Aldosterone: Role in the Cardiometabolic Syndrome and Resistant Hypertension

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Abstract

The prevalence of diabetes, hypertension, and cardiovascular disease (CVD) and chronic kidney disease (CKD) is increasing in concert with obesity. Insulin resistance, metabolic dyslipidemia, central obesity, albuminuria and hypertension commonly cluster to comprise the cardiometabolic syndrome. Emerging evidence supports a shift in our understanding of the crucial role of elevated serum aldosterone in promoting insulin resistance and resistant hypertension. Aldosterone enhances tissue generation of oxygen free radicals and systemic inflammation. This increase in oxidative stress and inflammation, in turn, contributes to impaired insulin metabolic signaling, reduced endothelial-mediated vasorelaxation and associated cardiovascular and renal structural and functional abnormalities. In this context, recent investigation indicates that hyperaldosteronism, which is often associated with obesity, contributes to impaired pancreatic beta-cell function as well as diminished skeletal muscle insulin metabolic signaling. Accumulating evidence indicates that the cardiovascular and renal abnormalities associated with insulin resistance are mediated, in part, by aldosterone’s non-genomic as well as genomic signaling through the mineralocorticoid receptor (MR). In the cardiometabolic syndrome there are increased circulating levels of glucocorticoids, which can also activate MR signaling in cardiovascular, adipose, skeletal muscle, neuronal, and liver tissue. Further, there is increasing evidence that fat tissue produces a lipid soluble factor that stimulates aldosterone production from the adrenal zona glomerulosa. Recently, have we learned that MR blockade improves pancreatic insulin release, insulin-mediated glucose utilization, endothelium-dependent vasorelaxation as well as reducing the progression of CVD and CKD. In summary, aldosterone excess exerts detrimental metabolic effects that contribute to the development of the CMS and resistant hypertension as well as CVD and CKD.
Keywords
Aldosterone; Insulin Resistance; Hypertension; Cardiometabolic Syndrome

Introduction
The prevalence of hypertension, cardiovascular disease (CVD) and chronic kidney disease (CKD) is progressively increasing in the United States, a phenomenon that closely parallels the burgeoning epidemics of obesity and the cardiometabolic syndrome (CMS).1–12 Approximately 70 million adults in the United States are obese and another 70 million have hypertension.1,6,13 Data from the National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of hypertension increases progressively with increasing body mass index (BMI) from 15% among persons with a BMI of 25 kg/m2 to approximately 40% among those who are obese, with a BMI of 30kg/m2 or more.2 Recent work supports the notion that hypertensive patients exhibit more frequent impairments of insulin metabolic signaling, dyslipidemia, microalbuminuria, and obesity, all components of the CMS.4–7

The pathogenesis of the CMS is complex and not fully understood.8,17 Increasing evidence reveals that the renin-angiotensin-aldosterone system is inextricably involved in linking obesity, metabolic dyslipidemia, insulin resistance, CKD, and hypertension,10–29 and a number of successful compounds have been developed around molecular targets of this pathway. Indeed, emerging evidence supports a crucial role for aldosterone in the pathogenesis and progression of the CMS. As recently summarized,17 elevated plasma aldosterone levels directly contribute to insulin resistance, endothelial dysfunction, glomerular hyperfiltration, and excess glomerular and tubular leakage of albumin; processes that lead to maladaptive cardiovascular and renal remodeling. It is increasingly recognized that obesity, which is often associated with elevated plasma levels of aldosterone, is a major factor for the development of albuminuria and CKD, in concert with other components of the CMS.7,17 Data are also emerging that suggest patients with resistant hypertension, those not controlled to goal on three antihypertensive medications, tend to be overweight, often have elevated plasma and urine levels of aldosterone, and have salutary blood pressure responses to mineralocorticoid receptor (MR) blockers.30–56

