Role of Prostaglandin E Receptor EP₁ Subtype in the Development of Renal Injury in Genetically Hypertensive Rats

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Abstract—One of the major causes of end-stage renal diseases is hypertensive renal disease, in which enhanced renal prostaglandin (PG) E₂ production has been shown. PGE₂, a major arachidonic acid metabolite produced in the kidney, acts on 4 receptor subtypes, EP₁ through EP₄, but the pathophysiological importance of the PGE₂/EP subtypes in the development of hypertensive renal injury remains to be elucidated. In this study, we investigated whether an orally active EP₁-selective antagonist (EP₁A) prevents the progression of renal damage in stroke-prone spontaneously hypertensive rats (SHRSP), a model of human malignant hypertension. Ten-week-old SHRSP, with established hypertension but with minimal renal damage, were given EP₁A or vehicle for 5 weeks. After the treatment period, vehicle-treated SHRSP showed prominent proliferative lesions in arterioles, characterized by decreased smooth muscle actin expression in multilayered vascular smooth muscle cells. Upregulation of transforming growth factor-β expression and tubulointerstitial fibrosis were also observed in vehicle-treated SHRSP. Moreover, EP₁A treatment significantly inhibited both increase in urinary protein excretion and decrease in creatinine clearance but had little effect on systemic blood pressure. These findings indicate that the PGE₂/EP₁ signaling pathway plays a crucial role in the development of renal injury in SHRSP. This study opens a novel therapeutic potential of selective blockade of EP₁ for the treatment of hypertensive renal disease. (Hypertension. 2003;42:1183-1190.)

Key Words: rats, stroke-prone SHR ▪ prostaglandins ▪ arachidonic acids ▪ transforming growth factors ▪ kidney ▪ proteinuria

Hypertensive renal disease is one of major causes of end-stage renal diseases, and the number of patients with this disease is still increasing despite of the development of various treatments to normalize systemic blood pressure.¹ Five-year survival rate of patients undergoing hemodialysis because of hypertensive renal disease is reported to be much lower than the rates of hemodialysis patients with other causes.² Therefore, the management of hypertensive renal disease is very important for clinical outcome. Stroke-prone spontaneously hypertensive rats (SHRSP), a substrain of spontaneously hypertensive rats (SHR), represent a useful model of human malignant hypertension and show more serious hypertensive renal injury as compared with SHR.³ Human malignant hypertension and SHRSP share extremely similar pathophysiological features in the kidney that are characterized by marked medial and intimal thickening, fibrosis and fibrinoid necrosis of arterioles and small arteries,⁴ followed by ischemic glomerular changes and tubulointerstitial fibrosis. Renal fibrosis is the final common pathway to end-stage renal diseases regardless of the initial insult. In the fibrogenic process of SHRSP and of other renal injuries, transforming growth factor-β (TGF-β) has been shown to play a pivotal role.⁵⁻⁶

Prostaglandin (PG) E₂ is a predominant arachidonic acid metabolite in the kidney and plays an important role in renal physiology, including the regulation of vascular smooth muscle tonus, glomerular filtration, renin release, and tubular salt and water transport.⁷ PGE₂ exerts its biological effects through 4 receptor subtypes, EP₁ through EP₄.⁸⁻¹⁰ These receptors are encoded by different genes and differ in signal transduction mechanism.²⁻¹⁰ When activated, EP₁ increases cytosolic Ca²⁺ concentration, whereas EP₂ and EP₃ stimulate but EP₁ inhibits adenylyl cyclase activity. To date, little is known about the pathophysiological role of each EP subtype.
in renal disorders, although overall actions of PGE₂ on the whole EP subtypes have been intensively characterized. PGE₂ also participates in the control of microcirculation of the kidney.¹¹-¹⁴ In rats, EP₁, EP₃, and EP₄ subtypes are present in afferent arteriole and glomerulus.¹⁴,¹⁵ EP₁ exerts vasodilation in the afferent arteriole, whereas the vasoconstrictive effect of PGE₂ is presumed to be mediated by EP₁ or EP₃.¹⁴,¹⁶ EP₁- and EP₃-mediated signals oppose against EP₁- and EP₃-mediated signals not only as to smooth muscle tonus but also in other aspects. EP₁ stimulation causes cell proliferation in mesangial cells and hepatocytes through phosphorylation of extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAP kinase).⁹,¹⁰,¹⁷ EP₄ counteracts EP₁-mediated cell proliferation and ERK/MAP kinase phosphorylation.⁹,¹⁰

