Before the mid-1990s, much data supported the hypothesis that the primary mechanism action of aldosterone was to maintain sodium, volume, and potassium homeostasis. This is accomplished by a direct effect on epithelial cells of the distal segments of the nephron to actively promote sodium transport out of and potassium transport into the tubular lumen. This primary mechanism of action was reinforced by the 2 major mechanisms controlling adrenal aldosterone secretion: activation of the renin-angiotensin system (RAS) and, specifically, the concentration of angiotensin II, and the level of potassium.

For nearly 50 years, inappropriate activation of the renin-angiotensin-aldosterone system (RAAS), with a particular emphasis on increased angiotensin II production, has been documented to be a risk factor for cardiovascular disease. Less well appreciated are the adverse effects of the other major outcome from activation of the RAAS: potassium reduction. In experimental animals and humans, potassium reduction increases cardiovascular risk, and potassium replacement reduces it. Because of the adverse effects of potassium reduction, inhibitors of the mineralocorticoid receptor have been used for many years to counteract the adverse effects of thiazide diuretics or an activated RAAS.

Non epithelial Aldosterone-Induced Cardiovascular Injury

During the past 10 years, an increasing body of evidence has suggested that aldosterone and specifically activation of the mineralocorticoid receptor in nonepithelial cells also can induce cardiovascular damage. Data to support this conclusion come from clinical and experimental studies. The first major clinical study was the Randomized Aldactone Evaluation Study (RALES), in which the mortality of subjects with severe congestive heart failure already being given standard therapy (angiotensin-converting enzyme inhibitor + loop diuretic ± digoxin) was decreased by 23% over a period of 3 years by the addition of a low dose of spironolactone. The EPHESUS trial reported similar results in another population: acute myocardial infarction–precipitated heart failure. Subjects were randomized to placebo or a different mineralocorticoid receptor antagonist (eplerenone) on top of standard therapy (angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists + β-blockers + diuretics). The eplerenone-treated limb had a highly significant (P<0.008) reduction in mortality. The implications of these findings are that blocking the RAS achieves significant but not maximal benefits. Mineralocorticoid receptor blockade brings substantial additional benefits.

Mechanisms of Mineralocorticoid Receptor Activation-Induced Cardiovascular Disease

Weber was the first in the modern era to suggest that aldosterone can cause nonepithelial-mediated cardiovascular damage. He reported that uninephrectomized rats after 8 to 12 weeks of treatment with aldosterone develop cardiac fibrosis that can be prevented by the simultaneously administered spironolactone. Studies in the same model by Rocha et al suggest that the fibrosis is probably not the primary event but a reparative process secondary to an acutely induced perivascular inflammatory cell filtration with necrosis.

These studies strongly suggest that high aldosterone levels can induce substantial cardiac damage that begins with perivascular inflammation and ends with perivascular fibrosis and abnormal remodeling. Studies in a normal aldosterone model have provided similar results. In rat or mouse models of endothelial dysfunction induced by providing a liberal salt intake, an NO inhibitor (L-NAME) to suppress NO vasodilation and a subpressor dose of angiotensin II, substantial cardiovascular damage can be induced. This damage begins as a perivascular inflammation eventually leading to death or cardiac fibrosis. If animals are simultaneously treated with a mineralocorticoid antagonist or adrenalectomy, the damage is prevented without a significant reduction in the elevated blood pressure. Thus, elevated and normal aldosterone levels can induce cardiovascular damage in rodents in support of the clinical studies.

Rocha et al expanded on these studies by demonstrating that as early as 1 week after receiving aldosterone, the levels of several proinflammatory molecular messengers, including cyclooxygenase-2, osteopontin, and monocyte chemoattractant protein-1, but not transforming growth factor-β1, increase significantly. These effects are reduced by the addition...
of the eplerenone. Brown and Vaughn and their collaborators have been in the forefront of linking aldosterone-mediated adverse events to plasminogen activator inhibitor type 1 (PAI-1). They documented in humans that aldosterone levels and PAI-1 levels correlate in individuals who have cardiovascular damage. In animal studies, they documented that the PAI-1 knockout mouse has less 1-NAME–induced cardiovascular fibrosis. Thus, a number of inflammatory markers have been documented to be associated with aldosterone-induced cardiovascular damage.

