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Narrative Review: The Emerging Clinical Implications of the Role of Aldosterone in the Metabolic Syndrome and Resistant Hypertension

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Abstract

The prevalence of obesity, diabetes, hypertension, and cardiovascular and chronic kidney disease is increasing in developed countries. Obesity, insulin resistance, and hypertension commonly cluster with other risk factors for cardiovascular and chronic kidney disease to form the metabolic syndrome. Emerging evidence supports a paradigm shift in our understanding of the renin–angiotensin–aldosterone system and in aldosterone's ability to promote insulin resistance and participate in the pathogenesis of the metabolic syndrome and resistant hypertension. Recent data suggest that excess circulating aldosterone promotes the development of both disorders by impairing insulin metabolic signaling and endothelial function, which in turn leads to insulin resistance and cardiovascular and renal structural and functional abnormalities. Indeed, hyperaldosteronism is associated with impaired pancreatic β-cell function, skeletal muscle insulin sensitivity, and elevated production of proinflammatory adipokines from adipose tissue, which results in systemic inflammation and impaired glucose tolerance.

Accumulating evidence indicates that the cardiovascular and renal abnormalities associated with insulin resistance are mediated in part by aldosterone acting on the mineralocorticoid receptor. Although we have known that mineralocorticoid receptor blockade attenuates cardiovascular and renal injury, only recently have we learned that mineralocorticoid receptor blockade improves pancreatic insulin release, insulin-mediated glucose utilization, and endothelium-dependent vasorelaxation. In summary, aldosterone excess has detrimental metabolic effects that contribute to the metabolic syndrome and endothelial dysfunction, which in turn contribute to the development of resistant hypertension as well as cardiovascular disease and chronic kidney disease.

The prevalences of obesity, diabetes, hypertension, and cardiovascular and chronic kidney disease are increasing in the United States. Data from NHANES (National Health and Nutrition Examination Survey) III suggest that the prevalence of hypertension increases progressively with increasing body mass index from about 15% among people with a body mass index less than 25 kg/m^2 to approximately 40% among those with a body mass index of 30 kg/m^2 or

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greater (1). Obesity, insulin resistance, and hypertension commonly cluster with other risk factors for cardiovascular or chronic kidney disease to form the metabolic syndrome, which is associated with increased cardiovascular disease morbidity and mortality (1-5).

Our understanding of the role of the renin–angiotensin–aldosterone system in insulin resistance through the action of aldosterone has undergone a paradigm shift in recent years. We know now that aldosterone participates in the pathogenesis of the metabolic syndrome (4-6). Recent evidence shows that elevated plasma aldosterone levels directly contribute to the pathogenesis of insulin resistance and endothelial dysfunction, processes that in turn contribute to maladaptive renal and cardiovascular remodeling (4-6). These actions of aldosterone promote the development of resistant hypertension—defined as the need for 3 or more antihypertensive medications to control blood pressure—in association with obesity and the metabolic syndrome.

The Emergence of a New Paradigm for Aldosterone

Aldosterone was isolated and characterized by Simpson and Tait (7) more than 50 years ago and was initially termed *electrocortin*. During the subsequent 4 decades, clinicians and medical investigators thought of aldosterone as acting primarily to regulate extracellular fluid volume and potassium handling. Classic agonist–antagonist experiments in the toad bladder model in the 1960s (7,8) revealed that alterations in sodium–potassium ion flux did not occur immediately after aldosterone administration. This delay was due to aldosterone's binding to cytosolic steroid receptors; translocation to the nucleus; interaction with DNA; and, finally, genomic transcription and translation of effector proteins. Investigators applied molecular biology techniques over the next several decades to understand aldosterone-mediated gene transcription and subsequent protein synthesis (8,9).

In 1992, investigators reported rapid, nongenomic effects of aldosterone that did not require signaling through the classic pathways of gene activation, transcription, and protein synthesis. These nongenomic actions included regulation of intracellular cations, cell volume, redox status, metabolic signaling, and endothelial-mediated relaxation (5,8,10). It is increasingly evident that these nongenomic effects, which occur independent of hemodynamic factors, are a substantial part of the mechanisms by which aldosterone contributes to the pathogenesis of the metabolic syndrome and resistant hypertension, as well as enhanced risk for cardiovascular and chronic kidney disease (9-15).

