vanderbilt University Institutional Animal Care and Use Committee, and all experiments were conducted according to National Institutes of Health guidelines. An 8.5-kb fragment of the murine 5′ nephrin promoter was ligated to the murine COX-2 gene in pBluescript SK−, beginning at the ATG in exon 1 (Figure 1A). B6/D2-F1 founders were identified by PCR and Southern analysis of tail DNA. As shown in Figure 1, B and C, the 5′ PCR primer (ACA GAA AGA CTG CGA CAG TCA CAG AC) is in the nephrin 5′ untranslated region and the 3′ primer (GCT CAT ACA TTC CCC CAC GGT TTT GAC) is in exon 2 of COX-2. PCR was performed at 95°C for 5 min; then 95°C for 30 s, 62°C for 30 s, and 72°C for 90 s for 38 cycles, with an additional 10 min extension at 72°C. This primer set generated a 972-bp fragment in transgenic mice (Figure 1C). A 600-bp probe for Southern analysis was generated from COX-2 plasmid DNA that was digested with Hpal and PacI and used to identify both genomic integration of the transgene (5.2 kb) and the wild-type (1.78 kb) COX-2 gene after EcoRV digestion (Figure 1B).

Male age-matched (10 to 12 wk old) mice were divided into five groups: (1) Wild-type B6/D2 control; (2) wild-type + Adriamycin (10

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**Figure 1.** Genotyping of nephrin promoter-driven cyclooxygenase-2 (COX-2) transgenic mice. (A) Schematic illustration of genotyping strategy: An 8.5-kb fragment of the murine 5′ nephrin promoter was ligated to the murine COX-2 gene, beginning at the ATG in exon 1. (B) Southern hybridization: Lanes 1, 2, and 4 from transgenic mice F10, F14, and F16, respectively, which exhibited an expected 5.2-kb band in EcoRV-digested DNA, whereas only a 1.78-kb band from endogenous COX-2 was detected in wild-type mice (lane 2). (C) Southern hybridization: Lanes 1, 3, and 4 are from transgenic mice F16; lanes 2 and 5 are from wild-type mice. Lanes 1 and 4 represented homogeneous transgenic mice, and lane 3 was from a mouse that was heterozygous for the transgene, which was confirmed further by genotyping of their offspring. (C) A single PCR product of 972 bp was detected for the respective transgenic mouse lines (lanes 1, 3, and 4) but not in wild-type (lane 2).
mg/kg by retro-orbital injection); (3) transgenic control; (4) transgenic + Adriamycin; and (5) transgenic + Adriamycin + SC58236. SC58236 was administered in the drinking water at a concentration of 6 mg/L, a dosage that we documented previously to provide continuous and selective COX-2 inhibition (16), and was begun 1 d after Adriamycin injection. An equal number of mice that were administered Adriamycin received water with vehicle alone (0.2% PEG 200). Urine was collected weekly in metabolic cages, and the mice were killed at the end of 6 wk. In similar studies, 10- to 12-wk-old male BALB/c mice received Adriamycin and were killed 2 wk later.

Assessment of Glomerular Injury
The ratio of urinary albumin/creatinine was determined by ELISA (with Abuwelk kit from Exocell) with the creatinine companion kit (Exocell). Glomerular injury was assessed histologically by light microscopy and electron microscopy.

Immunoblotting
For COX-2, renal cortices were homogenized in 30 mM Tris-HCl (pH 8.0) and 100 μM PMSF (1:9 wt/vol). After a 10-min centrifugation at 10,000 × g, the supernatant was centrifuged for 60 min at 110,000 × g to prepare microsomes, as described previously (11). Proteins were resuspended in SDS sample buffer. For detection of other proteins, renal cortices were homogenized with RIPA buffer and centrifuged, heated to 100°C for 5 min with sample buffer, separated on SDS gels under reducing conditions, and transferred to Immobilon-P transfer membranes (Millipore, Bedford, MA). The blots were blocked overnight with 100 mM Tris-HCl (pH 7.4) that contained 5% nonfat dry milk, 3% albumin, and 0.5% Tween-20, followed by incubation for 1 h with polyclonal rabbit COX-2 antisera or other indicated antibodies. The second biotinylated antibody reagent was detected using avidin and horseradish peroxidase (Pierce) and exposed on film using ECL (Amersham). The membrane was rehybridized with goat anti-β-actin antibody (Santa Cruz Biotechnology) to normalize protein loading.