Several investigators have suggested that the primary mechanism leading to mineralocorticoid receptor–activated cardiovascular damage is the same as that known classically, namely, potassium reduction. There is ample precedent for suspecting that lower potassium levels can induce damage and that raising potassium levels can reduce it. Giving aldosterone will lower potassium levels, and giving a mineralocorticoid receptor antagonist will raise them. In this issue of Hypertension, Ma, working with Brown and Vaughn, provided further support to the hypothesis that blockade of the mineralocorticoid receptor, independent of any effect on potassium homeostasis, reduces a marker of cardiovascular damage: PAI-1. Intriguingly, they demonstrated that in hypertensives, spironolactone, but not the potassium-sparing diuretic triamterene, lowers PAI-1 levels. In normotensives, it had no effect, whereas triamterene raised PAI-1 levels likely secondary to the increased aldosterone and angiotensin levels induced by triamterene. Studies in hypertensive rats treated with 1-NAME/angiotensin II/NaCl and fed large amounts of dietary potassium or treated with eplerenone also report that eplerenone treatment significantly reduced myocardial necrosis. Thus, these clinical and experimental animal studies strongly suggest that reduced cardiovascular damage is, indeed, associated with nonpituitary mineralocorticoid receptor blockade in addition to whatever effects it may have by increasing potassium levels secondary to blockade of the classical renal epithelial mineralocorticoid receptor.

With clarification of the role of potassium, what about the role of sodium intake? The experimental rodent model 1-NAME/angiotensin II/NaCl has been used to compare the effects of high-salt diet (low aldosterone levels) and low-salt diet (high aldosterone levels). Despite very high levels of serum aldosterone in the low-salt diet animals, only minimal cardiac damage was observed. There are 2 implications of this study. First, at least a modest amount of salt intake is an obligate cofactor for aldosterone-induced cardiovascular damage. Second, direct correlations between aldosterone levels and the severity of aldosterone-induced cardiovascular damage are likely not possible. However, uncertain is the independent effect of changes in blood pressure on the dietary sodium, vascular damage, and mineralocorticoid activation interaction in experimental animal studies. Whereas some studies have reported minimal changes in blood pressure, others have reported significant reductions with this paradigm with 24-hour measurements. Resolution of the independent role of an elevated blood pressure in this sodium-mediated change in experimental animals will require studies in which vascular damage is induced without an increase in blood pressure (ie, diabetes) or maintaining an elevated blood pressure during sodium restriction. Importantly, in human studies, a decrease in blood pressure is not required for blockade of the mineralocorticoid receptor to reduce cardiovascular morbidity and mortality. Indeed, in the EPHESUS trial, the individuals in the eplerenone treatment arm actually increased their blood pressure compared with the control group.

Thus, several of the steps in the chain of aldosterone-associated events that eventually lead to cardiac fibrosis have been identified. Uncertain are potential additional steps and the mechanism(s) responsible for the obligatory requirement of dietary sodium.

Conclusions
Overall, the results of the studies reviewed here demonstrate that aldosterone is associated with cardiovascular injury. Inflammation is a major mechanism of aldosterone-induced cardiovascular injury, but it may not be the major mechanism. The adverse effects of aldosterone can be prevented by blockade of the mineralocorticoid receptor or by eliminating salt from the diet. In summary, over and above its classic effects on sodium retention, volume expansion, and potassium loss, aldosterone is associated with cardiovascular injury by a mechanism that seems to involve an interaction between the aldosterone (mineralocorticoid) receptor, dietary sodium, and activation of a variety of molecular messengers. Finally, the currently available clinical and experimental data strongly support the hypothesis that the beneficial effect of blockade of the mineralocorticoid receptor is not just secondary to a change in potassium homeostasis.

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Cardiovascular Benefits of Aldosterone Receptor Antagonists: What About Potassium?
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_Hypertension_. 2005;46:265-266; originally published online July 18, 2005;
doi: 10.1161/01.HYP.0000174329.99569.52

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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