Mineralocorticoid Receptors, Salt-Sensitive Hypertension, and Metabolic Syndrome

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Abstract—Obese persons with metabolic syndrome often have associated with salt-sensitive hypertension, microalbuminuria, and cardiac dysfunction, and the plasma aldosterone level in one-third of metabolic syndrome patients is clearly elevated. Hyperaldosteronism, which may be caused at least partially by certain adipocyte-derived factors, contributes to the development of proteinuria in obese hypertensive rats, and salt loading aggravates the proteinuria and induces cardiac diastolic dysfunction because of inadequate suppression of plasma aldosterone level. However, mineralocorticoid receptor (MR) antagonists prevent salt-induced renal and cardiac damage, suggesting that aldosterone excess and a high-salt diet exert an unfavorable synergistic action on the kidney and heart. In Dahl salt-sensitive rats, however, despite appropriate suppression of plasma aldosterone with a high-salt diet, salt loading paradoxically activated renal MR signaling, and the renal injury was markedly prevented by MR antagonists. Accordingly, we discovered an alternative pathway of MR activation in which Rac1, a small GTP-binding protein, activates MRs. Salt loading activates renal Rac1 in Dahl salt-sensitive rats, and Rac1 in turn induces MR activation, which results in renal injury, and the renal injury has been found to be prevented by Rac1 inhibitors. Moreover, several metabolic syndrome-related factors induce Rac1 activation, and one of them, hyperglycemia, activates MRs via Rac1 activation. Consistent with this, Rac1 inhibitors attenuated the proteinuria and renal injury in obese hypertensive animals. Thus, both salt and obesity activate Rac1 and cause MR activation. Abnormal activation of the aldosterone/MR pathway plays a key role in the development of salt-sensitive hypertension and renal injury in metabolic syndrome. (Hypertension. 2010;55:813-818.)

Key Words: salt • aldosterone • mineralocorticoid receptor • Rac1 • obesity

It is well known that populations with a high dietary salt intake have higher incidences of hypertension, and salt loading not only increases blood pressure (BP) but causes cardiovascular damage in animals and humans.1-3 We showed recently that salt exerted a more injurious effect on the kidneys and heart of obese hypertensive rats with metabolic syndrome than in lean hypertensive rats.4-6 In a recent investigation to identify the mechanism of the salt-induced cardiovascular damage, we discovered signaling cross-talk between Rac1 and mineralocorticoid receptor (MR), an alternative pathway that modulates MR activity,7 and we obtained evidence suggesting that abnormal activation of the aldosterone/MR pathway is involved in the development of salt-induced hypertension and cardiovascular damage in metabolic syndrome.8,9

Mechanism of Salt-Sensitive Hypertension in Metabolic Syndrome

The BP of individual hypertensive patients responds differently to salt loading,1-4 and environmental factors and genetic factors may be involved in the salt sensitivity of BP. Recent clinical studies have demonstrated that metabolic syndrome is an important non-genetic factor that increases the salt sensitivity of BP.10,11

Although the precise mechanism of the salt-induced BP elevation is still unknown, impaired renal sodium excretion has been hypothesized to be the primary cause of all hypertension.12 Patients with salt-sensitive hypertension have abnormal renal function curves for urinary sodium excretion.13 Several factors modulate renal sodium excretion capacity: race, aging, psychological stress, and obesity.12 Indeed, the renal function curve of obese hypertensives is identical to that of salt-sensitive–type hypertensives,10 and, consistent with this finding, obese hypertensive patients have a greater depressor response to salt restriction on a low-salt diet than lean hypertensive patients.10 In addition, a recent Chinese study showed that the subjects with metabolic syndrome exhibited a greater depressor response to a low-salt diet and a greater pressor response to a high-salt diet than a control group that did not have metabolic syndrome.14 There is a close relationship between insulin resistance, which is essential in metabolic syndrome, and salt sensitivity of BP,10,11 because insulin resistance appears in salt-sensitive compared with salt-resistant normotensive subjects,15 and salt loading causes the development of insulin resistance in young adult black subjects.16
According to the mechanism of obesity-induced, salt-sensitive hypertension, several factors induce abnormal natriuresis and increased salt sensitivity of BP in metabolic syndrome. Compression of the kidney, compensatory hyperinsulinemia because of insulin resistance, sympathetic overactivity, increased activity of the renin-angiotensin (RA) system, and aldosterone excess in plasma have been found to be common in obese persons, and all of these parameters modulate natriuresis. Hall and colleagues demonstrated that aldosterone administration to dogs not only induced sodium retention but increased their BP. We have shown recently that abnormal activation of the aldosterone/MR pathway may be involved in the development of cardiovascular damage, as well as salt-sensitive hypertension in metabolic syndrome.