Immunohistochemistry
Under deep anesthesia with Nembutal (70 mg/kg intraperitoneally), mice were exsanguinated with 50 ml/100 g heparinized saline (0.9% NaCl, 2 U/ml heparin, and 0.02% sodium nitrite) through a transcardiac aortic cannula and fixed with glutaraldehyde-periodate acid saline for COX-2 staining as described previously. Glutaraldehyde-periodate acid saline contains a final concentration of 2.5% glutaraldehyde, 0.011 M sodium metaperiodate, 0.04 M sodium phosphate, 1% acetic acid, and 0.1 M NaCl and provides excellent preservation of tissue structure and antigenicity. Antigens were retrieved in 0.01 M citrate buffer (pH 6.0) by microwave for 2 min, followed by steam for 25 min.

COX-2 immunoreactivity was localized with COX-2 antisera diluted to 2.5 ng/ml. The second antibody was localized using Vectastain ABC-Elite (Vector, Burlingame, CA) with diaminobenzidine as the chromogen, followed by a light counterstain with toluidine blue. The fixed kidneys were dehydrated through a graded series of ethanols, embedded in paraffin, sectioned at 4-μm thickness, and mounted on glass slides.

Immunofluorescence
The freshly removed kidneys were embedded in OCT compound for frozen sections and were stored at −80°C. Five-micrometer sections were fixed with acetone and 4% paraformaldehyde, followed by blocking with the corresponding serum and incubation with primary and second antibodies. Cy3 donkey anti-goat antibody and anti-rabbit antibody were used as secondary antibodies.

Figure 2. Adriamycin induced albuminuria in COX-2 transgenic mice (n = 6 to 12; P < 0.05 versus control transgenic mice or Adriamycin-treated wild-type mice).

Isolation of Glomeruli
For efficient glomerular isolation, we used Dynabeads (modified from reference [17]). Briefly, mice were perfused through the heart after anesthesia with 8 × 105 Dynabeads (Dynal Biotech ASA, Oslo, Norway) diluted in 40 ml of PBS. The kidneys were removed and minced and digested in collagenase (1 mg/ml collagenase A and 100 U/ml deoxyribonuclease I in HBSS) at 37°C for 30 min with gentle agitation. The tissue was pressed through a 100-μm cell strainer and washed twice with 5 ml of HBSS. After centrifugation, the cell pellet was resuspended in 2 ml of HBSS, and glomeruli that contained Dynabeads were gathered by a magnetic particle concentrator and washed three times with HBSS.

RNA Extraction and Real-Time and Quantitative Reverse Transciptase–PCR
Total glomerular RNA was extracted using TRI-reagent (Molecular Research Center, Cincinnati, OH) and chloroform extraction and then further purified with RNeasy kit (Qiagen, Valencia, CA). Nephrin and WT-1 mRNA were determined by real-time reverse transcriptase–PCR (RT-PCR) with TaqMan One-Step RT-PCR Master Mix Reagents (Applied Biosystems, Branchburg, NJ) and an ABI Prism 7000 Sequence Detection System (18). Briefly, 50 ng of RNA from isolated glomeruli was used to perform RT-PCR at 48°C for 30 min, 95°C for 10 min, and 40 cycles of 95°C for 15 s and 60°C for 1 min. Primers and TaqMan probe for nephrin were as follows: Forward primer 5'-AAG CTG GTG CAT TAT GCT-3', reverse primer 5'-CGG TGC AGA CTA TAT GCT-3', and probe 6FAM-TGC CCT GAA GGA CCC TAC TGA GGT GAA-TAMRA. Primers and TaqMan probe for WT-1 were as follows: Forward primer 5'-TCT TGG AGG GTA TCT AT-3', reverse primer 5'-TGC TGA CCG GAC AAG AGT TG-3', and probe FAM-TGC GGC GTG TAT CTG GAG TGG C-TAMRA. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in each sample was used as a control, determined by a TaqMan Rodent GAPDH Control Reagent kit (Applied Biosystems).
To distinguish endogenous from transgene-driven COX-2 mRNA by real-time PCR, we used primer 5'-GGA GTC TGC TCA GGA AGG AA at exon 1 as the 5' primer for endogenous COX-2 and primer 5'-GCT CAG GGA AGA CAG CAA CAA at the nephrin promoter for the nephrin-driven COX-2 5' primer. The reverse primer 5'-GCT CAT ACA TTC CCC CAC GGT TTT GAC was used in both reactions. GAPDH (with upper primer 5'-TTC ACC ACC ATG GAG AAG GC and reverse primer 5'-GCC ATG GAC TGT GGT CAT GA) was used for an internal control. Real-time PCR was performed with IQ SYBR Green Supermix Kit (Bio-Rad Laboratories, Hercules, CA) at 95°C for 3 min and then 95°C for 20 s, 62°C for 20 s, and 72°C for 60 s in 40 cycles. Comparative C$_T$ and statistical analysis were calculated as per instructions of User Bulletin #2 from ABI (Applied Biosystems).