Regulation of Aldosterone Secretion and Mineralocorticoid Receptor Activation

For decades, we believed that activation of the renin–angiotensin system, largely in response to intravascular volume contraction, regulated the biosynthesis of aldosterone (5-9). Hyperaldosteronism may occur when the relationship between salt ingestion or volume status and aldosterone secretion is perturbed (Figure 1). In fact, inappropriate aldosterone secretion occurs in diverse disease states, including the metabolic syndrome, heart failure, and chronic kidney disease, despite high salt and volume retention.

Mounting evidence in recent years suggests that mineralocorticoid receptors on the surface of nonepithelial cells send extracellular signals that do not require gene transcription for their action. These so-called “nongenomic” actions of aldosterone are involved in the pathophysiology of insulin resistance and endothelial dysfunction (Figure 1). The mineralocorticoid receptor has a high affinity for both aldosterone and 11β-hydroxyglucocorticoids (4). Cells at the distal end of the nephron have relatively high levels of the enzyme 11β-hydroxysteroid dehydrogenase, which prevents glucocorticoids from acting

in the distal tubule and collecting duct. However, cardiovascular and metabolic tissue, such as skeletal muscle, liver, and fat, have much lower levels of this enzyme, which allows glucocorticoids to signal through the mineralocorticoid receptors (2-5). This signaling is particularly important in persons with the metabolic syndrome, because they have circulating glucocorticoid concentrations that are several orders of magnitude greater than their aldosterone concentrations. Mineralocorticoid receptor activation by glucocorticoids promotes inflammation, oxidative stress, fibrosis, insulin resistance, and endothelial dysfunction (5,9, 10).

Pathophysiology

A new paradigm indicates that elevated levels of plasma aldosterone mediate several maladaptive changes that contribute to the pathogenesis of the metabolic syndrome, resistant hypertension, and associated cardiovascular and renal structural and functional abnormalities.

Accumulating evidence indicates that adipose tissue produces aldosterone secretory factors that promote excessive adrenal aldosterone production. Elevated plasma aldosterone levels in turn promote insulin resistance, inflammation, oxidative stress, and sodium retention. These maladaptive processes contribute to the development of a hypertensive state that is relatively resistant to pharmacologic therapy.

Clinical Implications

Evidence is emerging that mineralocorticoid receptor blockade is useful in treating hypertensive patients who have both the metabolic syndrome and resistant hypertension.

Mineralocorticoid antagonism therapy seems to have considerable clinical utility for reducing cardiovascular and renal disease associated with the metabolic syndrome, diabetes, and resistant hypertension.

Aldosterone Antagonists

17-Spirolactone steroids, or *spirolactones*, were developed 50 years ago to antagonize the action of aldosterone and other sodium-retaining hormones on the renal distal tubule (12). Initially, the mineralocorticoid receptor antagonist spironolactone was used widely as a potassium-sparing diuretic in volume-overload states, such as congestive heart failure, cirrhosis, and primary hyperaldosteronism (8,12). Later, RALES (Randomized Aldactone Evaluation Study) (14) showed that mineralocorticoid receptor antagonists reduced cardiovascular events. This study demonstrated that a low dose of spironolactone improved morbidity and mortality in patients with severe heart failure. Subsequently, EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study) (15) demonstrated that treatment with eplerenone, a selective mineralocorticoid receptor antagonist, reduced mortality after myocardial infarction. These studies refocused attention on aldosterone's effects on the mineralocorticoid receptors of nonrenal cells and have allowed investigators to use both spironolactone and eplerenone as pharmacologic probes to delineate the role of aldosterone and mineralocorticoid receptor signaling in various clinical disorders. Eplerenone is a newer, selective mineralocorticoid receptor antagonist that offers the same benefits as generic spironolactone, but it is no longer actively promoted.

The protective effects of mineralocorticoid receptor blockade complement the effects of renin–angiotensin system blockade (6). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists act on the angiotensin peptides and receptors, respectively, and also suppress aldosterone secretion by the adrenal glands. Although the clinical effects are not fully elucidated, the complementary actions of these 2 classes of drugs provide a potential

framework for treating various disorders, including resistant hypertension, cardiovascular disease, and chronic kidney disease.