**Involvement of Aldosterone Excess in Obesity-Induced Proteinuria**

Aldosterone was long thought to be a hormone that regulates electrolytes, fluid volume, and BP homeostasis. However, a paradigm shift has occurred in the field of aldosterone research, with recent studies suggesting that aldosterone is an important mediator of target-organ damage. Aldosterone acts directly on the heart, the brain, and the kidney, and aldosterone excess causes proteinuria and chronic kidney disease. Immunoostaining for MR in the rat kidney has revealed clear staining not only in the cortical collecting ducts but also in the glomeruli, and both MR mRNA and protein are expressed in cultured podocytes. Exposure to aldosterone induces apoptosis in cultured podocytes, and aldosterone administration and a high-salt diet induce massive proteinuria and less intense immunostaining for nephrin, a podocyte marker, in unilaterally nephrectomized rats. These findings suggest that aldosterone-induced proteinuria and renal damage are attributable to podocyte injury, because several investigators have demonstrated that podocyte injury plays a pivotal role in the development of albuminuria and the progression of kidney disease.

Epidemiological studies have shown that metabolic syndrome increases the risk of microalbuminuria, and some investigators have reported clearly increased plasma aldosterone levels in severely obese subjects. In obese spontaneously hypertensive rats (SHRs), a model of metabolic syndrome manifested by a cluster of visceral obesity, hypertension, insulin resistance, and dyslipidemia, urinary protein excretion was found to be markedly increased in an age-dependent manner that was associated with foot process effacement, suggesting podocyte injury. Interestingly, the serum aldosterone level was clearly higher in the obese SHRs than in the nonobese SHRs. Gene expression of serum- and glucocorticoid-inducible kinase1 (Sgk1), a downstream molecule of MR signaling, was also upregulated in the kidney of the obese SHRs. Consistent with these findings, administration of the MR blocker eplerenone markedly decreased the proteinuria, and reversed the podocyte injury in salt-loaded obese SHRs. Although aldosterone excess may contribute to the renal damage in obese SHRs, it now recognized as a dynamic endocrine organ that secretes a variety of adipokines, tumor necrosis factor (TNF)-α, nesfatin-1, fatty acids, and interleukin (IL) 6. Adipokine dysregulation in metabolic syndrome is the consequence of both adipose cell enlargement and the associated infiltration by macrophages. Cytokines, such as TNF-α and IL-6, which are overproduced by the macrophages that infiltrate adipose tissue, impair insulin action and signaling by different mechanisms, leading to insulin resistance. Components of the RA system, including angiotensinogen, are also present in adipose tissue, and their presence may not only induce insulin resistance and hypertension but may also stimulate aldosterone secretion. Goodfriend et al also reported that some adipocyte-derived factors, including an epoxy-keto derivative of linoleic acid, stimulate aldosterone secretion by the adrenal glands, and Ehrhart-Bornstein et al recently reported the existence of as-yet-unidentified adipocyte-derived factors that contribute to aldosterone synthesis in the adrenal gland. In our own study we evaluated the aldosterone secretagogue activity of fat-cell–conditioned medium from adrenal cell cultures and found that the activity of fat-cell–conditioned medium in obese SHRs was significantly greater than that in nonobese SHRs. Adipocyte-derived aldosterone releasing factors (ARFs) stimulate aldosterone secretion by the renal gland, leading to aldosterone excess in obese SHRs. There are several candidates for adipocyte-derived ARFs in addition to the as-yet-unidentified ARFs, TNF-α, C1q/ TNF-α–related protein-1, linoleic acid oxidative products, leptin, and IL-6.

