Regression of Existing Glomerulosclerosis by Inhibition of Aldosterone

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In this study, the effects of inhibition of aldosterone on regression of existing hypertension-related glomerulosclerosis were investigated. Adult male Sprague Dawley rats (220 to 250 g) underwent 5/6 nephrectomy (Nx). Severity of glomerulosclerosis was assessed by renal biopsy 8 wk later, and rats were divided into four groups with equal biopsy sclerosis and then randomized by group to 4-wk treatments as follows: Control with no further treatment (CONT; \( n = 6 \)); spironolactone (SP) alone (200 mg/kg per d, by gavage, \( n = 6 \)); or SP combined with nonspecific triple antihypertensive drugs (TRX; reserpine, hydralazine, and hydrochlorothiazide in drinking water; SP+TRX, \( n = 7 \)) or with angiotensin type 1 receptor antagonist (AT1RA; losartan in drinking water; SP+AT1RA, \( n = 8 \)). When the rats were killed 12 wk after Nx, autopsy glomerulosclerosis index (SI; 0 to 4+ scale) was compared with biopsy SI in the same rats. Systolic BP was increased at 8 wk after Nx and continued to increase at 12 wk after Nx in the CONT and SP groups but not in SP+TRX- or SP+AT1RA-treated rats. Serum creatinine at 12 wk was significantly decreased in all SP-treated groups versus CONT. CONT rats had on average a 157% increase in SI from biopsy to killing at 12 wk, compared with only 84% increase in SP rats, with regression of SI in some rats. The effects on glomerulosclerosis by SP were further enhanced (when systolic BP was controlled by TRX or by AT1RA). It is concluded that inhibition of aldosterone by SP not only slows development of glomerulosclerosis but also induces regression in some rats of existing glomerulosclerosis.


**Materials and Methods**

**Experimental Design and Animals**

Adult male Sprague Dawley rats (250 to 300 g; Charles River, Nashville, TN) were studied. Rats were housed under normal conditions...
with a 12-h light/dark cycle at 70°F with 40% humidity and 12 air exchanges per hour and received standard rat powdered diet (Purina Rodent "5001" meal, 23.4% protein, 4.5% fat, 6% fiber, 0.40% sodium; Tusculum Feed Center, Nashville, TN) and water. Rats underwent 5/6 nephrectomy (Nx) by right Nx and ligation of two or three main branches of the left renal artery by silk ligature to remove approximately 5/6 renal mass. The surgery was performed under anesthesia with sodium pentobarbital (50 mg/kg body wt, intraperitoneally). Eight weeks after reduction in renal mass, rats underwent a renal biopsy by shave biopsy under anesthesia by laparotomy approach to determine the severity of existing sclerosis (15). The number of glomeruli available for biopsy analysis was, on average 30 (range 11 to 59).

Rats then were stratified on the basis of this analysis and assigned to one of four treatment groups with initial sclerosis index equivalent in all groups (Figure 1). The four treatment groups were (1) control, no further treatment (n = 6); (2) spironolactone 200 mg/kg per d solubilized in peanut oil, by gavage (SP; n = 6); (3) SP + antihypertensive triple therapy [reserpine 5 mg/L drinking water [DW], hydralazine 80 mg/L DW, and hydrochlorothiazide [HCTZ] 25 mg/L DW; SP+TRX; n = 7); or (4) SP as above combined with angiotensin type 1 receptor antagonist (losartan 80 mg/L DW; SP+AT1RA; n = 8). The dose of losartan is four-fold higher than the usual antihypertensive dose and regressed sclerosis in this model in two thirds of rats in a previous study (15). This dose of TRX was chosen as it normalizes systemic BP, as we and others have previously shown in previous studies in this model, but does not protect against glomerulosclerosis (1,16). The dose of SP is based on our previous study (11). These treatments were continued for the next 4 wk. Body weight, BP, and proteinuria were evaluated at weeks 0, 4, 8, and 12. At 12 wk, animals were killed and kidneys were harvested for analysis of morphologic and molecular parameters. The average number of glomeruli available for analysis in the remnant kidney at killing was 84 (range 53 to 123).

