Aldosterone in Chronic Kidney and Cardiac Disease

THOMAS H. HOSTETTER*† and HASSAN N. IBRAHIM†
*National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland; and †Division of Renal Diseases and Hypertension, University of Minnesota, Minneapolis, Minnesota.

Regulatory systems, which are normally involved in homeostasis, can take on maladaptive roles. This paradoxical situation has been convincingly demonstrated in heart failure. The evidence is strongest with respect to the beneficial effects of sympathetic and renin-angiotensin-aldosterone system blockade (1,2). Activation of these regulators had been viewed as a compensatory response to circulatory embarrassment, but the clinical evidence proved that at some level the activation actually further impaired function. Although the success of drugs such as angiotensin-converting enzyme (ACE) inhibitors was initially attributed to hemodynamic actions unloading the left ventricle, additional direct cellular effects on cardiac remodeling have been discovered (3).

In the case of chronic progressive renal disease, substantial evidence attests to the efficacy of ACE inhibitors and, more recently, angiotensin receptor blockers in slowing the progression of both experimental and clinical renal disease (4–8). Largely on the basis of this pharmacologic evidence, the renin-angiotensin-aldosterone system has been implicated as a major contributor to renal disease. In contrast to heart failure, a compensatory role for this system had not been considered in chronic renal disease before the value of the blocking agents became apparent. However, as with heart failure, both hemodynamic and nonhemodynamic actions of the system have attracted attention.

Angiotensin II (AngII) has received the greatest consideration as the mediator of injurious actions of this hormonal system in the heart and kidney. Elevations in glomerular pressure attributable to AngII in the kidney and vasoconstrictive afterload effects in the general circulation constitute potentially injurious actions of the peptide. Moreover, growth-promoting and other fibroproliferative effects of AngII have been demonstrated. However, aldosterone has also been implicated as a deleterious component of the renin-angiotensin-aldosterone system in both cardiac and renal tissue (3,9). This review highlights and updates the evidence linking aldosterone to injury.

Aldosterone in Cardiac Disease

In addition to the adrenal glands, the heart and vasculature can produce aldosterone (10–12). Although neither of these extra-adrenal sites can manufacture sufficient aldosterone to supply systemic needs, important local functions may be served and pathologic consequences may result from production at these sites. The same stimuli that provoke adrenal synthesis of aldosterone, i.e., AngII, potassium, and ACTH, stimulate aldosterone generation by the heart. Intracardiac levels of aldosterone exceed levels in the circulation, presumably because of this local production (11). Several cell types in the heart harbor mineralocorticoid receptors (13) (Figure 1). An important corollary finding involves the glucocorticoid-degrading enzyme 11β-hydroxysteroid dehydrogenase (11-BHSD). The classic genomic action of aldosterone in a target tissue requires not only the mineralocorticoid receptor but also 11-BHSD. This dual requirement results from the similar affinities of the glucocorticoids and aldosterone for the mineralocorticoid receptor and the much higher circulating levels of glucocorticoids. Therefore, targets of aldosterone generally express 11-BHSD as a means of conferring aldosterone specificity to the response of the tissue. The heart exhibits 11-BHSD activity and, in conjunction with appropriate receptors and elevated local levels of aldosterone, a paracrine system may operate (13). The first and perhaps essential protein is serum glucocorticoid kinase, the translation of which is stimulated by aldosterone (14). This protein seems to be linked to such cellular events as the increase in sodium transport in epithelia. The normal or homeostatic function of this mineralocorticoid system in the heart is currently unknown.

Nongenomic membrane effects of aldosterone might also mediate direct renal or cardiac responses to aldosterone (15) (Figure 1). An unidentified membrane receptor is thought to mediate the rapid responses involving this pathway. The term nongenomic is derived from the fact that, in contrast to signaling through the classic genomic pathway, gene transcription and protein synthesis are not required. Therefore, these responses may be quite swift. Also, these nongenomic actions are not inhibitable by standard mineralocorticoid receptor blockers such as spironolactone. The rapid effects of aldosterone on the isolated heart and perhaps on the circulation may occur through this route (16). Renal epithelial cells and glomerular cells in vitro mount rapid nongenomic responses to aldosterone (15–17). However, no net renal events (either homeostatic or pathologic) are known to depend on the nongenomic mechanism.
Hyperaldosteronism regularly accompanies heart failure. Both increased production and decreased metabolism contribute, although the increased secretion is dominant (3). Renal secretion of renin, with consequent AngII production, stimulates adrenal aldosterone production. Aldosterone production by the heart was recently reported to be elevated among patients with heart failure and rats with experimental myocardial infarction (18,19). Diminished hepatic perfusion associated with heart failure reduces aldosterone metabolism, further increasing circulating levels.