Although the precise mechanism of the secretion of ARFs by adipocytes remains unknown, there is an abnormal relationship between ARF secretion and dietary salt intake. The activity of the RA-aldosterone system is usually counterbalanced by salt intake, and then high-salt intake suppresses the activity of the RA-aldosterone system. However, there is no negative feedback regulation of adipocyte ARF secretion by salt. Since Brilla and Weber published their landmark article on experimental cardiac fibrosis, several investigators have demonstrated that salt is required for aldosterone-induced cardiovascular damage to occur, because severe aldosterone-induced cardiac fibrosis occurred on a high-salt diet, but no fibrosis occurred on a low-salt diet. This suggests that aldosterone exerts adverse effects when its concentration in plasma is inappropriate for salt status. Consistent with this, the high-salt diet markedly aggravated the proteinuria and podocyte injury that were associated with the inadequate salt-induced suppression of plasma aldosterone level in obese SHRs, although plasma aldosterone was appropriately decreased by salt loading in nonobese SHRs. Moreover, gene expression of MR and Sgk1 in the kidney upregulated by a high-salt diet in obese SHRs suggests that salt loading potentiates MR activation. Corroborating this, treatment with the MR blocker eplerenone dramatically improved the proteinuria and reversed the podocyte injury in salt-loaded obese SHRs (Figure 1). Moreover, administration of a high-salt diet to obese SHRs induced cardiac diastolic dysfunction that was associated with perivascular fibrosis and upregulation of Sgk1 and connective tissue growth factor in the heart. However, the salt-induced diastolic dysfunction in the obese...
SHRs was reversed by eplerenone, and all of the parameters were recovered (Figure 1).

Thus, adipose tissue secretes ARFs in metabolic syndrome, and ARF-induced aldosterone secretion cannot be adequately suppressed by a high-salt diet, suggesting that inappropriate secretion of ARFs by adipocytes causes hyperaldosteronism (type 1 metabolic syndrome). Therefore, aldosterone excess and a high-salt diet can synergistically induce MR activation, and the MR activation leads to the development of renal injury and cardiac dysfunction (Figure 2). Supporting this, an epidemiological study showed that obese subjects on a high-salt diet developed proteinuria in a salt intake–dependent manner but that nonobese subjects did not develop proteinuria at all. We suspect that most of the obese subjects in that study must have had an aldosterone excess, although plasma aldosterone was not measured in that study.

Alternative Pathway of MR Activation
In one study, one third of the metabolic syndrome subjects had hyperaldosteronism, but not all of the subjects had a high plasma aldosterone concentration. Despite the absence of hyperaldosteronism, treatment with an MR antagonist is the most effective way to reduce urinary albumin excretion in diabetic hypertensives with albuminuria. It should be noted, however, that serum aldosterone levels are not always predictive of the efficacy of MR antagonists, suggesting that MR activation occurs even in the absence of aldosterone excess, possibly via an alternative pathway of MR activation. It is interesting that Quinkler et al demonstrated a 5-fold increase in renal MR expression in patients with renal failure and heavy proteinuria, thereby linking MR activation to kidney disease.