On the basis of initial observations in the above SP+TRX group, we also studied the effects of the diuretic HCTZ component of the TRX on plasminogen activator inhibitor-1 (PAI-1) expression in normal rats, as the HCTZ could influence the RAAS axis. We thus hypothesized on the basis of our initial results showing higher PAI-1 in the group with added TRX than in other groups that the well-known diuretic-induced RAAS activation could have activated PAI-1. Therefore, we treated an additional group of normal male Sprague Dawley rats (n = 10) without 5/6 Nx with hydrochlorothiazide 50 mg/L DW and killed them at day 3 and at weeks 4, 8, and 12. Effects of treatment on plasma concentration of PAI-1 and renal PAI-1 mRNA were assessed.

**Analysis of Kidney Function**

Systolic BP (SBP) was measured using tail-cuff plethysmography in unanesthetized prewarmed trained rats at ambient temperature of 29°C. Animals were placed in metabolic cages for 24 h for urine collection, and urine protein was measured by Bio-Rad Protein Assay Kit (Bio-Rad Laboratories, Hercules, CA). Serum creatinine was measured by Vitros CREA slides (Johnson & Johnson Clinical Diagnostics Inc., Rochester, NY). The plasma concentrations of PAI-1 were determined using a double antibody enzyme immunoassay (Innotest; Byk-Sangtec, Dietzenbach, Germany).

**Structural Analysis**

Kidney tissue from rats was immersion-fixed in 4% paraformaldehyde/PBS solution and processed routinely, and 4-μm sections were stained with periodic acid-Schiff and Masson’s trichrome. A semiquantitative sclerosis index (SI) score was used to evaluate the degree of glomerular sclerosis. The severity of sclerosis for each glomerulus was graded from 0 to 4+ as follows: 0, no lesion; 1+, sclerosis of up to 25% of the glomerulus; while 2+, 3+, and 4+, sclerosis of >25 to 50%, >50 to 75%, and >75% of the glomerulus, respectively (16). A whole kidney average SI was obtained by averaging scores from all glomeruli on one section. Tubulointerstitial fibrosis and vascular lesions were assessed qualitatively. All sections were examined without knowledge of the treatment protocol.

Portions of kidney tissues from paraffin blocks from kidneys at killing from representative rats from the above studies were processed for electron microscopy (EM). We chose three to four rats from each group, representative of the average proteinuria for that group. Non-sclerotic glomeruli from the middle of each scan section were then chosen for ultrastructural examination. EM sections were examined directly using a Fei Morgagni electron microscope, without knowledge of the treatment protocol or degree of proteinuria, and foot process effacement was assessed by estimating degree of effacement for each grid square and averaging for all portions.

**Northern Blot Hybridization**

Total RNA from renal cortex was extracted by the RNAzol B method (Tel-Test, Inc., Friendswood, TX). Twenty micrograms of total RNA was loaded and fractionated by electrophoresis in 1% agarose gel and transferred to a nylon membrane. Mouse PAI-1 and TGF-β cDNA were labeled with [32P]dCTP, and hybridization was performed in buffer (4× SSC, 1× Denhardt’s, 1% SDS, 100 μg/ml denatured salmon sperm DNA, and 10% dextran sulfate) overnight at 65°C. The membrane was washed, air-dried, and exposed to XAR film (Eastman Kodak, Rochester, NY) in intensifying screen at −70°C for 3 to 5 d. Autoradiographs were scanned by image scanner JX-330 (Sharp, Tokyo, Japan), and the intensity of the signals was measured by National Institutes of Health Image (Bethesda, MD). The ratio of specific message to the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase was used to quantify the expression for each tissue sample.

In Situ Hybridization

[35S]-labeled sense and antisense riboprobes for PAI-1 and TGF-β were prepared as described previously (16). Briefly, sections were treated with proteinase K and triethanolamine/acetic anhydride, and hybridization was done at 50°C. Sections were washed in buffer with 5× SSC and 20 mmol/L β-mercapto-ethanol at 50°C for 15 min, then washed in 2× SSC, 50% formamide at 68°C for 20 min, in TEN twice at 37°C for 10 min and incubated twice in 2× SSC and 0.1× SSC at 68°C for 15 min. Sections then were dehydrated in ethanol and air-dried, dipped in photographic emulsion, and exposed at 4°C for 10 d. The

![Figure 1. Schema of treatment protocols.](image-url)
sections were developed with D-19 developer (Eastman Kodak) and counterstained with toluidine blue. Negative control in situ hybridizations were done with sense probes and showed no specific signal.

