Podocyte Injury Underlies the Glomerulopathy of Dahl Salt-Hypertensive Rats and Is Reversed by Aldosterone Blocker

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Abstract—Recent clinical studies implicate proteinuria as a key prognostic factor for renal and cardiovascular complications in hypertensives. The pathogenesis of proteinuria in hypertension is, however, poorly elucidated. Podocytes constitute the final filtration barrier in the glomerulus, and their dysfunction may play a pivotal role in proteinuria. In the present study, we examined the involvement of podocyte injury in Dahl salt-hypertensive rats, an animal model prone to hypertensive glomerulosclerosis, and explored the effects of inhibition of aldosterone. Four-week-old Dahl salt-resistant and salt-sensitive rats were fed a 0.3% or 8.0% NaCl diet. Some salt-loaded Dahl salt-sensitive rats were treated with a selective aldosterone blocker eplerenone (1.25 mg/g diet) or hydralazine (0.5 mmol/L). After 6 weeks, salt-loaded Dahl salt-sensitive rats developed severe hypertension, proteinuria, and glomerulosclerosis. Immunostaining for nephrin, a constituent of slit diaphragm, was attenuated, whereas expressions of damaged podocyte markers desmin and B7-1 were upregulated in the glomeruli of salt-loaded Dahl salt-sensitive rats. Electron microscopic analysis revealed podocyte foot process effacement. Podocytes were already impaired at as early as 2 weeks of salt loading in Dahl salt-sensitive rats, when proteinuria was modestly increased. Both eplerenone and hydralazine partially reduced systemic blood pressure as measured by indirect and direct methods in salt-loaded Dahl salt-sensitive rats, but only eplerenone dramatically improved podocyte damage and retarded the progression of proteinuria and glomerulosclerosis. Our findings suggest that podocyte injury underlies the glomerulopathy of Dahl salt-hypertensive rats and that inhibition of aldosterone by eplerenone is protective against podocyte damage, proteinuria, and glomerulosclerosis in this hypertensive model. (Hypertension. 2006;47:1084-1093.)

Key Words: kidney ■ proteinuria ■ glomerulosclerosis ■ aldosterone ■ mineralocorticoids

Proteinuria is regarded as an important prognostic factor in hypertensives.1 Proteinuria is not only a hallmark of renal complication in hypertension, but it is also a major deteriorating factor for the progression to end-stage renal disease, determining renal survival.2 Recent clinical studies further revealed that proteinuria is an independent risk factor for cardiovascular events, such as myocardial infarction, and a predictor of life prognosis.3,4 However, the pathogenesis of proteinuria in hypertension has not been clearly delineated.

The glomerular filtration barrier to plasma macromolecules is composed of 3 layers: the fenestrated capillary endothelium, the glomerular basement membrane, and the visceral epithelial cells (podocytes). Podocytes line the outer aspect of the basement membrane and serve as the final defense against urinary protein loss in the normal glomerulus. Accumulating evidence suggests that podocytes and their slit diaphragm, a unique apparatus formed at the junction of the interdigitating foot processes of podocytes, are the major size-selective permeability barrier and that podocyte injury is intimately related to proteinuria.5–7 Podocytes are actually reported to be injured in many types of proteinuric renal diseases, including nephrotic syndrome, diabetic nephropathy, and lupus nephritis.8,9 It is also noteworthy that podocytes are terminally differentiated cells and do not typically proliferate in response to injury.5 Once damaged, podocytopenia follows, ultimately culminating in glomerulosclerosis.

Hypertensive glomerular lesions were conventionally characterized by mesangial proliferation, matrix accumulation, and glomerulosclerosis,10 and attention had long been focused on mesangial cells. Several reports also suggested the roles of endothelial dysfunction and impaired glomerular basement membrane in hypertension-associated albuminuria.11,12 On the other hand, few studies explored the involvement of podocyte damage in experimental hypertensive glomerulopathy.13 This might be attributed in part to the limitation until recently of sensitive markers for podocyte injury. Podocyte damage can now be assessed by analyzing the expressions of normal components of slit diaphragm, such as nephrin.14

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Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000222003.28517.99
injured podocyte markers desmin,\textsuperscript{15} and B7-1 (also termed CD80),\textsuperscript{16} in addition to conventional morphological study by electron microscopy.