Although the precise mechanism of regulation of MR activation remains unknown, several lines of evidence suggest that nuclear receptor activation is influenced by factors other than the ligand, that is, by nuclear translocation, chromatin, histones, coactivators, corepressors, other transcription factors, and cross-talk with intracellular signaling. Several investigators have reported identifying activators of steroid receptors, including activators of estrogen receptors, glucocorticoid receptors, androgen receptors, and MRs, that is, SRC-1, Ras, mitogen-activated protein kinase, Smad3, protein kinase A, Ubc9, and Rho GTPases. Small GTP-binding protein Rac1 is a member of the Rho family of GTPases, which includes RhoA and Cdc42, and it regulates diverse biological processes, including actin cytoskeletal organization, cell migration, and activation of NADPH oxidase. Several investigators have recently reported a novel role of Rac1 in the regulation of nuclear translocation of transcription factors. Rac1 is essential for the nuclear translocation of β-catenin in canonical Wnt signaling, and Rac1 also plays a key role in the nuclear translocation of signal transducer and activator of transcription 3/5 in cytokine signaling. We recently identified a new role for Rac1 as a potent activator of MR signal transduction.

In an in vitro study assessing the nuclear trafficking of MR in HEK 293 cells, MR-green fluorescent protein (GFP) was
found to be mainly distributed in the cytoplasm but to promptly become targeted to the nucleus on activation by aldosterone. Even without aldosterone, overproduction of constitutively active (CA)-Rac1 in cells apparently can induce nuclear translocation of MR-GFP, and, consistent with this, Western blotting showed that CA-Rac1 substantially increased nuclear MR-GFP in the absence of aldosterone. In the presence of aldosterone, CA-Rac1 further increased nuclear MR-GFP, suggesting that aldosterone potentiates Rac1-induced MR activation. Corroborating this, a luciferase reporter assay showed that overexpression of CA-Rac1 in HEK 293 cells significantly potentiated aldosterone-stimulated MR transcriptional activity. CA-Rac1 potentiated MR transcriptional activity even in the absence of aldosterone, but when aldosterone was added, the level of transcriptional activity was 20 times greater, suggesting that aldosterone increases Rac1-induced MR activation. CA-Rac1 was also found to promote nuclear translocation of MR-GFP in glomerular podocytes. We attempted to identify the possible downstream target of Rac1 and found that CA-Rac1 facilitated phosphorylation of p21-activated kinase. However, the CA-Rac1–induced nuclear translocation of MR was inhibited by a p21-activated kinase inhibitor, suggesting that Rac1 promotes nuclear shuttling of MR via p21-activated kinase. Taken together, the results of in vitro studies show that activation of Rac1 in both HEK cells and podocytes induces MR activation, both in an aldosterone-dependent and -independent manner.

To investigate whether the Rac1-evoked MR activation contributes to the pathogenesis of kidney disease, we performed an in vivo study in Rho GDP dissociation inhibitor (RhoGDI)α-knockout (KO) mice, in which kidney-specific Rac1 activation has been found to occur. RhoGDIα is a negative regulator of the Rho GTPase. Upregulation of GTP-Rac1, that is, active Rac1, was observed in the kidney of the RhoGDIα-KO mice, and it exhibited severe proteinuria and glomerulosclerosis. Electron microscopy revealed extensive foot process effacement, suggesting podocyte injury. Rac1 activity was found to be upregulated in the kidneys of RhoGDIα-KO mice, but RhoA activity was not. Consistent with this finding, urinary albumin excretion was inhibited by administration of the Rac1-specific inhibitor, whereas the Rho kinase inhibitor fasudil had no effect on it. Moreover, nuclear MR protein in the kidney is upregulated in Rac1-activated mice, despite comparable serum aldosterone levels, suggesting the occurrence of aldosterone-independent MR activation. This was supported by our preliminary study showing that the absence of aldosterone in the body induced by adrenalectomy moderately inhibited the albuminuria in salt-loaded RhoGDIα-KO mice, but the level of the albuminuria was still higher than that in wild-type mice by the increased renal Rac1 activity. Administration of a Rac1 inhibitor antagonized the increased MR signaling in the kidneys of these mice, as assessed by measurements of Sgk1, plasminogen activator inhibitor 1, and monocyte chemotactic protein 1, which are downstream mediators of MR signaling, suggesting that Rac1-induced MR activation had occurred. In support of this, administration of the MR blocker eplerenone markedly decreased urinary albumin excretion. Moreover, the protective effect of MR blockade on podocytes was confirmed by histological analysis, showing that downregulation of the podocyte marker Wilms’ tumor 1 was corrected by eplerenone, and there was an associated reversal of the foot process effacement.

