

The Renin-Aldosterone Axis in Two Models of Reduced Renal Mass in the Rat

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Abstract. The renin-angiotensin-aldosterone system participates in chronic progressive renal disease. The studies presented here assessed the importance of aldosterone in two different methods of reduced kidney mass in the rat, *i.e.*, the infarction model (INF; uninephrectomy plus infarction of approximately two-thirds of the other kidney) and surgical excision or polectomy (POL; uninephrectomy plus surgical excision of both poles of the other kidney). Equivalent degrees of reduction in renal mass were confirmed by the similarity of serum creatinines 3 d after the ablative procedure. Measurements were made thereafter at 2 and 4 wk postablation. Systolic arterial pressure was greater with INF at both 2 and 4 wk. Proteinuria was also greater in the INF group at both time

periods. The percentage of glomeruli with sclerosis measured at 4 wk tended to be greater in the INF group; however, this difference was not of statistical significance. At 2 wk, plasma renin activity and plasma aldosterone levels were lower in the POL group. The renin concentration in the scar region of the kidneys in the INF group was higher than in the kidney of the POL group. In conjunction with the lower plasma aldosterone, rats in the POL group had higher plasma potassium concentrations at 2 wk. In summary, higher aldosterone and plasma renin levels distinguish the INF model from the POL and likely contribute to the greater proteinuria and hypertension in the INF model. (*J Am Soc Nephrol* 9: 72–76, 1998)

Interruption of the renin-angiotensin-aldosterone system (RAAS) by converting enzyme inhibition or angiotensin II (Ang II) receptor antagonism alters the course of renal disease in the remnant kidney model (1–3). Furthermore, converting enzyme inhibition has proven clinically effective in slowing the decline in renal function of diabetic nephropathy and other progressive renal diseases (3,4). These findings have provided the major basis for viewing Ang II as a damaging factor in progressive kidney disease (1–3). Both hemodynamic and non-hemodynamic actions of Ang II in the kidney have been posited as the major mechanisms by which it produces injury. We have recently studied the contribution of circulating aldosterone to experimental progressive renal injury and have found that (1) hyperaldosteronism attends the progression of the remnant kidney; (2) suppression of aldosterone with angiotensin-converting enzyme inhibition and Ang II receptor antagonism reduced hypertension and glomerulosclerosis; and (3) infusion of exogenous aldosterone on the background of the blocking drugs restored hypertension and glomerular injury, all supporting a role for aldosterone in the pathogenesis of this model (5).

The model of progressive renal disease used most often has been produced by uninephrectomy and infarction of two-thirds of the other kidney (1,2,5,6–8). Although hypertension is a

consistent feature of this experimental model, its pathogenesis remains undefined (3,8–10). Severe reduction in nephron number has been postulated to be the principal contributor to this phenomenon (11). However, when renal mass reduction is achieved by uninephrectomy and surgical excision of the poles of the other kidney, the BP response is less (12–14). The development of hypertension in the surgical excision model occurs most clearly with rats on high-sodium diets (12,15), whereas the infarction model is generally salt-insensitive (8,16,17). Plasma renin activity (PRA) and intrarenal renin may be lower in the surgical excision model (12,14). Whether sustained renin production (local and systemic) or hyperaldosteronism in the infarction model (5,18), or both, are responsible for the differing patterns of hypertension and injury in these two models is still unknown.

In the present experiment, we studied the contribution of the renin-aldosterone axis to the two different models of reduction in renal mass, *i.e.*, subtotal nephrectomy by infarction (INF) and surgical excision or polectomy (POL).

Materials and Methods

Adult male Sprague Dawley rats weighing 225 to 300 g were fed a standard rat chow (22% protein, 0.44% sodium; Teklad Premier Laboratory Diets, Madison, WI), had free access to water, and were subjected to subtotal renal ablation by two different methods. All animal procedures were in accordance with National Institutes of Health guidelines for the care and use of laboratory animals. The first group (INF) ($n = 16$) underwent right nephrectomy and infarction of the left kidney by ligation of two segmental renal arteries. The second group (POL) ($n = 18$) underwent right nephrectomy and surgical excision of both poles of the left kidney. To accomplish this latter procedure, the left main renal artery was clamped for 5 to 10 s while excision was performed. After resection, bleeding was allowed into