Aldosterone is synthesized in the zona glomerulosa of the adrenal gland in response to angiotensin II (Ang II), adrenocorticotropic (ACTH), potassium, and lipid soluble factor(s) produced in fat tissue (Fig 1).17,30 The classical genomic pathway of aldosterone action involves binding to cytosolic MRs and subsequent translocation to the nucleus, gene transcription, and translation of effector proteins involved in regulating sodium and potassium balance across renal tubular epithelial cells.17,23 Aldosterone also exerts rapid, non-genomic effects that mediate maladaptive tissue remodeling throughout the cardiovascular and central nervous system, further perpetuating the CMS, insulin resistance, and the hypertensive state. The non-genomic pathways of aldosterone are independent of renal tubular reabsorption of sodium and volume expansion and utilize rapid activation of the tyrosine kinase signaling and subsequent downstream activation of extracellular receptor kinase (ERK1/2), Rho kinase, and protein kinase (PKC) in association with increased cytosolic calcium and generation of reactive oxygen species (ROS).8,16–18 The consequences of activating these pathways are increased NADPH oxidase activation/ROS generation, mitochondrial electron transport uncoupling, and downstream activation of redox-sensitive serine kinases (Fig 1–4).8,17,23,24 As MRs are expressed in numerous tissues, elevated circulating aldosterone levels signaling via nongenomic as well as genomic mechanisms result in a number of maladaptive tissue-specific effects (Fig 1).
The Contribution of Aldosterone to the Pathogenesis of CMS

Aldosterone secretion from the adrenal gland has been classically considered to be regulated by renin-angiotensin system activation in response to intravascular volume contraction.\textsuperscript{5,6} When this axis is perturbed, as seen in diverse disease states including the CMS, heart failure and CKD, inappropriate aldosterone secretion occurs despite high salt and volume retention and contributes to a state of hyperaldosteronism.\textsuperscript{6,16,22,23} Recent evidence suggests that increased non-genomic MR signaling, in response to these elevated levels of aldosterone, is involved in the pathophysiology of insulin resistance and other components of the CMS.\textsuperscript{17} Indeed, the MR has a high affinity for both aldosterone as well as 11-beta-hydroxyglucocorticoids, the levels of which are often elevated in clinical states characterized by central obesity, such as the CMS.\textsuperscript{17} The enzyme 11-beta-hydroxysteroid dehydrogenase, which prevents glucocorticoids from signaling through the MR, is present at much lower levels in cardiovascular and metabolic tissue such as skeletal muscle, liver and fat,\textsuperscript{23,24} thereby allowing for both aldosterone as well as 11-beta-hydroxyglucocorticoids to act through the MR to impact insulin metabolic signaling with consequent maladaptive tissue remodeling.\textsuperscript{17} This is of particular significance in the CMS wherein circulating glucocorticoid concentrations may be several orders of magnitude greater than aldosterone.

As summarized in a recent review,\textsuperscript{17} there is emerging evidence that adipose tissue produces a lipid soluble factor that stimulates aldosterone secretion.\textsuperscript{30} There is also emerging evidence that both aldosterone and glucocorticoids can interact via MRs to promote adipogenesis and increases in fat macrophage infiltration.\textsuperscript{29,30} Thus, the interaction of fat, the adrenal cortex, and aldosterone/glucocorticoids is a positive servoregulatory relationship whereby fat increases aldosterone and glucocorticoid production, and these hormones, in turn, promote further adipogenesis and inflammation in fat tissue (Fig 1). In this context, MR blockade has been shown to reverse obesity-related increases in the pro-inflammatory adipokines TNF-alpha, MCP-1, and IL-6 and improve expression of adiponectin.\textsuperscript{31,32} Thus, in clinical conditions characterized by increased obesity, MR activation by glucocorticoids, in addition to aldosterone, further potentiates inflammation, oxidative stress, fibrosis, and insulin resistance.\textsuperscript{22–24}

Elevations in plasma aldosterone levels are associated with the CMS independent of other renin-angiotensin-aldosterone (RAAS) components such as Ang II.\textsuperscript{17,26,27} For example, it has been observed that in primary hyperaldosteronism, in which there are low levels of plasma renin activity and Ang II, there are higher blood glucose levels and a higher prevalence of CMS compared to that observed in individuals with essential hypertension.\textsuperscript{27} In another study, insulin resistance as measured by homeostatic model assessment (HOMA) was higher, and adiponectin levels were lower in primary hyperaldosteronism than in essential hypertension.\textsuperscript{28} The relationship between elevated plasma levels of aldosterone and insulin resistance is further strengthened by the observation that resection of aldosterone-producing tumors improves insulin sensitivity.\textsuperscript{33}