**Statistical Analyses**

All values are presented as means ± SEM. ANOVA and Bonferroni t test were used for statistical analysis, and differences were considered significant at $P < 0.05$.

**Results**

**Characterization of the Nephrin-Driven COX-2 Transgenic Mice**

We obtained three founders with COX-2 overexpression in podocytes (Figure 1B); copy number was detected with Southern hybridization by comparing samples with control lanes that contained various amounts of the construct calculated to estimate copies of the transgene per haploid genome. For this study, two founders (F16 and F14) were used, with copy numbers of 3 and 6, respectively. None of the lines demonstrated fetal lethality or decreased fertility. Under control conditions, renal histopathology was normal by light microscopic examination, and no albuminuria was detectable (Figure 2). Immunoblotting revealed no differences in expression of COX-1 in the whole-kidney homogenate in transgenic compared with wild-type mice. Although there was only a minimal elevation of COX-2 in the whole-kidney homogenate of transgenic mice, COX-2 expression was elevated profoundly in isolated glomeruli (Figure 4A). COX-2 was undetectable by immunohistochemistry in wild-type kidney but was appreciated readily in podocytes from transgenic mice (Figure 4, B and C).

**Adriamycin-Induced Podocyte Injury in COX-2 Transgenic Mice**

Although Adriamycin nephropathy is well characterized in rats, Adriamycin-induced podocyte nephrotoxicity in mice is strain dependent: Balb/C is the strain that is documented to be most susceptible to injury, whereas most other strains are resistant (19,20). In wild-type mice on the B6/D2-F1 background, a single dose of Adriamycin (10 mg/kg) did not induce albuminuria. In contrast, the urine albumin-to-creatinine ratio increased significantly in transgenic mice by week 2 (Figure 2) and remained elevated at week 6 (55.0 ± 11.7 μg albumin/mg creatinine in transgenic with Adriamycin versus 21.5 ± 3.2 in wild-type with Adriamycin; $n = 11$ to 12; $P < 0.05$). Albuminuria still was present in the transgenic mice at 10 wk after injection (data not shown). No significant abnormality was detected in either group by light microscopic examination. Electron microscopy at 6 wk indicated a significant increase in foot process effacement and mild mesangial sclerosis only in transgenic mice with Adriamycin (foot process effacement showed modest foot process effacement in the transgenic mice (Figure 3). Immunoblotting revealed no differences in expression of COX-1 in the whole-kidney homogenate in transgenic compared with wild-type mice. Although there was only a minimal elevation of COX-2 in the whole-kidney homogenate of transgenic mice, COX-2 expression was elevated profoundly in isolated glomeruli (Figure 4A). COX-2 was undetectable by immunohistochemistry in wild-type kidney but was appreciated readily in podocytes from transgenic mice (Figure 4, B and C).
effacement 57 ± 6%), compared with wild-type with Adriamycin (21 ± 3%; n = 10; P < 0.05; Figure 3).

**Upregulation of Endogenous COX-2 by Adriamycin Administration**

Adriamycin significantly increased COX-2 expression in glomeruli from transgenic mice (from 1.9 ± 0.2 to 2.8 ± 0.4-fold wild-type control; n = 4; P < 0.05; Figure 2C), which was confirmed by immunohistochemistry (Figure 2B) and immunofluorescence (data not shown) to be localized to podocytes. Real-time PCR with primers that distinguished endogenous from transgene-driven COX-2 mRNA demonstrated that the increase in podocyte COX-2 expression represented an increase in endogenous COX-2 mRNA expression (2.6 ± 0.1-fold of untreated controls; n = 4; P < 0.05), rather than COX-2 mRNA driven by the nephrin promoter (Figure 4D).