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Gel-foam (methylcellulose) (Upjohn, Kalamazoo, MI) surrounding the kidney. Reclamping of the renal artery was repeated for an additional 5 s to ensure homeostasis. After bleeding stopped, the Gel-foam was removed. Three days after reduction in renal mass, serum creatinine was measured by creatinine auto analyzer (Beckman Instruments, Brea, CA) to ensure equal reduction in renal mass. Hematocrit measurements were also performed at this time. Two weeks after renal ablation, the rats were placed in metabolic cages for collection of urine for 24 h. Systolic BP was measured in the awake state by the tail cuff method. Tail vein blood was obtained for determination of hematocrit, potassium, and creatinine levels. Rats were then returned to their standard housing for 1 d and killed the following day by decapitation (nine rats from each group). Trunk blood was obtained and organs were removed for biochemical analysis and weighing. The remnant kidney was snap-frozen in liquid nitrogen and stored at -70°C for determination of kidney renin concentration (KRC). Remnant kidneys from the INF group rats were divided longitudinally into two pieces, one having the scar plus the scar-adjacent tissue (posterior half) and the other with the renal tissue "distant from the scar" or nonscar (anterior half), as described previously (18). Remnant kidneys from the POL group rats were divided into three pieces: two comprising both incisional edges and the third comprising the center of the remnant kidney.

For KRC determination, the remnant kidney was homogenized in a buffer containing 2.6 mM ethylenediaminetetra-acetic acid, 1.6 mM dimercaprol, 3.4 mM 8-OH quinoline sulfate, and 5 mM ammonium acetate, spun at 5000 rpm. The supernatant was removed and frozen and thawed four times (18). KRC was determined on an aliquot of supernatant after dilution to 1:1000 by the quantitation of generated Ang I (Rianen assay system, DuPont, Billerica, MA). Two hundred microliters of the sample was incubated for 1 h with 100 μl of plasma obtained from nephrectomized male rats, 50 μl of 4% ethylenediamine tetra-acetic acid, 10 μl of 1.7% dimercaprol, 10 μl of 6.6% 8-OH quinoline sulfate, and 630 μl of 2 M maleate buffer, pH 6.0. KRC per milligram protein was determined by dividing KRC by the protein concentration of the aliquot of kidney piece assayed. Total kidney renin content is the sum of renin concentration in the different kidney pieces (scar and nonscar for INF, edges and center pieces for POL). Plasma potassium was determined by flame photometry. Plasma protein and kidney homogenate protein concentration was measured by the Coomassie dye method. PRA and aldosterone were determined by RIA. For renin activity, the generation of Ang I was measured using a kit from New England Nuclear (Boston, MA). For aldosterone, Coat A-Count kit was used (Diagnostic Products, Los Angeles, CA). Adrenal weights were measured and expressed as the sum of both glands.

Rats similar to those decapitated at 14 d in terms of reduction in

renal mass, the degree of proteinuria, and range of BP at 2 wk ($n = 7$ in the INF group and $n = 9$ in the POL group) were maintained for 2 more weeks. Then, at 4 wk after renal mass reduction, under methohexital anesthesia, their kidneys were perfusion-fixed with formaldehyde, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Plasma potassium, PRA, and aldosterone levels were not assessed at 4 wk because the kidneys were perfusion-fixed under anesthesia for histologic studies.

Morphologic and Morphometric Studies

The prevalence of glomerular sclerosis was determined on these sections in a blinded manner. For each rat, at least 100 glomerular profiles were assessed for the presence or absence of any sclerosis. The results are expressed as the percentage of glomeruli having any sclerotic component. Morphometric analysis was based on the method of point counting, as described previously (16).

For measurement of mean glomerular volume (MGV), a grid containing a tessellation of points 6.0 mm apart was used. The MGV was defined as follows: $MGV = (P \times A)^{3/2} \times B/k$, where P is the average number of points per profile, A is the area in square micrometers represented by each point, B is 1.38 and represents a correction factor that assumes glomeruli are spherical, and K is 1.01 and represents a correction factor that assumes the variation in glomerular volume has a coefficient of variation of 10%.

Measurement of Percent Interstitial Volume

Grid tessellations were 4.0 cm apart. The coarse-to-fine point ratio was one-ninth. Percent interstitial volume was equal to the sum of fine points falling on interstitium (excluding tubules and luminal space) divided by the sum of fine points falling on whole kidney profile.

Statistical Analysis

Statistical analysis was performed by unpaired t test. All results are given as mean \pm 1 SD.