Growing evidence suggests that aldosterone contributes to the progression of renal disease.\textsuperscript{17,18} Conversely, aldosterone receptor blocker was reported to decrease proteinuria and renal injury in hypertensive patients,\textsuperscript{19} as well as hypertensive animal models.\textsuperscript{20,21} In the present study, we examined the participation of podocyte injury in the glomerulopathy of Dahl salt-hypertensive rats using the above-mentioned molecular markers and explored whether inhibition of aldosterone can improve podocyte damage.

## Methods

### Animals

Four-week-old male Dahl salt-resistant rats ([DNRs] = 36) and salt-sensitive rats ([DSs; n = 58]) were obtained from Japan SLC. All of the animal procedures were in accordance with the guideline for the care and use of laboratory animals approved by University of Tokyo Graduate School of Medicine. Rats were housed in a room maintained at constant temperature, humidity, and light cycle (12-hour light/dark) and were fed an 8% NaCl diet (DR high [DRH], n = 26; DS high [DSH], n = 48) or a 0.3% NaCl diet (DR low [DRL], n = 10; DS low [DSL], n = 10) for 6 weeks. Some DSHs were treated with eplerenone (1.25 mg/g rodent chow; n = 11) or hydralazine (0.5 mmol/L in tap water; n = 11).\textsuperscript{22} Antihypertensive treatment was started 5 days before salt loading and continued throughout the experimental period.

Systolic blood pressure (BP) was measured by the tail-cuff method.\textsuperscript{23} Direct BP measurement was performed as described,\textsuperscript{24} except that a catheter was inserted in the femoral artery, not the carotid artery under ether anesthesia. Mean BP was monitored at night over 6 hours in a conscious and unrestrained condition, and 5 measurements were averaged. Rats were placed in metabolic cages for 24-hour urine collection. The rats were anesthetized with ether, and kidneys were harvested. Glomerular fraction was isolated by the care and use of laboratory animals approved by University of California, CA) after antigen retrieval. For B7-1, sections were processed with biotinyl tyramide.

Transmission Electron Microscopy

Electron microscopic analysis was performed as described.\textsuperscript{25} Foot process effacement was graded into 0, 1+, 2+, 3+, and 4+ by a blinded observer (8 to 15 glomeruli per rat).

Western Blotting

Western blotting of nephrin was performed as described.\textsuperscript{25} The membrane was reprobed with anti-actin (1:500; Sigma, St Louis, MO) as a loading control.

### Histological Analysis

Renal sections embedded in paraffin (3-μm thick) were stained with periodic acid–Schiff and examined under light microscopy. The glomerulosclerosis index was semiquantitatively calculated as described previously\textsuperscript{26} by examining 100 glomeruli per section. Vas- cular injury score was semiquantitated as 0, 1+, 2+, and 3+ according to the criteria by Ishimitsu et al.\textsuperscript{27} Tubulointerstitial injury score was graded into 0, 0%; 1+, 1% to 10%; 2+, 11% to 25%; 3+, 26% to 50%; 4+, 51% to 75%; and 5+, 76% to 100%, according to the scoring system reported previously with some modification.\textsuperscript{28} All of the morphometric measurements were performed by 2 examiners without knowledge of the treatment protocol (n = 4 per group).

### Immunohistochemistry

Immunohistochemistry of desmin and nephrin were carried out as described.\textsuperscript{25,27} Immunostaining for desmin, nephrin, and CD80 was performed as described.\textsuperscript{28} Glomerulonephritis was defined by the participation of podocyte injury, in the kidneys of Dahl rats at 6 weeks (Figure 1A through 1G).

Temporal Profile of BP, Proteinuria, and Renal Impairment in Dahl Rats

As shown in Figure 1A, DRLs, DRHs, and DSLs remained normotensive during 6 weeks of low or high salt feeding (n = 5 per group). On the other hand, systolic BP gradually rose in response to high salt loading in DSHs (n = 5). In parallel with the changes in BP, urinary protein excretion was not altered in normotensive DRL, DRH, and DSL groups but markedly increased in DSHs (Figure 1B; n = 5 per group). DSH already developed mild hypertension and proteinuria at 2 weeks of salt loading.