Statistical Analyses

Results are expressed as mean ± SEM. Statistical difference was assessed by a single factor variance followed by unpaired t test or Mann-Whitney U test for nonparametric data. Podocyte foot process effacement and proteinuria were compared by Spearman correlation coefficient. P < 0.05 was considered to be significant.

Results

Body Weight and Renal Function

Body weights were similar in all groups at 8 wk after 5/6 Nx (CONT 336.0 ± 8.4, SP 338.9 ± 5.8, SP+TRX 347.0 ± 10.9, SP+AT1RA 341.1 ± 7.1 g). However, by 12 wk, body weight was higher in treated rats versus untreated control, primarily as a result of weight loss in the controls, likely reflecting severe uremia (CONT 310.7 ± 7.5, SP 339.2 ± 9.9, SP+TRX 339.1 ± 22.9, SP+AT1RA 362.8 ± 6.1 g; CONT versus all treated groups, P < 0.05).

SBP was increased significantly in all groups by 4 wk versus baseline (115.2 ± 2.9 mmHg; P < 0.01) after 5/6 Nx and was similar at 8 wk (CONT 180.7 ± 7.2, SP 209.5 ± 9.7, SP+TRX 203.9 ± 9.6, SP+AT1RA 202.2 ± 8.8 mmHg). After randomization to treatment groups, SBP decreased significantly compared with control (213.3 ± 5.0 mmHg) from 8 to 12 wk in the SP+TRX (172.3 ± 13.0 mmHg; P < 0.01) and SP+AT1RA groups (186.8 ± 7.9 mmHg; P < 0.01) but not in the SP alone group (225 ± 2.8 mmHg; Figure 2).

Serum creatinine increased over 12 wk in untreated control 5/6 Nx rats. In all treated groups, renal function was better preserved (serum creatinine SP 0.88 ± 0.13, SP+TRX 0.86 ± 0.05, SP+AT1RA 0.97 ± 0.08 versus CONT 2.90 ± 0.58 mg/dl; P < 0.05; Figure 3).

Urinary protein excretion was dramatically increased by 4 wk after 5/6 Nx (167.0 ± 17.6 versus baseline 5.6 ± 0.8 mg/24 h; P < 0.001) and continued to increase (at 8 wk 182.0 ± 13.8 mg/24 h; P < 0.001 versus baseline). Untreated control rats had further increased proteinuria at 12 wk (397.6 ± 47 mg/24 h; P < 0.001 compared with baseline). SP alone or in combination did not significantly affect the course of proteinuria (at 12 wk: SP 295.2 ± 44.0, SP+TRX 364.7 ± 81.5, SP+AT1RA 331.1 ± 31.3 mg/24 h; NS versus CONT; Figure 4).

Renal Morphologic Changes

In all 5/6 Nx rats, glomerulosclerosis, tubular atrophy, dilation, and interstitial fibrosis were present at 8 wk. By study design, all groups had similar levels of sclerosis at 8 wk. Sclerosis progressed further by 12 wk in untreated 5/6 Nx controls. SP alone or in combination with either TRX or AT1RA significantly ameliorated the development of glomerulosclerosis compared with control 5/6 Nx (SI at 12 wk: CONT 2.11 ± 0.24 versus SP 0.89 ± 0.15, SP+TRX 0.40 ± 0.09, SP+AT1RA 0.82 ± 0.32; P < 0.01; Figure 5). In all untreated control rats, structural abnormalities worsened; over time, sclerosis involved more glomeruli and was more severe in affected glomeruli. In these untreated rats, glomeruli without lesions composed on average 50% at biopsy, decreasing to 29% at autopsy. Treatment with SP was associated with regression of glomerulosclerosis in 33% of rats (two of six) when used alone, 60% (four of seven) when used with TRX, and 50% (four of eight) when used with losartan (Figure 6). Glomeruli without lesions on average for all rats decreased slightly from biopsy to autopsy for SP alone but increased in SP+TRX and SP+AT1RA (Figure 7). Thus, regres-

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Figure 2. Systolic BP (SBP) changes after 5/6 nephrectomy (Nx). SBP decreased significantly in treatment groups, except spironolactone (SP) alone, versus control with no further treatment (CONT) at 12 wk after 5/6 Nx. *P < 0.01 versus CONT.