Results

Three-Day Results

At 3 d, serum creatinine and body weight were not different. However, the infarction group had a significantly higher hematocrit (53 ± 5 versus 41 ± 5 , $P < 0.0001$).

Two-Week Results

Body weight was not different between the groups (Table 1). However, the weight gain was significantly higher in the POL group (40.7 ± 15.3 g versus 17.3 ± 33.5 g, $P < 0.01$). Adrenal

Table 1. Two weeks postablation data^a

Group	Serum Creatinine at 3 Days (mg/dl)	Final Body Weight (g)	Left Kidney Weight (g)	SBP (mmHg)	Uprot.V (mg/24 h)	Adrenal Weight (mg)	Heart Weight (g)	Plasma Potassium (mEq/L)
INF	0.75 ± 0.11	268 ± 27	1.50 ± 0.14^b ($n = 9$)	166 ± 31^c	249 ± 124^c	73 ± 10^c ($n = 9$)	1.14 ± 0.15 ($n = 9$)	4.6 ± 0.70^b ($n = 9$)
POL	0.80 ± 0.11	289 ± 22	1.31 ± 0.19 ($n = 9$)	120 ± 16	154 ± 73	62 ± 7 ($n = 9$)	1.12 ± 0.10 ($n = 9$)	5.3 ± 0.6 ($n = 9$)

^a Values are means \pm SD. SBP, conscious systolic BP; Uprot.V, protein excretion rate ($n = 16$ for INF, 18 for POL unless specified otherwise); INF, infarction; POL, polectomy.

^b $P < 0.05$.

^c $P \leq 0.01$.

glands and remnant kidney weights were significantly lower in the POL group. Systolic BP was less in the POL group compared with the INF group (120 ± 16 mmHg *versus* 166 ± 31 mmHg, $P < 0.0001$). Proteinuria was significantly higher in the INF group (249 ± 124 mg/d *versus* 154 ± 73 mg/d, $P < 0.01$).

PRA, plasma aldosterone, and KRC were lower in the POL group (Table 2) (2.5 ± 1.8 *versus* 10.2 ± 8.9 ng/ml per h, $P < 0.06$ for PRA, and 194 ± 107 *versus* 672 ± 591 pg/ml, $P < 0.0001$ for aldosterone). KRC was significantly higher in the scar area of the INF remnants compared with the nonscar area (3.2 ± 2.4 *versus* 0.05 ± 0.03 μ g A1/mg of protein per h, $P < 0.01$). KRC was similar in the POL group in all pieces (edges and center) (0.36 ± 0.30 *versus* 0.36 ± 0.34 μ g A1/mg of protein per h). In addition, KRC was lower in the nonscar area of the INF remnants compared with the average of the three pieces of the POL group ($P < 0.05$). Total kidney renin content was markedly higher in the INF group (127 ± 115 *versus* 26 ± 18 μ g A1/h per kidney, $P = 0.04$). Plasma potassium was lower in the INF group (4.6 ± 0.7 *versus* 5.3 ± 0.6 mEq/L, $P < 0.04$).

Four-Week Results

By 4 wk, body weight and weight gain were similar in both groups (275 ± 31 *versus* 286 ± 1 g and 78 ± 26 *versus* 56 ± 22 g, INF *versus* POL) (Table 3). Remnant kidney weights, heart weights, and adrenal weights also were not different.

Systolic BP remained lower in the POL group (120 ± 12 *versus* 161 ± 28 mmHg, $P < 0.001$). Proteinuria was significantly higher in the INF group (225 ± 93 *versus* 135 ± 78 mg/d, $P < 0.05$).

The prevalence of glomerular sclerosis was somewhat lower in the POL group ($16 \pm 4\%$ *versus* $20 \pm 5\%$). However, this difference did not reach statistical significance.

MGV was no different between the two groups (1.89×10^6 *versus* 1.93×10^6 μ 3, INF *versus* POL). Also, the fractional volume occupied by the interstitium was similar in the two groups ($7.9 \pm 1.4\%$ *versus* $9.4 \pm 3.7\%$, INF *versus* POL).

Discussion

Our studies demonstrate different responses between the two methods of renal mass reduction. The POL group had lower arterial pressure, less proteinuria, and a tendency toward less

glomerulosclerosis. Adrenal weights, PRA, KRC, and serum aldosterone levels at 2 wk were also lower in the POL group, whereas plasma potassium was higher with polectomy.