Serum creatinine level was elevated only in DSHs at 6 weeks (Figure 1C). Figure 1D shows typical light micrographs of renal and glomerular sections stained with periodic acid–Schiff. Glomerular morphology was grossly normal in DRHs at 2 and 6 weeks and in DSHs at 2 weeks. On the other hand, DSHs at 6 weeks exhibited severe focal-segmental or glomerulosclerosis, together with arteriosclerosis, inflammatory cell infiltration, interstitial fibrosis, and tubular cast formation. Glomerulosclerosis index and vascular and tubulointerstitial injury scores were significantly increased in DSHs at 6 weeks (Figure 1E through 1G).

Podocytes Are Injured in DSHs

To evaluate the presence of podocyte injury in this model, we first performed immunohistochemistry of desmin, a conventional podocyte injury marker, in the kidneys of Dahl rats at 6 weeks (Figure 2A). Signals were not detected in the glomeruli of DRLs, DRHs, and DSLs. By contrast, multiple glomeruli were positive for desmin along the capillary tufts in DSH.

Real-Time PCR

RNA extraction, reverse transcription, and real-time PCR were performed as described.\textsuperscript{28} Assay-on-demand primers and probe sets (Applied Biosystems) were used.

Northern Blotting

The cDNA probe for the rat nephrin (AF161715; bases 2558 to 2961) was prepared by PCR using the primers 5′-AGCTGCGTTGAATGTAA-CCCGAGC-3′ (sense) and 5′-TGGGGGCGAAATCGAGCAAAG-3′ (antisense). Preparation of poly (A)\textsuperscript{+} RNA and Northern blotting were performed as described.\textsuperscript{29}
We next carried out immunostaining for B7-1, a recently identified podocyte injury marker (Figure 2C). Whereas very low signals were observed in the renal cortex including the glomeruli in DRLs, DRHs, and DSLs, distinct staining was detected in some glomeruli in DSH. B7-1 expression was also augmented in some tubules (data not shown). The specificity of the signals was confirmed by the negligible staining when performed without primary antibody (data not shown).

Immunofluorescence study for nephrin, a constituent of podocyte slit diaphragm, revealed that glomeruli from normotensive DRLs, DRHs, and DSLs showed a normal intense and linear staining pattern along the capillary tufts, suggesting the absence of podocyte damage in these groups (Figure 2E). In contrast, multiple glomeruli displayed drastic attenuation of nephrin staining with granular expression pattern in DSHs.

Semiquantitative analyses indicated that desmin staining score was significantly enhanced, the percentage of B7-1-positive glomeruli was significantly increased, and nephrin staining score was significantly reduced in DSHs (Figure 2B, 2D, and 2F). The change of nephrin expression was also analyzed at the mRNA level. Northern blot analysis revealed that the nephrin transcript level was similar in DRLs, DRH, and DSLs but apparently decreased in DSHs (Figure 2G). Quantitative analysis using real-time PCR indicated that nephrin mRNA expression was significantly reduced in DSHs at 6 weeks (~47% versus DRH; P<0.01; Figure 2H).

Podocyte Injury Commences at Early Stage in DSH

Time course analysis of podocyte injury revealed that desmin, an early injury marker, was already expressed in some
glomeruli of DSHs at 2 weeks of salt loading (Figure 3A and 3B). We further assessed podocyte damage by transmission electron microscopy (Figure 3C). Podocyte foot processes, which line the outer surface of glomerular basement membrane, were intact in DRH at 2 weeks. On the other hand, effacement and fusion of podocyte foot processes were already observed in DSHs at as early as 2 weeks.

Effects of Eplerenone and Hydralazine on BP, Proteinuria, and Renal Injury in DSHs

Recently, much attention has been focused on the proteinuric action of aldosterone. Therefore, we next explored whether inhibition of aldosterone by eplerenone can ameliorate podocyte injury and slow the progression of glomerulopathy in DSHs. Tail-cuff measurement of BP revealed that eplerenone significantly reduced systolic BP of DSHs (Figure 4A; \( P < 0.01; n = 5 \)). Although its hypotensive action was partial, eplerenone completely prevented the development of proteinuria in DSHs (165±15 mg per day; open triangles in Figure 4B) and glomerulosclerosis (Figure 4D and 4E), although serum creatinine elevation, which reflects tubulointerstitial injury, was suppressed (Figure 4C).

We also treated DSHs with another class of antihypertensive drug, hydralazine. Hydralazine significantly reduced systemic BP of DSHs (Figure 4A; \( P < 0.01; n = 5 \)). In contrast to eplerenone, hydralazine did not improve the development of proteinuria in DSHs (165±15 mg per day; open triangles in Figure 4B) and glomerulosclerosis (Figure 4D and 4E), although serum creatinine elevation, which reflects tubulointerstitial injury, was suppressed (Figure 4C).