In SHR, the vasodilatory effect of PGE₂ is impaired in the afferent arteriole.⁷ We and others have also reported defective adenyl cyclase responses to PGE₂ in homogenates of the whole kidney from SHR and in cultured mesangial cells from SHRSP.⁹,¹⁶,¹⁹ Furthermore, DNA synthesis and ERK/MAP kinase phosphorylation by PGE₂ are larger in cultured mesangial cells from SHRSP as compared with normotensive control Wistar-Kyoto rats (WKY), suggesting that EP₁ is the predominant PGE₂ receptor subtype and function of EP₁ is diminished in SHRSP.⁹ Not only clinical hypertensive renal disease but also SHRSP and SHR show enhanced renal PGE₂ production.²⁰-²² We therefore hypothesized that the relatively augmented EP₁ function contributes to the development of hypertensive renal injury in vivo. In this study, we showed that an orally active EP₁ selective antagonist (EP₁A) prevents the progression of renal damage in SHRSP both histologically and functionally, suggesting that selective blockade of EP₁ may be a novel therapeutic strategy to treat hypertensive renal disease.

**Methods**

**Animals and Drug Treatment**

All animal experiments were conducted in accordance with our institutional guidelines for animal research. SHRSP and WKY were obtained from Shionogi Research Laboratories. Rats were fed standard chow (CE-2 containing 0.5% NaCl; Japan Clea) and given tap water. We maintained these animals under alternating 12-hour cycles of light and dark. Ten-week-old male SHRSP and WKY were randomized to 2 groups. Groups of SHRSP (n=15) and WKY (n=5) were given a selective EP₁ antagonist, ONO-8713 (ONO Pharmaceutical), in regular chow at 0.1% (wt/wt) as previously described.²³ Other groups of SHRSP (n=15) and WKY (n=5) were given vehicle. ONO-8713 exhibits a Kᵢ value of 0.3 nmol for both mouse and human forms of EP₁ and >1000 nmol for all other types of prostanoid receptors.²³ This compound inhibits PGE₂-induced elevation of intracellular calcium with IC₅₀ values of 0.46 and 0.14 μmol/L in mouse and human EP₁-expressing cells, respectively, but shows no agonistic or antagonistic actions on other types of prostanoid receptors. Rats were euthanized under ether anesthesia before and after the 5-week treatment.

**Blood Pressure and Blood and Urinary Parameter Measurements**

Blood pressure was measured by a programmable sphygmomanometer (BP-98A, Softron), by means of the tail-cuff method.²⁶,²⁷ Measurement of blood and urinary parameters was carried out as previously described.²⁴,²⁶,²⁷

**Cell Culture**

Cultured mesangial cells were established from glomeruli of SHRSP and WKY and used at passages 8 to 9 in RPMI 1640 medium (Nissui) with 10% fetal calf serum (Sanko Junyaku), as previously described.⁹

**In Situ Hybridization**

The localization of EP₁ expression in the kidney of SHRSP and WKY was analyzed by in situ hybridization as previously described.²⁴ Briefly, a radiolabeled cRNA probe for rat EP₁ was synthesized with [³⁵S]CTP. Control hybridization experiments with the use of the same riboprobe with excess of unlabeled cRNA gave no significant signals.²⁴

**Northern Blot Analysis**

Northern blot analysis was performed as previously described.⁹,²⁷ In brief, 40 μg of total RNA from the kidney cortex and 4 μg of poly(A)⁺ RNA from cultured mesangial cells were electrophoresed on a 1.4% agarose gel and transferred to a nylon membrane (Biodyne, Pall BioSupport). The antisense RNA probe for rat EP₁ and the cDNA probes for rat TGF-β1, fibronectin, and cyclooxygenase-2 were used.⁹,²⁴ As an internal control, the filter was rehybridized with a human GAPDH cDNA probe (Clontech).