The elevated aldosterone levels in heart failure have been convincingly implicated in progressive myocardial damage (Figure 2). ACE inhibition improves the course of heart failure and has represented standard therapy for more than a decade (1). Additional specific blockade of aldosterone has proved clinically rewarding. The first large clinical trial testing the efficacy of spironolactone in heart failure was reported in 1999 (20). The rationale for the trial was based in part on the success of ACE inhibition, with its associated suppression of aldosterone, but also developed from animal studies linking aldosterone to cardiac fibrosis (21,22). The Randomized Aldactone Evaluation Study demonstrated that spironolactone conferred a 30% reduction in mortality rates, compared with placebo, among patients with severe heart failure. More recently, investigators tested the newer mineralocorticoid receptor blocker eplerenone among patients with left ventricular dysfunction after myocardial infarction (23). Even when added to currently accepted optimal therapy with ACE inhibitors and β-receptor blockers, eplerenone reduced morbidity and mortality rates. These findings not only established mineralocorticoid receptor blockade as a valuable therapeutic approach but also strengthened the view that aldosterone can exert deleterious actions in cardiac disease.

**Aldosterone in Models of Renal Disease**

Although the actions of AngII in progression have been extensively discussed, the contribution of aldosterone has been much less discussed. However, adrenal hypertrophy and hyperaldosteronism (with plasma levels approximately 10 times normal values) accompany the hypertension, proteinuria, and glomerulosclerosis characteristic of the remnant kidney model (9). Furthermore, combined therapy with the AngII receptor blocker losartan and the ACE inhibitor enalapril in this model nearly nullified the hypertension, proteinuria, and glomerulosclerosis of the remnant kidney, as expected (9), but also attenuated the hyperaldosteronism. Most importantly, reproduction of the hyperaldosteronism with exogenous aldosterone infusion during administration of the pharmacologic blockers restored most of the arterial hypertension, proteinuria, and glomerulosclerosis observed with the untreated, subtotally ablated kidney (9). These results demonstrate that aldosterone is a potentially important component of the renin-angiotensin-aldosterone system activity in this model (Figure 3).

Although elevated plasma aldosterone levels have been noted in clinical renal impairment (see below), hyperaldosteronism has not been a well recognized feature of the remnant kidney model. However, adrenal hypertrophy was previously linked to this experimental model. Morrison (24) documented increased adrenal weight after subtotal ablation and, in qualitatively evaluating this growth, noted that the zona glomerulosa was more prominently widened than was the reticulata. Other observations in this experimental model have suggested...
that aldosterone may contribute to progressive injury. Quan et al. (25) performed adrenalectomy in rats after subtotal nephrectomy. Despite high doses of replacement glucocorticoid, several cardinal features of the disease, including hypertension, proteinuria, and structural renal injury, were mitigated, compared with similarly nephrectomized rats with intact adrenal glands. Aldosterone was not replaced for the adrenalectomized rats; perhaps its absence accounted for the attenuation of renal disease after adrenalectomy, despite adequate glucocorticoid therapy.

Examination of a Wistar rat strain known as the Wistar-Furth strain has supported the role of aldosterone in generating injury after subtotal nephrectomy (26). Fitzgibbon et al. (26) chose the Wistar-Furth strain because of its demonstrated resistance to aldosterone. When subtotal renal ablation was performed with Wistar and Wistar-Furth strains, the Wistar strain developed substantially more hypertension, proteinuria, and histologic injury. Even when BP was adjusted between the two groups with antihypertensive therapy, the Wistar strain sustained greater injury. These differences in hypertension and injury were associated with differences in aldosterone levels and adrenal gland weights. Specifically, aldosterone levels increased in the Wistar strain, as observed for Sprague-Dawley rats (see above), but failed to increase in the Wistar-Furth strain. Therefore, the previously noted resistance to aldosterone action did not seem to explain the differences in the responses to reductions in renal mass, and some fundamental difference in the tendency to develop hyperaldosteronism was indicated. Comparisons of these rat strains support the idea that aldosterone is critical for expression of the main features of the remnant kidney model in rats.