Figure 3. Serum creatinine at 12 wk after 5/6 Nx. Renal function, assessed by serum creatinine, was improved in all treatment groups versus CONT.

Figure 4. Proteinuria changes after 5/6 NX. Proteinuria was less in all treated groups versus CONT at 12 wk after 5/6 Nx.
sion was increased when SP was associated with effective systemic antihypertensive therapy (SP/AT1RA versus SP; P < 0.01). We next compared beginning severity of sclerosis in animals with regression response with those with continued progression. This analysis showed that in rats with regression in response to treatment, average SI of glomeruli at biopsy was 1.2. In rats with progression despite treatment, SI was >1.2 at biopsy. Tubulointerstitial fibrosis and vascular lesions improved in parallel with sclerosis. Electron microscopy showed variable but more severe foot process effacement in control versus all treated rats (n = 3; average 62%; 15, 85, and 85% in individual rats). In rats that were treated only with SP, foot process effacement was on average 13% (n = 4; 25, 7.5, 15, and 5% in individual rats). In rats that were treated with SP/AT1RA, tissue for EM was inadequate in one. The remaining two rats showed 45 and 7.5% foot process effacement. Best foot process restoration was observed in rats that were treated with SP/AT1RA, in which average foot process effacement was only 5% (n = 3; 5, 10, and 0% in individual rats; Figure 8).

However, for all rats examined, degree of foot process effacement did not correlate significantly with degree of proteinuria (r = 0.204, NS). Further comparison of degree of proteinuria in all rats with regression pooled versus all rats with continued progression, regardless of treatment group, showed no difference in proteinuria (361.1 mg/24 h versus 332.6 mg/24 h, respectively; NS).

**TGF-β1 mRNA Expression**

TGF-β mRNA levels that were assessed by Northern blot analysis in the renal cortex were increased in untreated control 5/6 Nx and were not significantly influenced by treatment

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**Figure 5.** Kidney histopathologic changes after 5/6 Nx. (A) SP alone or in combination with triple antihypertensive drugs (TRX; reserpine, hydralazine, and hydrochlorothiazide in drinking water) or angiotensin type 1 receptor antagonist (AT1RA) significantly decreased glomerulosclerosis (assessed by sclerosis index [SI]) versus untreated 5/6 Nx CONT. (B) Biopsy (left) at week 8 and autopsy (right) at week 12 from the same animal in untreated CONT with progression, SP-induced regression, or SP+AT1RA–induced regression. Magnification, ×400, periodic acid-Schiff.

**Figure 6.** Changes in SI from biopsy to autopsy. Each circle represents the change in SI from biopsy at week 8 to autopsy at week 12 after 5/6 Nx in an individual rat. SI was increased in untreated CONT rats from biopsy to autopsy. Regression, with less sclerosis at autopsy than at biopsy, occurred in some rats in all treated groups. *P < 0.01 versus CONT; #P < 0.01 versus SP.

**Figure 7.** Distribution of severity of glomerulosclerosis at biopsy at week 8 versus autopsy at week 12 for each treatment group.
(CONT 0.76 ± 0.27 versus SP 0.55 ± 0.09, SP+TRX 0.69 ± 0.08, SP+AT1RA 0.67 ± 0.09; NS CONT versus all treatment groups; Figure 6, A and C). By in situ hybridization, signal was marked in areas with increased tubulointerstitial fibrosis, surrounding large arteries, with focal increase in mesangial areas, and rare localization suggestive of podocyte signals. Bowman’s capsule also showed increased signal, especially in sclerotic glomeruli. With SP treatment, TGF-β signal was equally strong in areas with tubulointerstitial fibrosis, with remaining moderate to strong signals in glomerular mesangial areas and in Bowman’s capsule. Similar pattern and intensity were present in SP+TRX rats in the tubulointerstitium, but there was in addition mild to moderate signals in the tubules of the deep cortex and at the corticomedullary junction and only minimal signal in glomeruli, with remaining signal in Bowman’s capsule. With SP+AT1RA, there was mild to moderate signal in fibrotic areas, focal mild signal in mesangial areas and Bowman’s capsule, and moderate signal in artery adventitia (Figure 9).