The arterial hypertension of the INF model depends in part on the associated hyperaldosteronism (5). Our previous studies demonstrated that with suppression of aldosterone by the combination of angiotensin-converting enzyme inhibition and angiotensin receptor antagonist, hypertension was reduced. But with the exogenous infusion of aldosterone on the background of those pharmacologic blockers, much of the arterial hypertension was restored (5). The current data further support the view that elevated aldosterone levels are an important contributor to the greater hypertension demonstrated by the INF compared with the POL model, because the former manifested significantly higher plasma aldosterone and BP.

The mechanism by which aldosterone determines systemic hypertension in the INF remnant kidney model is not entirely clear. However, salt retention under the direction of mineralocorticoids would seem an obvious possibility and may indeed contribute through volume expansion in generating systemic hypertension (19–21). However, the hypertension of the INF model has been remarkably unresponsive to wide changes in dietary sodium intake (8,16,17). Thus, it is reasonable to consider other pathways by which aldosterone could sustain elevated BP in this model. Direct effects of aldosterone on the vasculature have been demonstrated. Notably, Ang II receptor levels increase in cultured smooth muscle cells with aldosterone treatment (22), and increases in vascular endothelin have been reported after systemic administration of mineralocorticoids to animals (23). Furthermore, it is possible that other direct pressor mechanisms may occur with aldosterone; however, these would necessarily be rather slow in onset because acute administration of the mineralocorticoid does not immediately elevate pressure. Considerable data do indicate that central nervous system actions of aldosterone activate pressor mechanisms. For example, infusion of aldosterone into the cerebrospinal fluid at very low rates (rates well below those that cause hypertension when administered systemically) led over several days to heightened arterial pressures in experimental animals (24,25). These or other “nonvolume” actions of aldosterone may contribute to the elevated arterial pressures observed in the INF remnant model. This difference in BP seems to persist for at least 6 wk after ablation (13). However,

Table 2. PRA, KRC, and aldosterone at two weeks postablation^a

Group	PRA (ng A1/ml per h)	Plasma Aldosterone (pg/ml)	TKRC (μ g A1/h per kidney)	KRC (μ g A1/mg of protein per h)	
INF (n = 6 to 9)	10.2 ± 8.9^b	672 ± 591^c	127 ± 115^c	Scar	3.2 ± 2.4^d
				Nonscar	0.1 ± 0.1
POL (n = 6 to 9)	2.5 ± 1.8	194 ± 107	26 ± 18	Resection edge	0.4 ± 0.3
				Nonresection edge	0.4 ± 0.3

^a Values are means \pm SD. PRA, plasma renin activity; TKRC, total kidney renin content; KRC, kidney renin concentration.

^b $P < 0.008$ by nonparametric testing.

^c $P < 0.01$.

^d $P \leq 0.05$ *versus* nonscar, resection and nonresection edges.

Table 3. Four weeks postablation data^a

Group	Serum Creatinine at 3 Days (mg/dl)	Final Body Weight (g)	Left Kidney Weight (g)	SBP (mmHg)	Uprot. V (mg/24 h)	Adrenal Weight (mg)	Heart Weight (g)	Glomerular Sclerosis (%)	Glomerular Volume ($\times 10^6 \mu^3$)	Fractional Interstitial Volume (%)
INF (n = 7)	0.84 \pm 0.10	334 \pm 58	1.85 \pm 0.41	161 \pm 28 ^b	225 \pm 93 ^c	70 \pm 9	1.41 \pm 0.19	20 \pm 5	1.89 \pm 0.5	7.9 \pm 1.4
POL (n = 9)	0.80 \pm 0.09	341 \pm 27	1.66 \pm 0.26	120 \pm 12	135 \pm 78	63 \pm 9	1.27 \pm 0.13	16 \pm 4	1.93 \pm 0.2	9.4 \pm 3.7

^a Values are means \pm SD. Abbreviations as in Table 1.^b $P \leq 0.01$.^c $P < 0.05$.

hypertension eventually develops in the POL model when observed for longer duration (12).