Recent investigation has helped delineate the mechanism by which aldosterone negatively impacts insulin metabolic signaling (Fig 2). For example, in murine brown fat tissue, aldosterone dose-dependently impaired insulin-induced glucose uptake by about 25% and increased mRNA of the proinflammatory adipokines.\textsuperscript{14} Data from our laboratory in a transgenic rodent model of RAAS activation and insulin resistance show that in-vivo MR blockade improves system insulin sensitivity as well as ex-vivo skeletal muscle glucose uptake.\textsuperscript{11,17} This improvement in skeletal muscle insulin metabolic signaling was associated with decreased NADPH oxidase activity and the attenuation of ROS (Fig 2).
Several other mechanisms of aldosterone-induced insulin resistance and impaired glucose sensitivity have been suggested, including negative effects on pancreatic beta cell function and stimulation of hepatic gluconeogenesis.\textsuperscript{17,34} In this context, hypokalemia has been shown to have a direct impact on pancreatic beta-cell function.\textsuperscript{17} Aldosterone also causes an impairment in hepatic insulin metabolic signaling which contributes, in part, to increased hepatic gluconeogenesis.\textsuperscript{34,35} In studies demonstrating an association between hyperaldosteronism and decreased pancreatic beta-cell mass, there were negative relationships between serum aldosterone, c-peptide levels and HOMA sensitivity.\textsuperscript{34} In that study, these abnormalities of beta-cell function and insulin sensitivity, occurred largely independent of decreased serum potassium, suggesting that aldosterone exerted negative effects on directly on beta-cell function. There is emerging data that aldosterone exerts these detrimental effects on beta-cell structural and functional integrity though increases in islet cell inflammation and oxidative stress.\textsuperscript{17,34}

**The Role of Aldosterone in Endothelial Dysfunction**

Endothelial dysfunction is commonly present in concert with insulin resistance and other components of the CMS (Fig 3).\textsuperscript{15–19} Several vascular metabolic abnormalities have been documented in obese, insulin resistant subjects. These abnormalities include impaired insulin-stimulated glucose uptake and reduced bioavailable nitric oxide (NO).\textsuperscript{17} In this context, insulin-dependent glucose utilization is partly dependent on insulin-mediated increases in blood flow and substrate delivery to tissues (Fig 3). In insulin resistance, there is decreased insulin stimulation of NO bioactivity (decreased endothelial NOS (eNOS) activation and increased NO destruction), diminished vasodilatation, and impaired substrate delivery. Increasing evidence demonstrates that elevated plasma levels of aldosterone contribute to this decrease in insulin metabolic signaling in vascular tissue.\textsuperscript{15–19} Increased generation of ROS plays an important role in aldosterone- and Ang II-mediated decreases in insulin metabolic signaling. Increases in RAAS generation of ROS activate redox-sensitive serine kinases, which promote serine phosphorylation of insulin receptor-1 (IRS-1) levels. This increase in serine phosphorylation of IRS-1 reduces engagement with phosphoinositol 3-kinase (PI3-K), with resulting diminution of protein kinase B (Akt) and atypical protein kinase activation of eNOS phosphorylation/activation (Fig 3).\textsuperscript{17} As a result, insulin-resistant individuals with obesity and elevated plasma levels of aldosterone are more prone to endothelial dysfunction and subsequent development of hypertension.

**Aldosterone and Hypertension**

Aldosterone mediates several maladaptive changes in the nervous and cardiovascular systems that promote hypertension in addition to CVD and CKD (Fig 1). Elevated plasma aldosterone levels are reported both in hypertensive patients and animal models of hypertension\textsuperscript{23,36–39,47} and have been correlated with increased left ventricular mass\textsuperscript{45,46,67} as well as established as a risk factor for developing hypertension.\textsuperscript{47,48} Primary aldosteronism, resulting from bilateral adrenal hyperplasia or an aldosterone-producing adenoma, occurs with prevalence estimated at 0.5% to 4.8% of the population with general hypertension, and 4.5% to 22% of those with resistant hypertension.\textsuperscript{40–44} Importantly, primary hyperaldosteronism leads to a greater frequency of resistant hypertension, as well as CVD and CKD morbidity and mortality, compared to essential hypertension.\textsuperscript{17,49,50} Primary hyperaldosteronism has also been linked to hypertension-related atrial fibrillation.\textsuperscript{70} Elevated levels of aldosterone, in association with obesity and insulin resistance, promote non-genomic inflammation and oxidative stress pathways that advance the development of resistant hypertension through a number of mechanisms.\textsuperscript{15–19} As previously noted, aldosterone has been demonstrated to inhibit endothelium-dependent relaxation by decreasing NO
bioavailability, a consequence of increased ROS generation (Fig 3). In addition, aldosterone-induced perivascular fibrosis reduces vascular compliance and increases stiffness, while increased Na+/H+ exchange promotes vascular smooth muscle cell proliferation.55,56 These actions potentiate the elevation of blood pressure that occurs from the classical effects of aldosterone to promote salt retention and volume expansion, collectively causing severe hypertension that is resistant to treatment unless an MR antagonist such as spironolactone or epleronone is employed as part of the therapeutic regime.17,20