The Role of Aldosterone in Resistant Hypertension

"Resistant hypertension" is defined as hypertension that requires more than 3 drugs in full doses to adequately control pressure. It is an increasingly common condition in industrialized nations (16-23) that parallels the exponential growth in global obesity and the diabetes and chronic kidney disease epidemics (4,5). Mounting evidence suggests that an elevated aldosterone level, in association with obesity and insulin resistance, contributes not only to salt retention and volume expansion but also to the inflammation and oxidative stress that promote the development of the metabolic syndrome and resistant hypertension (Figure 1) (4-6).

The 17% to 22% prevalence of primary aldosteronism in individuals with resistant hypertension, which is much higher than that in the general population with hypertension, suggests a relationship between elevated aldosterone levels and resistant hypertension (19-23). Moreover, individuals with resistant hypertension but without primary hyperaldosteronism have higher aldosterone levels and greater intravascular volume expansion than do control participants (17). The elevated 24-hour urinary levels of both aldosterone and cortisol suggest that a common stimulus, such as corticotropin, may promote aldosterone excess in patients with resistant hypertension (21,24). A recent study (21,24) shows that African-American patients with hypertension have higher plasma aldosterone, lower renin, and higher salivary cortisol levels than their normotensive counterparts. Although the mechanism by which higher cortisol and aldosterone levels coexist in resistant hypertension is not fully understood, several possible factors have been postulated. For example, enhanced sympathetic nervous system activation may stimulate both cortisol and aldosterone secretion (25). Adipocyte-derived secretory products are also known to stimulate adrenal production of aldosterone in addition to genetic polymorphisms that affect aldosterone synthase activity. Both are potentially important mediators of the excess aldosterone and cortisol secretion associated with obesity and insulin resistance (Figure 1) (26-29).

In addition to its classic effects on renal handling of sodium and potassium and expansion of intravascular volume, aldosterone promotes resistant hypertension—both alone and in conjunction with angiotensin II—by mediating maladaptive changes in the central nervous, renal, and cardiovascular systems (Figure 1). For example, aldosterone induces rapid (nongenomic) adverse responses in both vascular smooth muscle cell and skeletal muscle tissue by stimulating the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Figure 2, *step 1*), which generates excess reactive oxygen species (ROS), redox imbalance, and "oxidant stress" (Figure 2, *step 2*). The increased ROS thereby activates redox-sensitive serine kinase signaling molecules in these tissues, including protein kinase C, mitogen-activated protein kinases, c-Jun NH_2-terminal kinase, extracellular signal-regulated kinases 1 and 2, and ρ-kinase (Figure 2, *step 3*) (5,30-34). Reactive oxygen species–induced activation of these serine kinases promotes phosphorylation of serine moities of the insulin receptor substrate-1 docking protein (Figure 2, *step 4*) at the access point of altered insulin metabolic signaling. Serine phosphorylation of insulin receptor substrate-1 lessens its engagement with phosphatidylinositol 3-kinase (Figure 2, *step 5*), which leads to decreased activation of protein kinase B (Figure 2, *step 6*) and such downstream metabolic effects as impaired glucose transport and, ultimately, glucose utilization (Figure 2, *step 7*).

Collectively, increases in aldosterone promote miner-alocorticoid receptor–mediated dysregulation of downstream insulin metabolic signaling, which ultimately impairs glucose utilization—as observed in insulin resistance and resistant hypertension (5). In the vasculature, these effects occur through a redox-sensitive serine kinase associated with NADPH oxidase

and mitochondrial generation of ROS, which decrease bioavailability of nitric oxide and consequently impair endothelium-dependent relaxation (Figure 1) (5). Conversely, in animal models with an activated renin–angiotensin–aldosterone system, drugs that block the mineralocorticoid receptor reduce oxidative stress and improve insulin metabolic signaling and endothelial-dependent vascular relaxation (5,6,29-33).