**PAI-1 mRNA Expression**

PAI-1 mRNA levels that were assessed by Northern blot analysis in the renal cortex were increased in untreated control 5/6 Nx rats. The level of PAI-1 mRNA was attenuated after treatment with SP and SP+AT1RA. Rats that were treated with SP+TRX achieved only a numeric decrease in PAI-1 mRNA expression (CONT 1.50 ± 0.23 versus SP 0.78 ± 0.23, SP+TRX 1.10 ± 0.2, SP+AT1RA 0.66 ± 0.1; P < 0.01 CONT versus SP and SP+AT1RA, NS CONT versus SP+TRX; Figure 10).

In situ hybridization revealed high-level PAI-1 mRNA expression in untreated 5/6 Nx rats in sclerotic glomeruli and fibrotic tubules and interstitium. In contrast, the PAI-1 signal was markedly diminished in SP- and SP+AT1RA-treated rats (Figure 11, A through C). PAI-1 signal was moderately attenuated after SP+TRX treatment (Figure 11D).

**Plasma PAI-1 Concentration and Diuretic Treatment**

In view of the lack of significant PAI-1 mRNA decrease when TRX was added to SP, we next examined the effects of the diuretic component of the treatment, HCTZ, on PAI-1 levels.
Aldosterone also modulates the vascular tone, possibly through increased vasoconstrictive effects of catecholamines (28), impaired vasodilation in response to acetylcholine (29), and upregulation of β-adrenergic and Ang II receptors (30,31). Additional direct aldosterone effects are postulated to be mediated by nongenomic and/or nonhemodynamic mechanisms (24,32–34).

BP is an important factor associated with progression (35). In this study, we observed less renoprotection with SP alone than when conventional triple antihypertensive therapy, at doses that alone do not protect against glomerulosclerosis, or AT1RA was added. It is interesting that urinary protein excretion continued to increase in all groups, demonstrating that effects on proteinuria and glomerulosclerosis may be discordant. Persistent hypertension may have allowed higher levels of persistent proteinuria. We showed previously by micropuncture that proteinuria largely emanates from glomeruli without sclerosis, as the sclerotic glomeruli do not filter and thus cannot give rise to proteinuria (36). These studies further suggest that podocyte injury, reflected in increased permselectivity, persists even after light microscopically detectable sclerosis has regressed. We speculate that the podocyte with its limited regenerative capacity may have less ability to heal and/or require longer time for

Figure 10. Northern blot analysis of kidney mRNA expressions at week 12 for plasminogen activator inhibitor-1 (PAI-1; A and B) and TGF-β1 (A and C); n = 3 for normal, n = 4 to 6 for CONT and all treated groups.
regression of injury than remodeling of the extracellular matrix of the sclerotic lesion. Although EM studies showed less foot process effacement in treated rats than in control 5/6 Nx, there was no significant correlation with degree of proteinuria, suggesting that additional filtration barrier injury remained. Analysis of proteinuria in all rats with progression versus those with regression, regardless of treatment, also revealed no difference in proteinuria among all rats with progression versus all with regression. Thus, additional nonhemodynamic factors seem to have contributed to effects on proteinuria and sclerosis in this study, perhaps reflecting unique characteristics of this rat model (37,38).