**Histology and Morphometric Analysis**

Histological analysis was performed as previously described.²⁶,²⁷ For assessment of arteriolar damage, the number of afferent arterioles exhibiting proliferative lesion was enumerated with the use of periodic acid–Schiff (PAS) staining and expressed as a percentage of the total number of glomeruli examined. For assessment of renal fibrosis, Masson’s trichrome staining was carried out, and the proportion of blue-stained fibrotic area in the cortex of each section was graded semiquantitatively (0: ≤5%, 1: 5% to 25%, 2: 25% to 50%, 3: 50% to 75%, 4: ≥75%). These examinations were performed by two investigators without knowledge of the origin of the slides, and the mean values were calculated.

**Immunohistochemistry**

Immunostaining was carried out with the streptavidin/biotin immunoperoxidase complex method, as previously described.²⁶,²⁷ Primary antibodies used in the present study are as follows: mouse monoclonal anti–α-smooth muscle actin (αSMA, DAKO), mouse monoclonal antiproliferative cell nuclear antigen (PCNA, DAKO), rabbit polyclonal anti–TGF-β1 (Santa Cruz), and rabbit polyclonal antifibronectin (DAKO) antibodies. Sections were developed with 3,3’-diaminobenzidine tetrahydrochloride or 3-amin-9-ethyl carbazole and counterstained with hematoxylin.

**Data Statistical Analysis**

Data are expressed as mean±SEM. Statistical analysis was performed by means of ANOVA followed by the Scheffé test. A probability value <0.05 was considered statistically significant.

**Results**

**Characteristics of Experimental Animals**

To investigate the pathophysiological role of the PGE₂/EP₁ subtype signals in SHRSP, 10-week-old SHRSP and normotensive control WKY were treated for 5 weeks with EP₁A or vehicle. EP₁A was tolerated well, and no significant differences were observed in body weight, kidney weight, and serum alanine aminotransferase (ALT)/glutamic-pyruvic transaminase (GPT) level between EP₁A-treated and vehicle-treated groups at 15 weeks of age (Table). Urine volume of SHRSP was significantly larger than that of WKY. The EP₁A-treated groups tended to exhibit a decreased urine volume as compared with the vehicle-treated groups both in...
SHRSP and WKY, although the difference did not achieve statistical significance. By contrast, urinary sodium excretion was markedly reduced in SHRSP as compared with WKY, and EP1A treatment significantly increased urinary sodium excretion both in SHRSP and WKY. Urinary PGE2 excretion of SHRSP was 33% higher than that of WKY, but the difference was not statistically significant.

### Localization of EP1 and Regulation of Cyclooxygenase-2 in SHRSP

We next examined the localization of EP1 expression in the glomeruli of WKY and SHRSP by in situ hybridization. Strong hybridization signals for EP1 mRNA were observed mainly in the mesangial area, and there was no apparent difference between WKY (Figure 1A) and SHRSP (Figure 1B). Mesangial cyclooxygenase-2 expression showed a remarkable increase in SHRSP as compared with WKY (Figure 1C, 426±18%, P<0.01), suggesting the local overproduction of prostaglandins in the glomeruli of SHRSP.

### Effects of EP1A on Renal Histological Changes

Renal tissues of 10-week-old WKY (Figure 2A) and SHRSP (Figure 2B) were histologically almost indistinguishable. At 15 weeks of age, vehicle-treated SHRSP exhibited marked fibrocellular proliferative lesions in arterioles and tubulointerstitial damage (Figure 2C). EP1A treatment attenuated these histological changes (Figure 2D). Quantitative analysis revealed that EP1A treatment decreased the number of the proliferative lesions in arterioles in SHRSP by 41±13% (Figure 2E, P<0.05). There was no apparent difference in renal histology between vehicle-treated and EP1A-treated WKY at 15 weeks (not shown).

The affected arterioles, which are typical changes in malignant nephrosclerosis, were further examined by immunohistochemical study for αSMA and PCNA. Ten-week-old SHRSP (Figure 3A) and WKY (not shown) showed dense immunostaining of αSMA in arteriole walls, presumably in smooth muscle cells. In 15-week-old, vehicle-treated SHRSP, immunostaining of αSMA in the hyperplastic arteriole walls was heterogeneous and less intense (Figure 3B), suggesting that phenotypic change of vascular smooth muscle cells occurred. Some interstitial cells were also positive for αSMA. In 15-week-old EP1A-treated SHRSP, the immunostaining pattern of αSMA itself was not altered apparently as compared with that in vehicle-treated SHRSP (Figure 3C), but the area positive for αSMA immunostaining in EP1A-treated SHRSP tended to be smaller as compared with that in the vehicle-treated group. There was no apparent PCNA immunostaining in 10-week-old SHRSP (Figure 3D) and WKY (not shown), whereas PCNA-positive proliferating cells were observed in the affected arterioles, interstitial cells, and tubular epithelial cells both in 15-week-old vehicle-treated WKY and SHRSP.

