Aldosterone and Vascular Inflammation

Nancy J. Brown

Oxidative stress and inflammation contribute to increased cardiovascular morbidity and mortality associated with activation of the renin-angiotensin (Ang)-aldosterone system (RAAS). Studies in cultured cells in vitro and in rodent models in vivo demonstrate that aldosterone and/or mineralocorticoid receptor (MR) activation cause oxidative stress and vascular inflammation. Translational studies in humans suggest that endogenous aldosterone increases inflammatory biomarkers through an MR-dependent pathway. Clinical studies indicate that the prevalence of hyperaldosteronism may be increased in resistant hypertension, that aldosterone concentrations “escape” to pretreatment levels during chronic treatment of congestive heart failure or hypertension with an Ang-converting enzyme (ACE) inhibitor or Ang receptor blocker, and that MR antagonism decreases mortality in congestive heart failure. This article reviews the current literature regarding mechanism(s) of aldosterone-induced vascular inflammation and its implications for the prevention of vascular injury in humans.

Role of Inflammation in Atherosclerosis and Vascular Remodeling

Oxidative stress and inflammation play central roles in the pathogenesis of atherosclerosis. Reactive oxygen species, including superoxide and hydrogen peroxide, modify vascular low-density lipoproteins to form oxidized low-density lipoproteins. Low-density lipoproteins stimulate endothelial cells to express leukocyte adhesion molecules, such as vascular cell adhesion molecule, leading to the recruitment of monocytes and T lymphocytes, which invade the intima. Monocyte-derived macrophages, rich in nicotinamide-adenine-dinucleotide phosphate (NADPH) oxidase, amplify the generation of reactive oxygen species. Macrophages take up oxidized low-density lipoproteins via scavenger receptors to become foam cells. T cells and macrophages within atherosclerotic lesions produce chemokines and cytokines resulting in the migration and proliferation of vascular smooth muscle cells (VSMCs) within the intima. VSMCs, in turn, promote extracellular matrix formation and secrete matrix metalloproteinases, contributing to the pathogenesis of plaque rupture.

Inflammation also triggers a cascade that leads to fibrosis and vascular remodeling. During inflammation, the recruitment of monocytes and macrophages promotes a proliferation of fibroblasts in the perivascular space. Cytokines like interleukin (IL)-6 stimulate the expression of profibrotic factors, such as transforming growth factor (TGF)-β and plasminogen activator inhibitor (PAI)-1. TGF-β stimulates cellular transformation to fibroblasts, increasing the synthesis of matrix proteins and integrins and decreasing production of matrix metalloproteinases. The net effect is increased collagen production and decreased extracellular matrix degradation, leading to fibrosis.

Activation of the RAAS Contributes to Oxidative Stress and Vascular Inflammation

It is now well-established that Ang II activates NADPH oxidases in VSMCs, monocytes, macrophages, and endothelial cells to produce reactive oxidant species. These reactive oxygen species stimulate the activation of proinflammatory transcription factors activator protein-1 and nuclear factor (NF)κB. NF-κB induces the production of adhesion molecules, chemokines such as monocyte chemoattractant protein (MCP)-1, and inflammatory cytokines. Recruitment of monocytes and macrophages may enhance the activity of the local vascular RAAS, because monocytes and macrophages express angiotensinogen, renin, ACE, and the Ang subtype 1 (AT1) receptor. Thus, upregulation of the RAAS during monocyte differentiation to macrophages may amplify monocyte migration into the vascular wall.

Recent data from Guzik et al further support a role for vascular inflammation in the pathogenesis of Ang II–induced hypertension. Fourteen-day infusion of Ang II caused T-lymphocyte infiltration in the aortic adventitia and periaortic fat, vascular superoxide production, endothelial dysfunction, and hypertension in mice. Mice lacking T and B lymphocytes were protected against the development of oxidative stress, endothelial dysfunction, and hypertension, whereas adoptive transfer of T cells, but not B cells, restored the hypertensive response to Ang II. Hypertension was also prevented by the tumor necrosis factor-α antagonist etanercept.