To evaluate the BP-lowering effects of eplerenone and hydralazine more accurately,\(^3^1\) we performed direct BP measurement by inserting a catheter in the femoral artery (Figure 5). Mean arterial pressure monitored at night in a conscious and unrestrained condition was markedly higher in DSHs (n=3) compared with DRHs (n=5), which was partially reduced by both eplerenone (n=5) and hydralazine (n=3; Figure 5A). Only eplerenone improved proteinuria in DSHs (Figure 5B), similar to the result in Figure 4B.

Eplerenone but not Hydralazine Ameliorates Podocyte Injury in DSH

We examined the effects of eplerenone and hydralazine on podocyte injury in DSHs (Figure 6). Immunostaining for desmin
revealed that eplerenone dramatically reduced the induction of desmin expression in the glomeruli of DSHs (Figure 6A and 6B). On the other hand, hydralazine did not suppress the increased expression of desmin in DSHs. The reduced and disorganized expression pattern of nephrin in DSHs was improved by eplerenone but was unaffected by hydralazine (Figure 6C and 6D). We confirmed by Western blotting and real-time PCR that eplerenone but not hydralazine restored the reduced expression of nephrin toward normal in the glomeruli of DSHs at both protein and mRNA levels (Figure 6E and 6F). The enhancement of B7-1 mRNA expression in the glomeruli of DSH was also inhibited by eplerenone administration but not by hydralazine (Figure 6G).

Electron microscopic analysis showed that effacement of podocyte foot processes was exacerbated in DSHs at 5 weeks as compared with 2 weeks (Figure 6H compared with Figure 3C). Eplerenone markedly ameliorated foot process effacement, whereas hydralazine did not improve the foot process structure in DSHs (Figure 6H and 6I). The number of podocytes as assessed by W1-1–positive nuclei in the glomeruli was reduced in DSH compared with DRH, which was restored by eplerenone but not by hydralazine (Figure 6J and 6K).

**Effects of Eplerenone on Markers for Oxidative Stress, Fibrosis/Apoptosis, and Inflammation**

We finally searched molecules that might be involved in the podocyte damage in DSHs. We found that gene expressions of components of NADPH oxidase p22phox and gp91phox, transforming growth factor (TGF)-β1 and monocyte chemotactic protein-1, were upregulated in the glomeruli of DSHs and that their induction was suppressed by eplerenone treatment (Figure 7).

**Discussion**

In the current study, we have clearly demonstrated the presence of podocyte damage in hypertensive DSHs by analyzing the expressions of nephrin, desmin, and B7-1, as well as by electron microscopy. Recently, several reports suggest the crucial role of podocyte impairment in the etiology of diabetic nephropathy with or without hypertension. On the other hand, quite limited papers addressed podocyte dysfunction relevant to proteinuria in hypertensive nephropathy. Kretzler et al. in their pioneering work, showed ultrastructural alteration of podocytes in desoxycorticosterone-hypertensive rats using electron microscopy and reported that podocyte damage, rather than mesangial expansion, triggers the subsequent glomerular sclerosis. However, they evaluated podocyte injury only at 6 weeks, when the rats manifested advanced glomerular lesions. In our study, we indicated that podocytes were already injured at 2 weeks of salt loading, when proteinuria was only modestly increased, and longer duration of salt loading exacerbated the degree of podocyte injury together with proteinuria. Moreover, correction of podocyte damage by eplerenone prevented the development of proteinuria and glomerulosclerosis. Hydralazine failed to improve podocyte damage, proteinuria, and glomerulosclerosis. The close association between podocyte injury and proteinuria suggests that podocyte impairment underlies the proteinuria and glomerulopathy of DSHs. We should, of course, keep in mind that our findings are a correlational observation lacking evidence of causality. Al-
though the findings are consistent with a potential role of early podocyte injury in the pathogenesis of proteinuria, the early podocyte damage may not necessarily be the primary cause of the proteinuria.