Other models of experimental or animal renal disease are also marked by elevations in mineralocorticoid activity. The classic mineralocorticoid-salt model of hypertension, produced with the combination of high doses of exogenous mineralocorticoid, a high-salt diet, and unilateral nephrectomy, is characterized not only by systemic hypertension but also by substan-

tional glomerular injury (27). Furthermore, this injury seems to be unresponsive to angiotensin receptor blockers and ACE inhibitors, as would be expected for a disease in which renin production is suppressed (28). The adriamycin model of nephrosis, with progressive glomerulosclerosis and tubulointerstitial disease, has also been associated with elevated aldosterone levels (29). Finally, domestic cats with spontaneous chronic renal disease exhibit elevated levels of aldosterone (30).

Targeted interruption of the action of aldosterone with mineralocorticoid receptor blockers has been successful in several other models of renal disease. Spironolactone and its newer, more-selective, congener eplerenone have been used for this purpose in models of hypertension, radiation-induced nephritis, and cyclosporine toxicity (31–34). The blockers reduced proteinuria in the hypertensive and radiation-induced nephritis models and reduced renal structural injury in all models. In studies of stroke-prone, spontaneously hypertensive rats fed saline solution, spironolactone ameliorated kidney damage without notable reductions in arterial hypertension (31). In that model, as in the remnant kidney model described above, ACE inhibition prevented injury and decreased endogenous aldosterone levels; restoration of aldosterone levels with exogenous infusion reconstituted the proteinuria and renal microvascular lesions, despite ongoing ACE inhibition. Eplerenone and, separately, adrenalectomy attenuated renal injury in another hypertensive model, produced with angiotensin infusion combined with saline feeding and nitric oxide synthesis inhibition with N\textsuperscript{G}-nitro-L-arginine methyl ester (32). Again, the injury reduction was achieved without detectable antihypertensive action. In comparison, spironolactone and eplerenone each had only modest effects on renal injury in the remnant kidney model, perhaps because of major increases in endogenous aldosterone levels after their administration in that model. However, each of those mineralocorticoid receptor blockers decreased cardiac hypertrophy in the remnant kidney model (9,35).

**Aldosterone in Clinical Renal Disease**

Hyperaldosteronism without increased renin levels occurs in clinical chronic renal insufficiency. Hene et al. (36) described elevations in plasma aldosterone levels among patients with stable chronic renal insufficiency resulting from various causes. In their cross-sectional analysis of subjects with a range of renal function, aldosterone levels increased when creatinine clearance was less than approximately 70 ml/min, increasing three- to fourfold above normal levels as clearance values decreased. Other clinical investigations also identified increased aldosterone levels in renal insufficiency. For example, Bérl et al. (37) studied eight subjects whose average creatinine clearance was 14 ml/min; five of the subjects demonstrated plasma aldosterone levels above the normal range. Similarly, nine subjects with better renal function (average inulin clearance, 27 ml/min) who were studied by Reams and Bauer (38) demonstrated mean plasma aldosterone levels more than fourfold greater than normal values. Surprisingly, the significance of this hyperaldosteronism in progression has not been exten-
sively considered, although Walker (39) did note a significant correlation between aldosterone levels and rates of renal decay in a longitudinal study of patients with diabetes mellitus. Preliminary data reported by Ciraku et al. (40) also demonstrated a significant correlation between urinary aldosterone excretion and microalbuminuria among 252 members of 58 families identified on the basis of a proband with essential hypertension. Urinary aldosterone excretion was the strongest predictor of urinary albumin excretion, even after adjustment for mean arterial BP, age, gender, ethnicity, body mass index, cholesterol levels, triglyceride levels, and plasma renin activity (40).