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**Table 1. Body Weight, Kidney Weight, ALT/GPT, and Urinary Parameters in SHRSP and WKY After the 5-Week Treatment**

<table>
<thead>
<tr>
<th>Variables</th>
<th>WKY</th>
<th>SHRSP</th>
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<tbody>
<tr>
<td>Body weight, g</td>
<td>286±7</td>
<td>268±8</td>
</tr>
<tr>
<td>Kidney weight, g</td>
<td>0.98±0.03</td>
<td>1.00±0.05</td>
</tr>
<tr>
<td>Kidney weight/body weight, g/100 g</td>
<td>0.34±0.01</td>
<td>0.39±0.02</td>
</tr>
<tr>
<td>Serum ALT/GPT, IU/L</td>
<td>16.1±1.2</td>
<td>14.9±1.0</td>
</tr>
<tr>
<td>Urine volume, mL/d</td>
<td>13.9±2.3</td>
<td>9.5±1.2</td>
</tr>
<tr>
<td>Urinary sodium excretion, mEq/d</td>
<td>1.28±0.19</td>
<td>1.84±0.16*</td>
</tr>
<tr>
<td>Urinary PGE2 excretion, ng/d</td>
<td>2.08±0.17</td>
<td>2.57±0.22</td>
</tr>
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**Note:** ALT/GPT indicates serum alanine aminotransferase/glutamic-pyruvic transaminase. Ten-week-old male SHRSP and WKY were treated with ONO-8713, a selective EP1 antagonist (EP1A), or vehicle for 5 weeks. Values are expressed as the mean±SE for vehicle-treated WKY (n=5), EP1A-treated WKY (n=5), vehicle-treated SHRSP (n=10), and EP1A-treated SHRSP (n=10).

*P<0.05 vs vehicle-treated WKY; †P<0.01 vs vehicle-treated SHRSP.

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**Figure 1.** Gene expression of EP1 and cyclooxygenase-2 in glomeruli and cultured mesangial cells. In situ hybridization for EP1 mRNA expression (arrows) in glomeruli of WKY rats (A) and SHRSP (B). C, Northern blots of cyclooxygenase-2 in cultured mesangial cells from WKY and SHRSP.
and EP1A-treated SHRSP (Figures 3E and 3F). Quantitative analysis revealed that PCNA-positive cells in arterioles of 15-week-old vehicle-treated SHRSP were 3.8 times more abundant than those in EP1A-treated SHRSP (Figure 3G, P<0.05). These findings indicate that EP1A treatment significantly decreased both the incidence and the proliferative activity of arteriole lesions.

**Effects of EP1A on Renal Fibrosis**

To assess the extent of renal fibrosis, we stained the kidney sections by using Masson's trichrome method. Almost no fibrotic area was observed in 10-week-old SHRSP (Figure 4A) and WKY (not shown). Vehicle-treated SHRSP exhibited marked interstitial and perivascular fibrosis at 15 weeks of age (Figure 4B). EP1A treatment obviously attenuated these fibrotic changes (Figure 4C). Semiquantitative analysis on renal fibrosis revealed that EP1A treatment decreased scores for fibrotic area in SHRSP (Figure 4D) by 49±6% (P<0.01). We also examined the alteration in TGF-β1 expression by immunohistochemistry. Vehicle-treated SHRSP exhibited marked interstitial, periglomerular, and perivascular TGF-β1 staining at 15 weeks of age (Figure 4E). In contrast, EP1A treatment markedly inhibited TGF-β1 staining (Figure 4F). Fibronectin, a component of fibrosis that is inducible by TGF-β1, was also increased in the area similar to TGF-β1 in vehicle-treated SHRSP (Figure 4G), and the area of fibronectin deposition was significantly decreased in EP1A-treated SHRSP (Figure 4H).