The differences in proteinuria between the POL and INF model are consistent with previous reports and generally follow the pattern of hypertension, being greater in the INF model (12–14). A reasonable hypothesis for this worse glomerular permselectivity in the more hypertensive INF model would be that the glomerular capillary pressures are more elevated in this model. Indeed, several lines of evidence support this speculation. First, in the classic mineralocorticoid salt model of hypertension, both proteinuria and elevated glomerular pressure occur (26). Second, recent preliminary data of micropuncture studies in the POL model indicate that it indeed does sustain less capillary hypertension (14). Furthermore, a considerable body of evidence supports a relationship between capillary hypertension, glomerular permselective defects, and progressive sclerosis of glomeruli (6,9). In the present studies, there was a tendency, although not statistically significant, for greater glomerulosclerosis to develop in the INF model. The lack of clear-cut divergence in sclerosis between these two models may rest on the relatively short time interval of the studies. In any case, the greater proteinuria and tendency to glomerular sclerosis are consistent with and may indicate a hemodynamic injury to the glomerulus. However, direct, or “nonhemodynamic,” actions of aldosterone on the glomeruli could be, at least be in part, responsible for glomerular structural and functional changes, perhaps in conjunction with hemodynamic events. For example, aldosterone increases type IV collagen synthesis by cultured mesangial cells (27) and exerts fibrogenic effects in the heart (28,29). Thus, both hypertensive and direct cellular actions of mineralocorticoids may interact to provoke permselective defects and glomerular structural damage.

Although these and our previous studies demonstrate hyperaldosteronism in the INF remnant model, the stimuli to this elevated aldosterone have been perplexing. The present studies offer insight into this problem. PRA in the INF remnant model has consistently been noted to be “normal” compared with control animals with two kidneys (1,3,30,31). However, studies of the renal source of that renin indicate that the major site of synthesis is along the margin of the infarction scar and, to a lesser extent, within the glomerular capillary tufts (30). The present comparison of INF to the POL model indicates that this latter model has lower levels of renin concentration and that there is no augmentation of renin content along the resection margin. Thus, the lower kidney renin in the POL model can be explained by the lack of a renin-rich peri-infarction zone. Furthermore, *in vivo* and *in vitro* data indicate that Ang II and potassium interact in a multiplicative manner on adrenal cells to increase aldosterone secretion (32,33). Thus, we suggest that the hyperaldosteronism of the INF model represents a synergistic interaction between its “normal” but higher PRA (generating Ang II) and the potassium adaptation, which either group must undergo due to reduced renal mass. The lower PRA and total kidney renin with polectomy would yield a lower Ang II and hence less potent stimulation of aldosterone with attenuated potassium adaptation. The finding in the present study that potassium levels are higher in the POL model supports this scheme. This scenario suggests that dietary potassium intake

may be an important determinant not only of the hyperaldosteronism of the INF model, but also of its consequences, including systemic hypertension and renal injury.

In summary, these studies confirm the previously described lesser hypertension and proteinuria in the POL compared with the INF model, but also provide evidence that this lesser injury is associated with lower PRA and aldosterone levels. It is important that the higher plasma potassium level in the POL model constitutes experimental support for the proposal that hyperaldosteronism of the INF remnant derives from the interaction between renin produced in the scarred areas of the kidney with the requirement for potassium adaptation.