The effects of ACE inhibition on the course of clinical renal insufficiency have been generally beneficial, as previously noted (5,7,41). Aldosterone levels have not often been measured but, when examined, they have decreased with this therapy. Reams and Bauer (38) reported that the average baseline plasma aldosterone level of 234 pg/ml among their subjects decreased to 135 pg/ml after 1 mo of enalapril administration. Ruilope et al. (42), who also studied patients with renal insufficiency, observed a significant decrease in plasma aldosterone levels from 266 pg/ml to 105 pg/ml with 6 mo of captopril treatment. Dietary protein restriction attenuates the progression of renal disease. This dietary maneuver also decreases aldosterone levels among normal subjects and patients with a variety of kidney diseases (43–46). Therefore, the available clinical data suggest a dependence of progressive disease on aldosterone.

Clinical studies using mineralocorticoid blockers to attenuate chronic renal injury have begun to appear. However, to date they have used changes in proteinuria as an end point, rather than changes in GFR or other clinical events. Chrysostomou et al. (47) administered spironolactone (25 mg/d) to eight proteinuric patients who had been receiving enalapril for at least 1 yr. At the end of a 4-wk period, an additional 54% reduction in the 24-h protein excretion rate, without any change in creatinine clearance or plasma potassium levels, was observed. However, there was a difference in mean arterial BP of 10 mmHg at the end of the 4-wk period. This might have been a response to the antihypertensive properties of spironolactone. The lack of a control group raises concerns regarding this observation. More recently, Epstein et al. (48) conducted a 24-wk, double-blind study that compared the renal and antihypertensive effects and safety of the aldosterone antagonist eplerenone with those of enalapril, or the combination of the two agents, among hypertensive patients with type II diabetes mellitus and microalbuminuria. Each of the three groups included 70 to 80 subjects. The eplerenone-treated group demonstrated a 62% reduction in the urinary albumin excretion rate during the 6-mo period, compared with a 45% reduction in the enalapril group and a 74% reduction in the combination group. This significant reduction in proteinuria in the eplerenone-treated group was independent of the change in BP from baseline values. This newer selective aldosterone antagonist, which is characterized by a low binding affinity for progesterone and androgen receptors, also proved effective in reducing BP among patients with mild or moderate hypertension (49).

Finally, Sato et al. (50) identified 13 patients with type II diabetes mellitus who were treated with an ACE inhibitor but whose aldosterone levels increased after initial suppression (i.e., aldosterone escape). When spironolactone was added to the ACE inhibitor for those patients for 24 wk, albuminuria and left ventricular mass both decreased. BP and serum potassium levels did not exhibit detectable changes.

Although the results of these recent clinical trials are encouraging, they are preliminary; the studies involved small numbers of subjects, with proteinuria as the main end point. In addition to the need for more information from larger groups with additional end points, safety issues (especially involving hyperkalemia) remain a major concern with the use of mineralocorticoid receptor blockers in this population. Serious and occasionally fatal hyperkalemia has been observed as spironolactone has been widely, and in many cases inappropriately, used to treat heart failure (51). Further studies in renal disease are needed to assess the best means of monitoring and avoiding this potential complication.

Pathologic Actions of Aldosterone

Aldosterone promotes hypertension through sodium retention. This well known action remains a potential mechanism for both cardiac and renal injury. Central nervous system effects on vascular tone may sustain hypertension (52). However, some of the damage attributable to aldosterone, as well as the benefits observed with its suppression and antagonism, cannot be entirely assigned to changes in BP.

For several years, mineralocorticoids have been considered to be responsible for scarring and injury in the heart. Brilla and Weber (21) provided evidence that myocardial fibrosis could result from mineralocorticoid action, which was confirmed by Young and colleagues (22,53). Those data also suggested that the cardiac scarring effects might not be attributable solely to systemic hypertension produced by the steroids. In the cardiac models, however, fibrosis does seem to require a high salt intake, the molecular and cellular implications of which are unknown.

Aldosterone promotes the growth of cardiac myocytes and the proliferation of fibroblasts in vitro, demonstrating its capacity for nonhemodynamic actions on tissues (54,55). The initial pathologic step in cardiac fibrosis stimulated by aldosterone is not known, but one line of evidence points to myocardial necrosis preceding fibrosis (32). The necrosis may be a result of focal ischemia (Figure 2). The concept that oxidative stress mediated by NADPH oxidase lies proximal to fibrosis has also been proposed (56). The sequence of events leading to fibrosis remains underdetermined, but a recent report should be noted. Beggah et al. (57) observed that, when cardiac mineralocorticoid receptor expression was suppressed in mice, cardiac fibrosis ensued. Although they suggest the necessity of mineralocorticoid action in the normal heart, these results do not clarify the scarring effects of excess aldosterone. Perhaps a reactive excess of some other regulator (e.g., in the sympathetic nervous system) produces the pathologic features observed in this unusual model.