To further assess the changes of TGF-β1 expression more quantitatively, we examined the gene expression of TGF-β1 in the cortex of the kidney by Northern blotting (Figure 5). TGF-β1 expression was upregulated by 114±9% in 15-week-old, vehicle-treated SHRSP as compared with that in control WKY (P<0.01). EP1A treatment abolished the up-regulation of TGF-β1 in SHRSP (P<0.01). These findings suggest that EP1A ameliorated renal fibrosis, at least partly, by the inhibition of TGF-β1 induction.

**Effects of EP1A on Urinary Protein Excretion and Renal Function**

To evaluate the functional alterations in SHRSP, we examined urinary protein excretion and creatinine clearance (Figure 6). Ten-week-old SHRSP, which showed minimal histo-
logical changes, already exhibited significant increase in urinary protein excretion as compared with WKY (Figure 6A, $P<0.05$). In vehicle-treated SHRSP, urinary protein excretion was increased by 2.2-fold after 5 weeks. In EP1A-treated SHRSP, on the other hand, proteinuria was significantly suppressed ($P<0.05$). At 15 weeks, creatinine clearance was significantly better in EP1A-treated SHRSP as compared with vehicle-treated SHRSP, although the difference between vehicle-treated SHRSP and WKY did not achieve statistical significance (Figure 6B). In WKY, no significant changes in these parameters were observed by EP1A treatment (Figures 6A and 6B). These findings indicate that EP1A treatment ameliorated not only the renal histological changes but also the functional alterations in SHRSP.

**Effects of EP1A on Blood Pressure**

Analyses so far have indicated that EP1A treatment prevents the progression of renal injury in SHRSP. To explore whether chronic EP1A treatment affects blood pressure or not, we examined systemic blood pressure by the tail-cuff method (Figure 6C). Severe hypertension was already established in 10-week-old SHRSP (systolic blood pressure, 190±4 mm Hg) as compared with 10-week-old WKY (130±4 mm Hg), and systolic blood pressure in vehicle-treated SHRSP was gradually increased up to 213±3 mm Hg at 15 weeks of age. A mild blood pressure reduction was observed after 2-week-treatment of EP1A in SHRSP, but after 5-week-treatment there was no significant difference in blood pressure between the groups in SHRSP. EP1A treatment showed no blood pressure change in WKY. These findings suggest but do not prove that the blood pressure–lowering effect of EP1A is not the main mechanism of kidney protection by EP1A.

**Discussion**

In the present study, we examined whether selective blockade of PGE2 receptor EP1 subtype inhibits the development of...
renal injury in SHRSP. Vehicle-treated SHRSP showed not only prominent histological changes including fibrocellular proliferative lesions in arterioles and tubulointerstitial damages but also functional alterations including increased proteinuria and decreased creatinine clearance as previously described, whereas these changes were all significantly ameliorated by EP1A treatment. These findings provide, for the first time, the in vivo evidence that EP1 plays an important role in the progression of renal damage in SHRSP.

An onion peel–like proliferative lesion in the afferent arteriole is the characteristic feature in renal pathology of human malignant hypertension and SHRSP. The present study indicates that EP1A treatment potently suppressed the proliferation of afferent arteriole smooth muscle cells. Indeed, the EP1-mediated signal stimulates cell proliferation, at least in mesangial cells and hepatocytes. However, whether EP1 on afferent arteriole smooth muscle cells really conveys proliferative signals remains to be determined, since vascular smooth muscle cells from arterioles no longer express EP1 after cell culture, making the in vitro analysis difficult. Furthermore, we could not determine whether EP1 mRNA expression in the afferent arterioles differs between WKY and SHRSP, since EP1 gene expression level in afferent arterioles was not high enough for detection by in situ hybridization. Using microdissection and RT-PCR, Purdy et al. reported that EP1 expression can be detected in freshly isolated rat afferent arterioles. The present study also showed that perivascular and interstitial fibrosis together with upregulation of TGFβ was attenuated by EP1A treatment. These findings are in agreement with our recent observation showing that EP1-mediated signal induces TGFβ gene expression in cultured mesangial cells. Taken together, the present study elucidates that EP1A has protective effects for renal lesions in SHRSP at least by two mechanisms: suppression of smooth muscle proliferation in afferent arterioles and inhibition of TGFβ upregulation.