In the present study, we evaluated the effects of eplerenone and hydralazine on BP by both the indirect tail-cuff method and direct measurement via arterial catheter. Although the tail-cuff method is noninvasive, direct method by radiotelemetry or catheter insertion has been recommended recently to examine the relationship between BP and target organ damage or to study the BP-independent effect of drugs. It should be noted that several previous studies reported BP-independent renoprotective effects of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, but subsequent studies with more accurate BP measurements showed that, in fact, their renoprotective effects were closely related to the effects on BP. Therefore, we confirmed the hypotensive effects of eplerenone and hydralazine by direct method.

The present study indicated the usefulness of desmin, nephrin, and B7-1 as indicators of podocyte injury in hypertensive nephropathy. Our immunofluorescence staining for nephrin revealed reduced and granular expression pattern in

![Figure 4](http://ahajournals.org/)

**Figure 4.** Effects of eplerenone (EPL) and hydralazine (HYD) on systolic BP, proteinuria, and renal injury in DSHs. Systolic BP (A) and proteinuria (B) in DRHs (●), DSHs (●), DSHs treated with EPL (DSH+EPL; ▲), and DSHs treated with HYD (DSH+HYD; ▼) at 0, 2, and 5W after salt loading. Effects of EPL and HYD on serum creatinine (C), renal and glomerular histology stained with periodic acid–Schiff (D), and glomerulosclerosis index (E) after 5W of salt loading. Both EPL and HYD partially reduced systemic BP of DSHs, but only EPL ameliorated proteinuria and glomerulosclerosis. #P<0.05, ##P<0.01 vs DSH; n.s. indicates not significant. Bars represent 100 µm.

![Figure 5](http://ahajournals.org/)

**Figure 5.** Effects of EPL and HYD on mean BP and proteinuria in Dahl rats. (A) Mean arterial pressure was measured via a catheter inserted in the left femoral artery in conscious and unrestrained condition at night in DRHs (n=5), DSHs (n=3), DSH+EPL (n=5), and DSH+HYD (n=3) at 5W after antihypertensive treatment. (B) Proteinuria. Both EPL and HYD partially reduced BP of DSHs, but only EPL ameliorated proteinuria. *P<0.05, **P<0.01 vs DRHs. ###P<0.01 vs DSHs.
Figure 6. Effects of EPL and HYD on podocyte injury in DSHs. Representative micrographs of immunostaining for desmin (A) and nephrin (C) in DSH, DSH+EPL, and DSH+HYD at 5W after salt loading. Scale bars, 100 μm. Semiquantitative analyses of immunostaining for desmin (B) and nephrin (D) in the glomeruli (n=4 per group). (E) Western blotting of nephrin in the glomeruli of DRH, DSH, DSH+EPL, and DSH+HYD at 5W. Top, representative bands for nephrin and control actin. Bottom, result of densitometric analysis (n=3 per group). (F and G) real-time PCR of nephrin and B7-1. The expression in DRH is arbitrarily expressed as 1 (n=4 per group). (H) transmission electron micrographs of glomeruli. Scale bars, 1 μm. (I) podocyte foot process effacement was semiquantitatively compared. (J) representative micrographs of immunostaining for W1-1. Scale bars, 100 μm. (K) number of W1-1-positive cells per glomerulus as determined by W1-1 immunostaining (n=3 per group). Podocyte injury as assessed by induction of desmin and B7-1 expressions, attenuated and disorganized expression of nephrin, foot process effacement, and decreased podocyte cell number in DSHs was improved in DSH+EPL group but unaltered in DSH+HYD group.
DSH, in contrast to intense and linear signals in control rats. Similar change was reported in puromycin aminonucleoside–induced nephrotic rats.14 Nephrin constitutes the porous slit diaphragm and is thought to play a pivotal role in maintaining the normal function of the filtration barrier.7 Accordingly, the reduction of nephrin would represent altered structure of slit diaphragm and impaired barrier function. Indeed, the degree of granularity in nephrin staining was reported to correlate with the extent of foot process effacement determined by electron microscopic analysis.35

B7-1 was identified recently as an inducible marker for a damaged podocyte.16 It was traditionally recognized as a molecule involved in antigen-specific immune responses.36 Its expression was shown to be upregulated in the podocytes in nephrotic conditions, such as lupus nephritis, nephrin knockout mice, and lipopolysaccharide-treated mice.16 B7-1 expression was also increased by injurious stimuli in cultured podocytes.27 This is the first report of B7-1 upregulation in the experimental hypertensive glomerulopathy. Although the causative role for B7-1 in proteinuria was suggested by the finding that B7-1-null mice were protected from lipopolysaccharide-evoked nephrotic syndrome,16 future studies are necessary to substantiate the signaling cascades by which B7-1 activation leads to podocyte damage.