As in the heart, vasculature, pancreas, skeletal muscle, and fat, high levels of circulating aldosterone (as well as centrally-administered aldosterone) can also increase local RAAS activation in brain regions that contribute to increased sympathetic tone in hypertension.17,65,66 For example, brain MR blockade reduces NADPH-induced superoxide in the paraventricular nucleus (PVN) of the hypothalamus and reduces descending sympathetic PVN output.66 In addition to circulating levels, aldosterone is also synthesized in the brain67,68 and serves as an MR ligand to increase sympathetic drive to the heart, kidneys, and vascular smooth muscle. Sympathetic pathways are also activated by aldosterone-MR action in the central nervous system.69 Finally, aldosterone-induced increases in salt appetite and sodium intake in part, via MR activation in the amygdala, further promote hypertension.67,70

**Aldosterone Effects on Heart and Kidney**

Aldosterone has also been shown to mediate maladaptive remodeling in the heart. Left ventricular hypertrophy, cardiac fibrosis, and diastolic dysfunction are all associated with high aldosterone (Fig 1).57–59 In a feed-forward mechanism, cardiac MR activation potentiates the local RAAS by increasing angiotensin type 1 receptor (AT1R) and angiotensin converting enzyme (ACE) expression and enhancing Ang II-induced oxidative stress.8,54,61–64 MR antagonism reduces Ang II-mediated increases in NADPH oxidase subunit expression and ROS generation in hypertensive rats60 and abrogates left ventricular hypertrophy, collagen synthesis, and cardiac arrhythmias in human hypertensive patients.

Aldosterone has a number of adverse effects in the renal axis of the CMS as well. High circulating levels of aldosterone cause renal hyperfiltration and promote both glomerular and tubulointerstitial disease, as discussed in detail in a previous review.17 Aldosterone has been shown to induce hypertrophy of the glomerular mesangium in kidneys of hypertensive rats, leading to podocyte damage, glomerulosclerosis, and proteinuria.14,17,21 Aldosterone-induced renal damage is likely via redox-mediated deficits in insulin signaling (Fig 4), as MR antagonism abrogates local RAAS signaling, attenuates glomerular remodeling, and improves insulin signaling while decreasing NADPH oxidase activity and ROS generation. Additionally, in human patients with kidney disease, the addition of MR blockade to treatment with ACE inhibitors or AT1R blockers (ARBs) dramatically amplifies the improvements in proteinuria and albuminuria.

**Current and Future Clinical Perspectives**

While the evidence to date to support a role for MR antagonism on insulin sensitivity is best validated in preclinical models, there is observational data to drive future work. The bulk of current evidence supports a role for MR antagonism on CVD and CKD end-points. Current standards of practice advocate RAAS inhibition with an ACE inhibitor or AT1R blockade to retard progression of CVD and renal disease; however, neither ensures optimal control of cardiovascular morbidity and mortality. Optimal RAAS suppression is difficult to achieve with currently available antihypertensive agents, partly because ACE inhibition and AT1R blockade both activate compensatory feedback mechanisms that result in increased plasma renin activity, active Ang II, and aldosterone escape mechanisms.
Aldosterone breakthrough has been estimated to occur in 10–53% of patients on chronic ACE inhibitor or ARB therapy and can be associated with negative cardiovascular and renal consequences. To the best of our knowledge, at least fourteen clinical investigations have confirmed an incremental renal and cardiovascular benefit when MR blockade is added to a regimen comprising ACE inhibitors or ARBs. Indeed, mounting evidence suggests combination treatment with MR blockade may improve end organ disease outcomes and provide additional blood pressure-lowering effects in settings of resistant hypertension.

Conclusions

Increasing data suggests that excess circulating aldosterone promotes the development of impaired insulin metabolic signaling and endothelial function, which in turn contribute to hypertension and associated cardiovascular and renal structural and functional abnormalities. Central to the CMS is obesity, a condition that stimulates adrenal production of aldosterone which, in turn, is associated with insulin resistance, the metabolic syndrome and an increased propensity for development of type 2 diabetes (Fig 1). Many of these adverse effects of aldosterone are mediated through rapid membrane actions of this hormone. Accumulating evidence indicates that therapy with MR antagonists has considerable clinical utility in the treatment of resistant hypertension, and in the prevention of CVD and CKD in patients with the metabolic syndrome and diabetes. Future investigative efforts should focus on further delineation of the role of MR blockade in the management of the metabolic syndrome and resistant hypertension.

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