Aldosterone Induces Inflammation in Rodent Models

Seminal studies in rat models in the 1990s demonstrated that MR activation causes perivascular and interstitial fibrosis in rodent models.
inflammatory response. Aldosterone upregulates the lymphocyte chemoattractant factor MCP-1 and migration inhibitory factor in the kidney.

Increased cytokines and MR activation also increase the expression of PAI-1. PAI-1, a member of the serpin superfamily and the major physiological inhibitor of tissue-type plasminogen activator and urokinase plasminogen activator in vivo, decreases both direct and indirect effects of plasmin on extracellular matrix degradation but also decreases plasmin-mediated activation of TGF-β and cell migration. Thus, whereas PAI-1 contributes to vascular remodeling and renal injury during excess Ang II or aldosterone, increased PAI-1 expression protects against cardiac fibrosis, likely by decreasing urokinase-dependent macrophage infiltration.

**Microarray Studies Confirm the Proinflammatory Effects of Aldosterone**

Whole animal studies of the proinflammatory effects of aldosterone may be confounded by systemic effects on sodium and potassium homeostasis. Genetic expression studies in cultured VSMCs and cardiomyocytes confirm the proinflammatory and profibrotic effects of aldosterone. Exposure of human coronary artery smooth muscle cells to aldosterone upregulates the lymphocyte chemoattractant factor IL-16 and cytotoxic T-lymphocyte–associated protein 4, as well as type I and type III collagens. Fejes-Tóth and Náróy-Fejes-Tóth demonstrated that exposure of MR-expressing cardiomyocytes to a physiological concentration (1 nM) of aldosterone in vitro induces rapid increases in the

**Figure.** Cartoon of mechanism(s) of aldosterone-induced vascular fibrosis: aldosterone, acting at the MR, affects the transcription of proinflammatory genes. Aldosterone also causes rapid, transcription-independent effects. Aldosterone activates NADPH oxidases to produce reactive oxygen species (O2•−). Ang II increases MR-dependent transcription in VSMCs via its AT1 receptor. Aldosterone and Ang II phosphorylate ERK1/2 through genomic and nongenomic pathways. Nongenomic pathways involve transactivation of the EGFR. Increased oxidative stress and activation of ERK result in the expression of proinflammatory transcription factors, adhesion factors, such as intercellular adhesion molecule (ICAM)-1, and chemokines like MCP-1. Leukocytes secrete inflammatory cytokines (IL-6), which, in turn, promote expression of profibrotic factors, such as TGF-β and PAI-1.

The heart, aortic fibrosis and remodeling, and renal injury. Work, completed over the last decade, established a critical role for inflammation in initiating fibrosis and remodeling in response to exogenous aldosterone or MR activation. For example, Fiebeler et al investigated the contribution of MR activation to proinflammatory and profibrotic mediators in the heart of rats doubly transgenic for the human renin and angiotensinogen genes. MR antagonism prevented vascular injury and cardiac fibrosis, activation of activator protein-1 and NF-κB, and upregulation of basic fibroblast growth factor in the hearts of rats doubly transgenic for the human renin and angiotensinogen genes. MR antagonism prevents vascular injury and cardiac fibrosis, activation of activator protein-1 and NF-κB, and upregulation of basic fibroblast growth factor in the hearts of rats doubly transgenic for the human renin and angiotensinogen genes. Rocha et al demonstrated that 4-week treatment with aldosterone and salt caused extensive inflammatory arterial lesions with perivascular macrophages in the heart. MR blockade decreased this inflammatory response. Aldosterone/salt also increased the expression of intercellular adhesion molecule, cyclooxygenase-2, osteopontin, and MCP-1 effects that were decreased by MR blockade.

MR antagonism decreases aortic inflammation, fibrosis, and hypertrophy in hypertensive rats. MR antagonism decreases oxidative stress and inflammation, as measured by tumor necrosis factor-α and MCP-1 expression, in apoipoprotein E–deficient mice fed a high-cholesterol diet, a model of atherosclerosis. Furthermore, like Ang II, the mineralocorticoid deoxycorticosterone acetate causes aortic superoxide production and hypertension through a T-cell–dependent mechanism.