Aldosterone and Insulin Resistance

The adverse effect of excess aldosterone on insulin metabolic signaling (Figure 1) has generated increasing interest in the role of hyperaldosteronism in the pathogenesis of insulin resistance and resistant hypertension. This association was initially described more than 4 decades ago in individuals with primary hyperaldosteronism and impaired glucose tolerance (34). Increased plasma aldosterone levels are associated with insulin resistance independent of other components of the metabolic syndrome (35-37). In patients with primary hyperaldosteronism, resection of aldosterone-producing tumors and pharmacologic treatment both decrease blood insulin and glucose levels, which indicates an improvement in insulin sensitivity (37,38).

Aldosterone Interactions With Adipose Tissue

Aldosterone impairs insulin metabolic signaling by several putative mechanisms in cardiovascular and renal tissue, as well as in fat, skeletal muscle, and the liver (Figure 2). Visceral adipose tissue is thought to be a source of inflammatory cytokines (adipokines) that mediate systemic inflammation, oxidative stress, and insulin resistance (5,39). In rodent fat tissue, aldosterone increases proinflammatory adipokine expression, which causes reduced insulin receptor expression and impaired insulin-induced glucose uptake (39). Mineralocorticoid receptors on adipocytes promote inflammatory adipokine expression, as suggested by several studies (39-43). Similar to the nongenomic actions of the mineralocorticoid receptor in other nonepithelial tissues, the adipocyte mineralocorticoid receptors may mediate a proadipogenic effect of both aldosterone (39) and glucocorticoids (41). More recently, studies in obese diabetic mice have demonstrated that mineralocorticoid receptor blockade reduced expression of proinflammatory and prothrombotic factors in adipose tissue and increased the expression of adiponectin in heart and adipose tissue, which is a potential mechanism to protect against adipokines (42).

Human adipocytes produce an as-yet unidentified mineralocorticoid-releasing factor that stimulates adrenal aldosterone production by means of paracrine or endocrine mechanisms (43,44) (Figure 1). An epoxy-keto derivative of linoleic acid—a potent stimulator of aldosterone production—is present in obese persons with increased levels of free fatty acids (44), which suggests that oxidative stress drives the production of this aldosterone-stimulating free fatty acid. Similarly, patients with primary hyperaldosteronism have low levels of adiponectin, which is associated with reduced insulin sensitivity (45). Weight reduction decreases plasma aldosterone levels and improves insulin sensitivity in both normotensive and hypertensive patients (46,47), which is further evidence of the interrelationship between excess aldosterone and fat tissue. Collectively, these effects suggest that obesity is associated with increased aldosterone production and that elevated levels of aldosterone in turn promote development of the metabolic syndrome.

Aldosterone Effects on Systemic Insulin Metabolic Signaling

Given the strong relationship between resistant hypertension and the metabolic syndrome, it is interesting that nonepithelial cardiovascular tissues, including vascular smooth muscle cells, cardiomyocytes, and fibroblasts, express mineralocorticoid receptors (5). Moreover, aldosterone suppresses insulin metabolic signaling and glucose uptake in vascular smooth

muscle cells (48). In recent studies, mineralocorticoid receptor blockade improved systemic insulin sensitivity, insulin signaling, and skeletal muscle glucose uptake in a rodent model of renin–angiotensin–aldosterone system activation and insulin resistance (30). This improvement in insulin sensitivity was closely associated with decreases in skeletal muscle NADPH oxidase activity, decreased levels of ROS, and improved mitochondrial structural integrity.

Several other mechanisms of aldosterone-induced glucose intolerance have been suggested, including effects of hypokalemia on pancreatic β-cell function, direct effects on insulin receptors and signaling, stimulation of hepatic gluconeogenesis, effects on sodium-glucose transport, and fibrosis-induced dysfunction in insulin-producing or insulin-sensitive tissues (5,49,50). In studies demonstrating an association between aldosterone and lower pancreatic β-cell mass, serum aldosterone level was inversely related to c-peptide levels and homeostasis model assessment sensitivity (49). These abnormalities of β-cell function were largely independent of serum potassium, which suggests that aldosterone was the cause of the negative effects on β-cell function. Evidence now suggests that aldosterone exerts these detrimental effects on β-cell structural and functional integrity by promoting islet cell inflammation and oxidative stress (Figure 1) (50).