What is the mechanism for podocyte injury in hypertensive DSHs? It is postulated that mechanical stress and oxidative stress are key mediators of podocyte damage.5 Cultured podocytes exposed to mechanical strain and/or reactive oxygen species were reported to enhance the expression of proinflammatory cytokines, TGF-β, and angiotensin II type 1 receptor, resulting in podocyte damage, such as apoptosis or cytoskeletal rearrangement.5,37–39 Podocytes, of which the foot processes overlay on the glomerular capillary tufts, are known to be quite sensitive to mechanical stress.5 Indeed, podocytes in DSHs are subjected to increased mechanical factors because of intraglomerular hypertension, hyperfiltration, or hypertrophy.40 Podocytes in hypertrophied glomeruli should be stretched, especially in the situation of podocyte loss. Oxidative stress was also reported to be increased in the kidney of DSHs.41 Alternatively, podocyte damage can be ascribed to direct action of vasoactive substances. Podocytes express a diversity of vasoactive factors and their receptors, including angiotensin II, endothelins, NO.42,43 We previously reported the reduction of C-type natriuretic peptide in the glomerular podocytes of DSHs.24 We also demonstrated the modulation of adrenomedullin expression in response to various injurious stimuli in cultured podocytes.27 Furthermore, a recent article by Aldigier et al44 indicates the role of aldosterone in podocyte injury seen in a rat model of renal ablation. Thus, podocytes in DSHs might be injured by mechanical stress, oxidative stress, and/or vasoactive substances.

In the present study, podocyte injury in DSHs was rescued by administration of aldosterone blocker eplerenone but not by hydralazine. These results suggest the importance of aldosterone in podocyte injury seen in DSHs. Growing evidence indicates that aldosterone plays a pivotal role in target organ damage.45,46 The effects of aldosterone may be mediated by alteration of glomerular hemodynamics, as well as direct actions, such as induction of oxidative stress and proinflammatory and profibrotic responses. Although both eplerenone and hydralazine partially reduced systemic hypertension, their influence on renal hemodynamics might be different. Indeed, a previous ex vivo study suggests the role

![Figure 7. Effects of EPL on gene expressions of p22phox (A), gp91phox (B), TGF-β1 (C), and monocyte chemotactic protein-1 (MCP-1) (D) in the glomeruli of DSHs for 5W. The upregulated expression of these markers in DSH was suppressed in DSH+EPL group. n=4 per group.](http://ahajournals.org/bj)
for aldosterone in glomerular hypertension,\(^47\) whereas it was reported that hydralazine did not effectively reduce glomerular hypertension compared with systemic hypertension.\(^48\) The nonhemodynamic mechanisms might be suggested from our findings that eplerenone reversed the expression of oxidative stress markers, TGF-β1 and monocyte chemotactic protein-1, as shown in Figure 7. Further studies, such as continuous 24-hour BP monitoring and evaluation of intraglomerular pressure, will be required to properly assess whether the protective effects of eplerenone go beyond its effects on BP.

**Perspectives**

We demonstrated the presence of podocyte injury in proteinuric, Dahl salt-hypertensive rats, an animal model prone to hypertensive nephropathy. Podocyte injury commenced at a relatively early stage in the course of proteinuria and glomerulopathy. Treatment with eplerenone dramatically alleviated podocyte damage and prevented the development of proteinuria and glomerulosclerosis in this model. In contrast, another antihypertensive drug, hydralazine, did not reduce podocyte injury. Eplerenone is known to possess excellent antiproteinuric property in hypertensive patients.\(^19,49\) Our present data suggest that the reduction of proteinuria by eplerenone may be mediated, at least in part, via protection against podocyte damage. Proteinuria is postulated as an independent risk factor for cardiovascular disease and a prognostic factor in hypertension. Our results indicate that podocyte injury plays an important role in the pathogenesis of proteinuria in hypertension and implicate podocytes as an important therapeutic target in hypertensive renal disease.

**Acknowledgments**

This work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (No. 17590820) given to Dr Nagase. We thank Pfizer for providing us with eplerenone. We are grateful to Dr Satoru Fukuda for his help in electron microscopic analysis.

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