Treatment of rats with aldosterone and salt causes perivascular leukocyte infiltration and increased expression of osteopontin, MCP-1, IL-6, and IL-1β in the kidney, as well, through an MR-dependent mechanism. Treatment with deoxycorticosterone acetate and salt also causes leukocyte infiltration and increased expression of NADPH oxidase and hemoxygenase-1 subunits, cyclooxygenase-2, osteopontin, and TGF-β in the kidney; interestingly, Lam et al have reported that MR antagonism reduces expression of cyclooxygenase-2 and NADPH oxidase subunits but not leukocyte infiltration or osteopontin expression in this model. In contrast, Fiebeler et al reported that aldosterone synthase inhibition or AT1 receptor antagonism decreased monocyte, macrophage, and CD24 T-cell infiltration in the kidneys of rats doubly transgenic for the human renin and angiotensinogen genes. MR activation also contributes to inflammatory changes in diabetic nephropathy; thus, treatment of type 1 or type 2 diabetic rats with an MR antagonist decreases macrophage infiltration and expression of MCP-1 and migration inhibitory factor in the kidney.

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expression of genes involved in inflammation and fibrosis, including orosomucoid-1, PAI-1, and tenasin-X.

Aldosterone Stimulates Inflammation Through the Generation of Reactive Oxygen Species

Like Ang II, aldosterone activates NADPH oxidases in rat VSMCs.41 Similarly, aldosterone increases expression of the NADPH oxidase subunit p22phox in human monocytes52 and promotes apoptosis in human renal proximal tubular cells via the MR-dependent generation of reactive oxygen species.43 In human endothelial vein cells, aldosterone inhibits NO synthase by inducing the oxidation of its cofactor 5,6,7,8-tetrahydrobiopterin, as well as by activating protein phosphatase 2A.44 Aldosterone treatment also produces oxidative stress and endothelial dysfunction in mice by decreasing the vascular expression of glucose-6-phosphate dehydrogenase, which reduces oxidized nicotinamide-adenine dinucleotide phosphate to NADPH.45

Systemic administration of aldosterone increases oxidative stress in the heart,46 vasculature, and kidney47–49 and increases macrophage NADPH oxidase (Figure).50 MR activation contributes to Ang II–mediated activation of NADPH oxidase in the heart and aorta.51–53 Exogenous aldosterone stimulates aortic expression of p22phox and NOX2 (gp91phox) through an MR-dependent mechanism and of p47phox mRNA through both AT1 receptor and MR-dependent mechanisms.48 Increased oxidative stress activates the redox sensitive NF-κB, triggering inflammation. Hence, aldosterone-stimulated activation of NF-κB in the heart is prevented in NOX2-deficient mice.52 Likewise, the administration of antioxidant drugs, such as the superoxide dismutase mimetic Tempol,47,48,54 the NADPH oxidase inhibitor apocynin,55 or N-acetylcysteine56 decreases inflammation and injury in aldosterone-treated rodents. Increased expression of endothelin may also contribute to oxidative stress and increased expression of adhesion molecules during mineralocorticoid excess.56–58

High salt intake enables the effects of aldosterone on oxidative stress, inflammation, and fibrosis in whole animal models through a potassium-independent mechanism.59 Aho- kas et al60 have noted that, during high salt intake, activation of the MR causes Ca2+ loading and a fall in cytosolic free-ionized Mg2+ in monocytes and cardiomyocytes through a mechanism involving Na+-Mg2+ and Na+-Ca2+ exchangers. Intracellular Ca2+ loading, in turn, causes oxidative stress. Mihailidou and Funder61 suggest that changes in intracellular redox potential result in activation of cortisol (corticosterone)-MR complexes in non epithelial tissues, such as the heart. Uptregulation of local tissue RAAS (in contrast to the circulating RAAS) during high salt intake may also contribute to oxidant stress.62 Interestingly, in the presence of aldosterone, small increases in plasma sodium decrease NO release and increase the stiffness of endothelial cells in culture.63

Complex Interactions Among Ang II, Aldosterone, and Their Receptors Contribute to Inflammation