Several molecules, including nephrin, CD2AP, WT-1, ZO-1, podocin, and podocalyxin, have been implicated in maintenance of slit diaphragm integrity (1). Immunoblotting indicated no significant alteration in CD2AP, WT-1, ZO-1, podocin, or podocalyxin expression between wild-type and transgenic mice with or without Adriamycin (n = 4; NS; Figure 5); similar results also were demonstrated by immunofluorescence (data not shown). However, both immunofluorescence and immunohistochemistry indicated that Adriamycin reduced nephrin expression in transgenic mice (Figure 6A). Corresponding, Adriamycin significantly reduced glomerular nephrin mRNA in transgenic mice (30 ± 10% of wild type; n = 4; P < 0.05; Figure 6B) while only modestly reducing mRNA of WT-1 (another marker of podocytes; 68 ± 29%; NS).

Administration of a specific COX-2 inhibitor, SC58236, significantly ameliorated the albuminuria in Adriamycin-treated
transgenic mice (from 55.0 ± 11.7 to 22.6 ± 3.4 µg albumin/mg creatinine at the end of week 6; n = 8; P < 0.05; Figure 2) and significantly reduced foot process effacement (10 ± 0.5%; P < 0.05 compared with Adriamycin alone). SC58236 treatment also prevented decreases in nephrin mRNA (80 ± 15% of wild-type; n = 4; NS; Figure 6B) and protein (Figure 6A).

Response of Balb/C Mice to Adriamycin Administration

Unlike wild-type B6/D2-F1 mice, Adriamycin induced albuminuria in wild-type Balb/C mice (2 wk after Adriamycin 44.7 ± 7.6 versus control 22.1 ± 2.7 µg albumin/mg creatinine; n = 6; P < 0.05; Figure 7A). There was a corresponding increase in foot process effacement (80 ± 3.6 versus 10 ± 0.3% in control; n = 3; P < 0.05) with increased mesangial matrix (Figure 7C). Adriamycin administration also increased podocyte COX-2 (Figure 7B) and downregulated nephrin in wild-type Balb/C mice (Figure 7B). Similar to the B6/D2-F1 transgenic mice, long-term treatment with the COX-2 inhibitor SC58236 to wild-type Adriamycin-treated mice significantly decreased the amount of foot process effacement in Balb/C mice (30 ± 1.2%; n = 3; P < 0.05 versus no treatment) and also blunted the increase in mesangial matrix.

Discussion

In our studies, we generated a mouse model that constitutively expresses COX-2 in podocytes to examine whether

Figure 5. Expression of podocyte-specific proteins in response to Adriamycin: wild-type (A), wild-type with Adriamycin (B), transgenic (C), transgenic with Adriamycin (D), and transgenic with Adriamycin + SC58236 (E). No significant alteration of CD2AP, Wilms’ tumor 1 (WT-1), zonula occludens 1 (ZO-1), podocin, or podocalyxin expression was detectable by immunoblotting or by immunofluorescence.

Figure 6. Expression of nephrin in response to Adriamycin. (A) Immunohistochemistry for nephrin. Adriamycin decreased nephrin expression in the transgenic mice. Results also were confirmed with immunofluorescence. Order for A and B is as in Figures 4 and 5. (B) Glomerular nephrin mRNA expression measured by real-time PCR (n = 4; *P < 0.05 versus transgenic control or wild-type mice with Adriamycin; SC58236 partially restored nephrin mRNA (P < 0.05 versus transgenic mice + Adriamycin).
COX-2 expression predisposes podocytes to subsequent injury. Adriamycin causes well-described podocyte injury in rats (21), but its nephrotoxicity in mice is strain dependent. Balb/C mice are susceptible to podocyte injury by Adriamycin (22,23), whereas other strains that have been tested normally are resistant (24). We determined that preexisting expression of podocyte COX-2 in a mouse strain (B6/D2) that otherwise is resistant to Adriamycin injury sensitized the podocytes to injury, indicated by foot process effacement and albuminuria. These responses were associated with a further increase in endogenous podocyte COX-2 expression and a decrease in nephrin expression. Long-term treatment with a specific COX-2 inhibitor, SC58236, attenuated the albuminuria and foot process effacement and restored nephrin expression. Of interest, we found that in Balb/C mice, endogenous podocyte COX-2 expression also increased in association with Adriamycin-induced podocyte injury.