Recent reports revealed that angiotensin II induces cyclooxygenase-2 expression and PGE2 production in vascular smooth muscle cells and that selective cyclooxygenase-2 inhibitors attenuate angiotensin II–induced DNA synthesis. There is no doubt that the renin-angiotensin system is activated and angiotensin II plays a critical role in the progression of renal injury in SHRSP. The present study showed marked upregulation of cyclooxygenase-2 expression in cultured mesangial cells from SHRSP. We previously reported that EP1 exerts cell proliferation through ERK/MAP kinase phosphorylation and that the autocrine PGE2/EP1 pathway contributes to growth factor–mediated cell proliferation in cultured mesangial cells. Therefore, it is possible that the PGE2/EP1 signaling pathway is involved in angiotensin II–induced vascular smooth muscle cell proliferation in SHRSP.

Renal microcirculation plays a critical role in the progression of renal dysfunction and proteinuria. EP1A treatment significantly ameliorated proteinuria and worsening of creatinine clearance in SHRSP. Recently, EP1 and EP4 have been reported to be expressed in mesangial cells and podocytes in the glomerulus. As these cells contribute to the regulation of renal microcirculation, functional protection in EP1A-treated SHRSP may be partly due to the effects of EP1A on mesangial cells and podocytes.

Concerning the beneficial effects of EP1A on hypertensive renal injury, the influence of EP1A on the regulation of systemic blood pressure and urinary sodium excretion must be considered. We observed only minimal and transient effects on systemic blood pressure in SHRSP after 2-week treatment. After 5-week treatment, blood pressure of EP1A-treated SHRSP exhibited no significant difference from that of vehicle-treated SHRSP. The present study is the first report as to the long-term effect of EP1A on systemic blood pressure. EP1A treatment also showed no significant effects on blood pressure of WKY. These findings are not consistent with recent reports that EP1-deficient mice have lower blood pressure.
pressure compared with wild-type mice and that intravenous administration of an EP1/EP1 agonist increases blood pressure in mice. The reason for such a difference is currently unclear, but it might be due to species difference. It is noteworthy that EP1 also exists in the arteriolar smooth muscle in humans. In the present study, we also showed that SHRSP had much less urinary sodium excretion than WKY and that EP1A treatment significantly increased sodium excretion in SHRSP and WKY, suggesting that the EP1-mediated signal has an antinatriuretic effect. Antinatriuretic activity might be another example of involvement of PGE2/EP1 signaling in events downstream of angiotensin II. These findings are contradictory to acute natriuretic effect mediated by EP1 in the cortical collecting duct in rabbits. Tissue-specific knockout experiments of EP1 will elucidate distinct roles of the receptor in vessels, glomeruli, and collecting ducts. The present findings suggest that the effects of EP1A on systemic blood pressure do not play an important role in the protective effects of EP1A on renal injury in SHRSP.

In summary, we demonstrate that the long-term treatment of EP1A can ameliorate renal injury histologically and functionally in SHRSP even after the onset of hypertension and proteinuria. The present study suggests that the PGE2/EP1 pathway contributes to the development of renal injury in genetically hypertensive rats. The results also indicate that the renoprotective effects of EP1A in SHRSP are not due to systemic blood pressure reduction and might be applicable in other types of hypertensive renal injuries.

**Perspectives**

We previously reported that mesangial cell proliferation is exaggerated under conditions of high glucose and that this phenomenon can be explained in part by the attenuation of EP3-mediated cAMP production. Such imbalance between EP3- and EP4-mediated signaling is also observed in cultured mesangial cells from SHRSP, where augmentation of EP3-mediated DNA synthesis and ERK/MAP kinase phosphorylation as well as inhibition of EP4-mediated cAMP generation are observed. As in the case of hypertensive renal injury, local PGE2 production in the kidney is increased in diabetic nephropathy. Furthermore, treatment by EP3A ameliorates not only renal injury in genetically hypertensive rats as shown here but also diabetic nephropathy induced by streptozotocin. Therefore, it may be conceivable that relative overactivation of EP3 and functional impairment of EP4 are common mediators of renal injuries caused both by hypertension and diabetes. Further studies are required to prove this hypothesis.

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**References**


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