Although aldosterone induces vascular inflammation through direct effects at the MR, aldosterone also enhances the proinflammatory effects of Ang II. For example, aldosterone increases vascular ACE expression and local Ang II concentrations.48,64,65 Aldosterone upregulates vascular AT1 receptor expression.66,67 Aldosterone potentiates Ang II–induced signaling via activation of mitogen-activated protein kinases in VSMCs.68 Conversely, Ang II activates MR responsive elements through an AT1-dependent mechanism in human coronary artery smooth muscle cells.59 Activation of the MR by Ang II does not involve aldosterone synthesis, because aldosterone synthase inhibition does not prevent the effect. In vivo, treatment with an AT1 receptor antagonist can prevent aldosterone-induced perivascular inflammation and fibrosis in the heart.69

Glucocorticoids also activate the MR, possibly explaining the observation that MR antagonism decreases inflammation even under conditions when endogenous aldosterone concentrations are not elevated. The MR binds cortisol and aldosterone with equal affinity. In epithelial tissues, the enzyme 11β-hydroxysteroid 2 converts cortisol (or, in rodents, corticosterone) to its inactive 11-ketometabolite, such that MRs are activated primarily by aldosterone.70 Cardiomyocytes do not express 11β-hydroxysteroid 2, and, therefore, cortisol, present in higher concentrations, acts as the primary MR ligand.71 In contrast, the vasculature expresses 11β-hydroxysteroid 2 such that aldosterone activates the MR. The observation that cardiomyocyte-specific overexpression of 11β-hydroxysteroid 2 in mice causes cardiac hypertrophy and fibrosis, which is reversed by eplerenone, has led investigators to hypothesize that cortisol (corticosterone) exerts a tonic inhibitory effect at the MR in the heart54; as noted earlier, Mihailidou and Funder61 proposed that changes in intracellular redox potential activate cortisol MR during high salt intake.

Aldosterone Can Exert Proinflammatory Effects via MR-Dependent and -Independent Pathways

Activation of the MR by aldosterone results in its dissociation from molecular chaperones, translocation into the nucleus, and binding to hormone response elements in the regulatory region of target gene promoters to enhance expression. Aldosterone can also exert rapid, nongenomic effects, however, particularly in VSMCs, and many of these effects are not blocked by the MR antagonist spironolactone but may be blocked by its open-ring, water-soluble metabolite, canrenone, or by eplerenone.72,73 Studies in fibroblasts derived from MR-deficient mice and in MR-transfected cells suggest that the MR contributes to the rapid effects of aldosterone on the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and c-Jun NH2-terminal kinase pathway but not to rapid effects on calcium.74,75 In rabbit heart, aldosterone increases Na+/K+-2Cl− cotransporter activity and decreases Na+/K+ pump activity through a nongenomic effect on protein kinase C-ε,76 which stimulates NF-κB activation via mitogen-activated protein kinases.77 Although MR antagonists prevent the inflammatory effects of aldosterone in most rodent models, studies in cultured VSMCs suggest the possibility of an MR-independent proinflammatory effect of aldosterone.
Specifically, in VSMCs, phosphorylation or activation of p38, mitogen-activated protein kinases, and ERK1/2 results in the production of cytokines and chemokines. Aldosterone rapidly activates ERK1/2 in VSMCs. Aldosterone also enhances both rapid and delayed activation of ERK1/2 by Ang II. Treatment with spironolactone or with inhibitors of transcription and protein synthesis prevent the late effect of aldosterone and Ang II, suggesting that this effect occurs through an MR-dependent, genomic pathway. In contrast, spironolactone does not block rapid phosphorylation of ERK1/2 by aldosterone. The early phase involves the trans-activation of the epidermal growth factor receptor (EGFR), whereas the late phase involves increased expression of the fibrotic and proliferative small and monomeric GTP-binding protein Ki-ras2A and mitogen-activated protein kinase.