The sclerotic segment of the glomerulus is not static. There is ongoing cell proliferation and apoptosis, and modulation of matrix. To achieve regression, matrix degradation must exceed matrix synthesis. This balance is influenced by key factors that promote collagen synthesis and degradation. TGF-β has been recognized as a key mediator of renal fibrogenesis (39). Ang II increases TGF-β and promotes conversion of TGF-β to its active form (40,41). However, previous data on TGF-β and mineralocorticoids are conflicting. Aldosterone infusion in normal rats increased TGF-β mRNA in the kidney (42). In the uninephrectomized rat, TGF-β, ACE, and AT1R expressions were increased in the kidney after aldosterone infusion (41). In contrast, in the DOCA-salt model, the TGF-β level was not changed after treatment with mineralocorticoid antagonist (10). We previously in the radiation-induced injury model observed a mildly attenuated TGF-β expression by SP (11). In this study, we did not observe decreased TGF-β expression at the whole-kidney level when sclerosis was decreased, suggesting that modulation of TGF-β, at least at the mRNA level, is not a major mechanism for the beneficial effects on sclerosis in this setting. Expression by in situ hybridization remained prominent after treatment, especially in SP and SP+TRX, with mild decrease with SP+AT1RA, thus suggesting that although whole-kidney mRNA levels of TGF-β were not altered, local changes in TGF-β could have had a modulating influence on sclerosis.

Amelioration of glomerulosclerosis in our study by SP alone was linked to downregulated PAI-1 expression. PAI-1 is the major inhibitor of tissue-type plasminogen activator and urokinase-type plasminogen activators, which activate plasminogen to yield plasmin, which in turn degrades both fibrin and matrix and increases matrix metalloproteinase production and activates latent matrix metalloproteinase (43). PAI-1 may also have indirect effects on matrix synthesis, perhaps by increasing macrophage infiltration (44). Ang II induces PAI-1 expression directly through an AT1R-dependent mechanism and independently via TGF-β (45–47). Aldosterone interacts with Ang II to increase PAI-1 expression through a glucocorticoid-responsive element and a serum-inducible element localized in the PAI-1 promoter (48,49). Furthermore, serum aldosterone concentrations correlate with PAI-1 antigen concentration in humans (50), supporting a role of aldosterone in vivo in regulation of PAI-1 as well. Finally, inhibition of aldosterone downregulated PAI-1 expression in vivo, and local PAI-1 expression and sclerosis were tightly linked. These observations support the hypothesis that aldosterone induces renal injury at least in part through its effects on PAI-1 expression (11).

In this model, even SP alone had a modest effect on sclerosis and PAI-1, supporting the hypothesis of a direct effect of aldosterone on PAI-1 expression, with further benefit when effective BP control was added. One limitation of our study is that the status of RAAS activity was not defined. Regulated adrenal synthesis of aldosterone has been demonstrated (51–53). However, circulating concentrations of aldosterone do not reflect local tissue level of aldosterone. We thus speculate that SP effects are very likely secondary to adrenal and extra-adrenal aldosterone antagonism and that local levels of aldosterone are of primary importance for effects on sclerosis.

Our studies further show that chronic diuretic use stimulates PAI-1 expression. We have observed this effect in humans as well. Dietary NaCl restriction to 10 mmol/d was associated with a stimulation of the RAAS and increased PAI-1 in healthy volunteers (50). Furthermore, PAI-1 antigen correlated highly with serum aldosterone levels (50). In normal volunteers, diuretic use was associated with increased PAI-1. Acute administration of losartan and SP together but not either alone blunted this effect, suggesting that this effect was RAAS mediated (52,54). It is interesting that salt restriction but not HCTZ protected against proteinuria, sclerosis, and renal and glomerular hypertrophy in the uninephrectomized SHR rat (55). These results were not dependent on plasma renin or glomerular pressure effects. Classic studies have shown that “triple therapy” in the same doses used in our study did not protect against sclerosis, despite normalizing systemic BP, thought to reflect persistent glomerular hypertension (1). HCTZ itself was not protective against sclerosis (1,55). We speculate that an additional explanation for the above observations could be that HCTZ, a component of this triple therapy, may have proscleerotic effects via PAI-1. Our data also show that SP had a beneficial effect on sclerosis even with concomitant diuretic, a treatment that failed to decrease significantly PAI-1. This observation suggests that mineralocorticoid antagonism may exert additional beneficial nonhemodynamic effects on sclerosis beyond PAI-1. Further studies will be necessary to define precisely such additional potential mechanisms.

In conclusion, our study demonstrates that inhibition of aldosterone with SP not only slows the progression of glomerulosclerosis but also induces regression in some rats of existing glomerulosclerosis. These effects were independent of proteinuria changes and were enhanced by added BP control.

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