Nonhemodynamic actions of aldosterone may also partici-
pate in its renal and cardiac fibrotic consequences. Although the distal tubules are usually considered the targets of aldosterone action in the kidney, transcripts for the mineralocorticoid receptor have been detected in glomeruli, albeit at lower levels than in the distal tubular epithelium. If the receptors were confined to mesangial cells (approximately 15% of glomerular volume), for example, then their density would be essentially the same as in the distal epithelium (58). Such receptors might mediate actions at this site, including fibrogenesis and sclerosis. Aldosterone does stimulate type IV collagen synthesis by mesangial cells in vitro (59). Vascular smooth muscle cells contain mineralocorticoid receptors and respond to aldosterone in vitro, which is another example of a nonhemodynamic action but is one that might produce hypertension in vivo (60).

Mesangial cells have well known similarities to vascular smooth muscle cells, and they assume more of that phenotype in remnant glomeruli (61,62). Whether the shift in phenotype includes increases in mineralocorticoid receptor expression is not known, but such increases would be consistent with the other changes.

An increasing number of locally and systemically acting factors have been associated with progressive renal injury. For example, plasminogen activator inhibitor-1 is a major regulator of fibrinolysis, with both tissue and systemic expression. Aldosterone enhances its levels in the kidney and in the circulation, which should promote both thrombosis and extracellular matrix accumulation. Several lines of evidence support this additional profibrotic effect of aldosterone (33,63,64). Data indicate that the TGF-β message is associated with aldosterone in the remnant kidney, although the effect may be complex and may depend on both hemodynamic and more direct actions (65). Direct actions of aldosterone to increase TGF-β levels seem likely to underlie some recent results. Specifically, infusion of aldosterone for only 3 d in otherwise normal rats, receiving a normal diet, increased urinary TGF-β excretion rates (66). The aldosterone levels achieved with exogenous infusion were in the range of those observed in the remnant kidney model. However, because the animals had a full complement of nephrons and were receiving a standard-salt diet, this brief mineralocorticoid infusion did not induce hypertension or proteinuria. These studies suggest that increased production of the profibrotic cytokine TGF-β is likely to be at least partly attributable to a direct action of aldosterone on renal tissue. The exact sites within the kidney that generate TGF-β in response to aldosterone are currently not known. Therefore, both hypertensive and more direct cellular actions of aldosterone, including scarring, may account for its contributions to glomerulosclerosis and interstitial fibrosis.

The physiologic connection between TGF-β and aldosterone, in contrast to the pathophysiologic relationship noted above, may involve their antagonistic actions on sodium reabsorption in the terminal collecting ducts. Stokes (67) demonstrated that TGF-β is a potent inhibitor of aldosterone-induced sodium transport in inner medullary collecting duct cells. Therefore, we speculate that TGF-β may act as a local counter-regulator induced by the primary action of aldosterone. Anti-diuretic hormone and prostaglandins, with opposing actions on water transport in the same segment, represent an analogous effector hormone/local counter-regulator pair. In states with persistent elevation of aldosterone levels, such as the remnant kidney model, overproduction of TGF-β might produce fibrosis in addition to local fine adjustment of salt balance.

**Conclusion**

The renin-angiotensin-aldosterone system is centrally involved in the progression of renal disease and heart failure. The efficacy of drugs that block AngII production and/or action attests to this centrality. In addition to these effects on AngII, a reduction in aldosterone levels may be a critical component of the action of such drugs. Aldosterone may enhance BP, with consequent vascular damage, and may promote scarring through more direct actions. More specific targeting of mineralocorticoid action ameliorates heart failure, but its use for the treatment of progressive renal disease has undergone only preliminary study. Given the likely role of aldosterone in chronic kidney disease and the promise such a strategy has demonstrated, further exploration seems warranted. Safety issues, particularly involving hyperkalemia, must be carefully addressed as we explore this area.

**References**


Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/