Evidence for a Proinflammatory Effect of Aldosterone in Humans

In rodent models of hyperaldosteronism, vascular inflammation can be assessed directly by quantification of monocyte and macrophage infiltration of the vascular wall. New imaging techniques, such as fluorodeoxyglucose positron-emission tomography, allow for the assessment of local vascular inflammation in humans. To date, however, studies of the proinflammatory effects of aldosterone or MR activation in humans have relied on the measurement of circulating biomarkers of inflammation. These include the chemokines tumor necrosis factor-α and MCP-1, inflammatory cytokines, C-reactive protein, and PAI-1. Although beyond the scope of the present review, elevations of many of these biomarkers have been associated with the development of hypertension and with endothelial dysfunction, cardiovascular events, and renal injury in hypertensive patients.

Irita et al compared concentrations of IL-6, tumor necrosis factor-α, C-reactive protein, and osteopontin in the sera or plasma of patients with primary hyperaldosteronism and in age-matched patients with essential hypertension; osteopontin concentrations were higher in primary hyperaldosteronism. Increased osteopontin expression contributes to atherosclerosis and vascular remodeling, and primary hyperaldosteronism is associated with endothelial dysfunction, cardiac fibrosis, and increased risk of myocardial infarction, stroke, and atrial fibrillation.

Twelve-hour infusion of aldosterone increases circulating IL-6 and IL-12 concentrations in normal volunteers to levels comparable to those associated with endothelial dysfunction after vaccination. Intravenous infusion of Ang II also increases IL-6 concentrations. This effect is blocked by spironolactone, suggesting that Ang II induces inflammation via an MR-dependent mechanism. Although these studies used exogenous Ang II or aldosterone to achieve supraphysiological concentrations, activation of the endogenous RAAS by low salt intake or diuretic use is associated with increased circulating concentrations of IL-6 and PAI-1.

Studies using spironolactone or eplerenone further elucidate the effect of endogenous aldosterone or MR activation on oxidative stress and inflammatory biomarkers. The results of these studies differ, depending on the biomarker studied. Takebayashi et al compared the effect of spironolactone and the calcium channel blocker amlopidine on oxidative stress, as measured by urinary excretion of F2-isoprostanes, and on urinary excretion of MCP-1. Although both drugs decreased blood pressure, only spironolactone decreased urinary F2-isoprostanes and MCP-1.

Our group has studied the effect of spironolactone on circulating PAI-1 concentrations. PAI-1 represents both an acute-phase reactant and a potent inhibitor of fibrinolysis. Aldosterone and PAI-1 have been reported to predict the development of the metabolic syndrome in the Framingham Offspring Study. Spiroloactone decreases PAI-1 concentrations in hypertensive subjects taking hydrochlorothiazide, whereas the MR-independent potassium-sparing diuretic triamterene does not. MR and AT1 antagonists synergistically decrease PAI-1 concentrations in diuretic-treated normotensive subjects. Two other groups have reported that spironolactone decreases PAI-1 concentrations. In contrast, MR antagonists do not seem to decrease concentrations of C-reactive protein.

Perspectives

Studies in vitro and in vivo in rodent models indicate an important role for aldosterone and MR activation in the induction of oxidative stress and inflammation leading to endothelial dysfunction and vascular remodeling during activation of the RAAS. Oxidative stress and inflammation result from complex interactive effects of aldosterone on the actions of Ang II at its AT1 receptor, as well as from activation of the MR by Ang II and other ligands. Moreover, in the vasculature, the activation of inflammatory signaling pathways may involve both genomic and nongenomic mechanisms.

Studies indicating that exogenous aldosterone and Ang II increase, whereas MR blockade decreases, inflammatory or fibrotic biomarkers in humans confirm the relevance of these findings. MR blockade reduces mortality in patients with congestive heart failure or left ventricular dysfunction after myocardial infarction, and in the Randomized Aldactone Evaluation Study the effect of spironolactone on a biomarker of fibrosis, procollagen type III amino-terminal peptide, predicted the reduction in mortality. Given recent data in the mouse indicating that vascular inflammation contributes to the development of hypertension during activation of the RAAS, as well as data from epidemiologic studies indicating that circulating biomarkers of inflammation predict the development of hypertension, furthermore, it is possible that the proinflammatory effects of aldosterone or MR activation could also contribute to the development of hypertension in humans.

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References


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