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References

- Anderson S, Rennke H, Brenner B: Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 77: 1993–2000, 1986
- Lafayette RA, Mayer G, Park SK, Meyer TW: Angiotensin II receptor blockade limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 90: 766–771, 1992
- Rosenberg ME, Smith LJ, Correa-Rotter R, Hostetter TH: The paradox of the renin-angiotensin system in chronic renal disease. *Kidney Int* 45: 403–410, 1994
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
- Greene E, Kren S, Hostetter TH: Role of aldosterone in the remnant kidney model in the rat. *J Clin Invest* 98: 1063–1068, 1996
- Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *Am J Physiol* 241: F85–F93, 1981
- Shimura T, Morrison AB: A progressive glomerulosclerosis occurring in partial five-sixths nephrectomized rats. *Am J Pathol* 79: 95–106, 1975
- Purkerson ML, Hoffsten PE, Klahr S: Pathogenesis of the glomerulopathy associated with renal infarction in rats. *Kidney Int* 9: 407–417, 1976
- Brenner BM: Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. *Kidney Int* 23: 647–655, 1983
- Brenner BM: Nephron adaptation to renal injury or ablation. *Am J Physiol* 249: F324–F337, 1985
- Brenner BM, Garcia DL, Anderson S: Glomeruli and blood pressure: Less of one, more of the other? *Am J Hypertens* 1: 335–347, 1988
- Gretz N, Waldherr R, Strauch M: The remnant kidney model. In: *Experimental and Genetic Rat Models of Chronic Renal Failure*, edited by Gretz N, Strauch M, Basel, Switzerland, Karger, 1993, pp 1–28
- Griffin KA, Picken M, Bidani AK: Method of renal mass reduction is a critical modulator of subsequent injury and hypertension. *J Am Soc Nephrol* 4: 2023–2031, 1994
- Griffin KA, Picken M, Bidani AK: Differences in the potential functional and structural mediators of glomerulosclerosis between the infarction and surgical excision models of 5/6 renal mass reduction [Abstract]. *J Am Soc Nephrol* 7: 1854–1855, 1996
- Koletsky S: Role of salt and renal mass in experimental hypertension. *Arch Pathol* 68: 11–22, 1959
- Daniels BS, Hostetter TH: Adverse effects of growth in the glomerular circulation. *Am J Physiol* 258: F1409–F1416, 1990
- Lax DS, Benstein JA, Tolbert E, Dworkin LD: Effects of salt restriction on renal growth and glomerular injury in rats with remnant kidneys. *Kidney Int* 41: 1527–1534, 1992
- Correa-Rotter R, Hostetter TH, Manivel JC, Rosenberg ME: Renin expression in renal ablation. *Hypertension* 20: 483–490, 1992
- Cowley AW: Long-term control of arterial blood pressure. *Physiol Rev* 72: 231–278, 1992
- Onoyama K, Bravo EL, Tarazi RC: Sodium, extracellular fluid volume, and cardiac output changes in the genesis of mineralocorticoid hypertension in the intact dog. *Hypertension* 1: 331–336, 1979
- Pan Y, Young D: Experimental aldosterone hypertension in the dog. *Hypertension* 4: 279–287, 1982
- Suzuki H, Shibata H, Murakami M, Sato A, Naito M, Ichihara A, Matsumoto A, Tsujimoto G, Hirasawa A: Modulation of angiotensin II type I receptor mRNA expression in human blood cells: Comparison of platelets and mononuclear leukocytes. *Endocr J* 42: 15–22, 1995
- Schiffrin EL, Laviere R, Li JS, Sventek P, Touyz RM: Endothelin I gene expression and vascular hypertrophy in DOCA salt hypertension compared to spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol* 22[Suppl 1]: S188–S190, 1995
- Kageyama Y, Bravo EL: Hypertensive mechanisms associated with centrally administered aldosterone in dogs. *Hypertension* 11: 750–753, 1988
- Elise P, Gomez S: What is the role of the central nervous system in mineralocorticoid hypertension? *Am J Hypertens* 4: 374–381, 1991
- Dworkin LD, Hostetter TH, Rennke HG, Brenner BM: Hemodynamic basis for glomerular injury in rats with desoxycorticosterone-salt hypertension. *J Clin Invest* 73: 1448–1461, 1984
- Wakisaka M, Spiro MJ, Spiro RG: Synthesis of type VI collagen by cultured glomerular cells and comparison of its regulation by glucose and other factors with that of type IV collagen. *Diabetes* 43: 95–103, 1994
- Brilla CG, Weber KT: Mineralocorticoid excess, dietary medium and myocardial fibrosis. *J Lab Clin Med* 120: 893–901, 1992
- Young M, Fullerton M, Dilley R, Funder J: Mineralocorticoids, hypertension and cardiac fibrosis. *J Clin Invest* 93: 2578–2583, 1994
- Rosenberg ME, Correa-Rotter R, Inagami T, Kren SM, Hostetter TH: Glomerular renin synthesis and storage in the remnant kidney. *Kidney Int* 40: 677–683, 1991
- Pupilli C, Chevalier RL, Carey RM, Gomez A: Distribution and content of renin and renin mRNA in remnant kidney of adult rat. *Am J Physiol* 263: F731–F738, 1992
- Young DB, Smith MJ Jr, Jackson TE, Scott RE: Multiplicative interaction between angiotensin II and K concentration in stimulation of aldosterone. *Am J Physiol* 247: E328–E335, 1984
- Pratt JH, Rothrock JK, Dominguez JH: Evidence that angiotensin-II and potassium collaborate to increase cytosolic calcium and stimulate the secretion of aldosterone. *Endocrinology* 125: 2463–2489, 1989