These studies were stimulated by two sets of observations: In models of progressive glomerular injury, COX-2 inhibitors decrease proteinuria and retard progressive glomerulosclerosis (4–7,11,25,26), and in such experimental models, as well as in human biopsy specimens, COX-2 expression is detectable in podocytes (8,9). Although the beneficial effects of COX-2 inhibitors in these models of progressive glomerular injury likely are the result of multiple mechanisms, including inhibition of hyperfiltration (10,27), as well as direct anti-inflammatory effects (28), our studies indicate a potentially pathogenic role for COX-2 metabolites to increase the susceptibility of podocytes to further injury and therefore suggest that podocytes also might be a target for COX-2 inhibitors in progressive glomerular injury. In this regard, Kennedy et al. (13) demonstrated that mechanical stretch induced expression of COX-2 and the EP4 subtype of prostaglandin E2 receptor in cultured podocytes, and in the stretched podocytes, prostaglandin E2 administration induced actin stress fiber dissociation.

These studies did not determine the mechanism by which increased COX-2 expression predisposed podocytes to further injury. Future studies will examine the effects of individual prostanoids that are produced by the podocytes. In addition, the catalytic activity of COX can lead to increased reactive oxygen radical production and may promote lipid peroxidation and DNA damage (29).

Podocytes are polarized epithelial cells, with their interdigitating foot processes forming the outer barrier to urine protein as a high-volume/high-discrimination filter, through which the blood is filtered hydrostatically (30). Podocyte dysfunction leads to proteinuria and progression of renal diseases. The progression or regression of glomerular dysfunction is associated with reorganization of the slit diaphragm and foot process structure (1), and an increasing number of molecules have been
identified to be associated with the slit diaphragm. In this study, we found that a decrease in nephrin expression was correlated with the increase in COX-2 in podocytes during Adriamycin-induced nephropathy, although expression of other proteins associated with the slit diaphragm (CD2AP, ZO-1, podocin, and podocalyxin), as well as the podocyte-specific protein WT-1, was not altered by Adriamycin-induced injury.

Adriamycin administration upregulated endogenous podocyte COX-2 in both nephrin-COX-2 transgenic mice and wild-type Balb/c mice, indicating that podocyte COX-2 increased in response to podocyte injury. In contrast, nephrin promoter-driven COX-2 did not increase, consistent with the decreased nephrin expression that was observed in response to Adriamycin. In recent preliminary studies, we also found that our transgenic mice are susceptible to puromycin injury, so it is likely that increased podocyte COX-2 expression may predispose podocytes to a variety of injury. Recent studies suggested that susceptibility to Adriamycin nephropathy in mice may link to a gene locus on chromosome 16 (31). Although this locus is distinct from the COX-2 gene, which is found on chromosome 1, when the specific predisposing gene products are identified, it would be interesting to investigate potential interactions with COX-2 expression.

Conclusion

We found that mice that overexpressed COX-2 in podocytes were predisposed to the injury by Adriamycin. Unlike COX-1, COX-2 is inducible in response to inflammation, tumorigenesis, and mechanical stretch, suggesting that podocyte COX-2 that is induced by glomerular inflammation or other factors renders these cells susceptible to further injury. Although any potential clinical efficacy of COX-2 inhibitors in the treatment of progressive renal injury may be limited by their cardiovascular adverse effects, identification of the prostanoids and receptor subtypes that are involved may allow for more targeted therapy without accompanying adverse effects.

Acknowledgments

This work was supported by the Vanderbilt George O’Brien Kidney and Urologic Diseases Center (National Institute of Diabetes and Digestive and Kidney Diseases grant DK-39261), National Institute of Diabetes and Digestive and Kidney Diseases grant DK-62794, funds from the Department of Veterans Affairs, and Vanderbilt Diabetes Research and Training Center (NIH P60 DK20593). This work was presented in part in abstract form at the annual meeting of the American Society of Nephrology (St. Louis, MO; October 2004).

Disclosures.

None.

References