Taken together, Rac1 activates MR independent of aldosterone, but Rac1-induced MR activation is markedly enhanced in the presence of aldosterone. Thus, changes in plasma aldosterone concentrations and the Rac1 activity may modulate MR activation, interdependently, leading to the conclusion that Rac1-induced MR activation may be involved in the pathogenesis of proteinuric kidney diseases, both aldosterone dependently and independently.

**Factors Modulating Rac1 Activation**

Because RhoGDIα-KO mice are an artificial model of renal Rac1 activation, the next question is, what mechanism might contribute to renal Rac1 activation in metabolic syndrome? Several investigators have reported finding that certain cytokines are capable of activating Rac1, and adipocyte-derived factors, such as TNF-α and IL-6, also activate Rac1. Interestingly, Rac1 is essential for the nuclear translocation of signal transducer and activator of transcription 3/5 in cytokine signaling. Moreover, IL-6 increases gene expression of angiotensinogen in renal cells, and angiotensin II activates Rac1, leading to the activation of signal transducer and activator of transcription 3. This suggests that the RA system in the kidney is involved in renal Rac1 activation, because angiotensin II is present not only in plasma but also in the kidney and adipose tissue. This was supported by the discovery of increases in kidney angiotensin II levels in Otsuka Long-Evans Tokushima Fatty rats, a model of type 2 diabetic nephropathy. Moreover, hyperglycemia also activates Rac1 in the heart, and active Rac1 induces cardiomyocyte apoptosis. That led us to hypothesize that both cytokine overproduction and hyperglycemia play pivotal roles in Rac1 activation in metabolic syndrome, and, consistent with this hypothesis, we have obtained preliminary data showing that Rac1 is upregulated in the kidneys of obese SHR and obese metabolic syndrome mice, both of which are animal models.

![Salt](https://example.com/salt.png) ![Rac1](https://example.com/rac1.png) ![MR](https://example.com/mr.png) ![CKD](https://example.com/ckd.png) ![Salt-Sensitive](https://example.com/salt-sensitive.png) ![CVD](https://example.com/cvd.png)

**Figure 3.** Hypothesized involvement of aldosterone/MR pathway activation in the development of chronic kidney disease (CKD), cardiovascular disease (CVD), and salt-sensitive hypertension in obese patients with type 2 metabolic syndrome who do not have hyperaldosteronism. Both adipocyte-derived factors and a high-salt diet are capable of activating Rac1, and active Rac1, in turn, activates MRs.
of metabolic syndrome. Rac1 inhibitors moderately decreased proteinuria in both models, suggesting that adipokines or hyperglycemia might contribute to Rac1 activation in the kidney of these models of metabolic syndrome rat.

According to the effect of salt loading on Rac1 activation and proteinuria, in our study renal Rac1 was found to be activated by a high-salt diet in Dahl salt-sensitive rats, and the activation was associated with massive proteinuria. However, administration of Rac1 inhibitors moderately attenuated the proteinuria. Consistent with these findings, Sgk1, a downstream molecule of MR, was paradoxically upregulated by salt loading, despite appropriate suppression of plasma aldosterone, but Rac1 inhibition attenuated the upregulation, suggesting that salt loading induces MR activation via Rac1 activation. In support of this, administration of the MR blocker eplerenone markedly decreased the proteinuria.

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