In summary, the role of aldosterone in promoting these multiple metabolic effects suggests that mineralocorticoid receptor blockade, alone or in conjunction with ACE inhibitors or angiotensin II receptor antagonists, can play a central role in the management of the resistant hypertension that often accompanies the metabolic syndrome. Mineralocorticoid receptor blockade improves insulin sensitivity, enhances endothelial-mediated relaxation, and facilitates the management of chronic kidney disease and cardiovascular disease.

Aldosterone and The Cardiovascular System

In addition to its classic effects on renal handling of sodium and potassium and blood and volume expansion, aldosterone mediates several maladaptive changes in the central nervous and cardiovascular systems that promote resistant hypertension and cardiovascular disease (Figure 1). Aldosterone, acting both directly and indirectly through potentiation of an angiotensin II effect, impairs endothelium-dependent relaxation (5). This effect is associated with increased NADPH oxidase activation and oxidative stress in the vessel wall, which reduces bioavailability of nitric oxide. Mineralocorticoid receptor blockade improves nitric oxide bioavailability and consequently enhances endothelium-dependent vasorelaxation (5, 10,51).

Aldosterone promotes vascular injury and its sequelae, collagen synthesis and fibrosis, which increase arterial stiffness (5,10,51). Cross-talk between aldosterone and angiotensin II augments these maladaptive changes. Both angiotensin II and aldosterone stimulate vascular growth and remodeling, perhaps mediated through effects on serine kinase and ROS signaling. Aldosterone upregulates angiotensin receptor 1, ACE activity, and growth signaling in vascular cells (5,10,32,33,51). In addition, the blockade of both mineralocorticoid receptor and angiotensin receptor 1 protects against generation of excess ROS and resultant vascular remodeling (5,10,51).

Similarly to angiotensin II, aldosterone mediates endothelial dysfunction in animal models and humans by means of rapid nongenomic effects (5,9,11). Aldosterone can also contribute to abnormal cardiac remodeling, including fibrosis and perivascular inflammation (5,52). In rodent models of excessive tissue angiotensin and aldosterone, mineralocorticoid receptor blockade reduces cardiac inflammation, oxidative stress, fibrosis, remodeling, and hypertrophy and improves diastolic function (51–53). Although the pathways have distinct stimuli (angiotensin II or aldosterone), these beneficial effects of mineralocorticoid receptor blockade

highlight the importance of NADPH oxidase and mitochondrial-mediated oxidative stress in aldosterone-induced cardiovascular injury (51-53).

In summary, aldosterone has an important role in vascular pathobiology, as deduced from the effects of mineralocorticoid receptor blockade, which reduces fibrosis and left venticular hypertrophy and improves endothelial-mediated vasorelaxation and cardiac diastolic relaxation (5,9,17).

Aldosterone and The Kidney

Aldosterone plays an important role in the development of renal disease of diverse causes, including chronic kidney disease associated with obesity, diabetes, and hypertension (4,6,13, 54-55). Although the current standard of practice is to block the renin–angiotensin system with an ACE inhibitor or an angiotensin II receptor antagonist to slow the progression of renal disease, this strategy attenuates but does not prevent progression. At least 14 clinical investigations (6) have now confirmed an incremental renal benefit when mineralocorticoid receptor blockade is added to a regimen of ACE inhibitors or angiotensin II receptor antagonists. Most (12 of 14) of these studies used spironolactone to promote mineralocorticoid receptor blockade. Addition of either a selective or nonselective mineralocorticoid receptor blocker to recommended therapies reduced albuminuria in patients with diabetes, chronic kidney disease, nephropathy, or persistent microalbuminuria. For example, when eplerenone was added to baseline ACE inhibitor therapy in diabetic patients, the combination markedly reduced the urinary albumin–creatinine ratio (13). Recent studies (4,6) have extended these observations, demonstrating that mineralocorticoid receptor blockade also attenuated the decline of glomerular filtration rate in kidney disease in persons with the metabolic syndrome and diabetes.

Several mechanisms may account for aldosterone's ability to promote fibrosis and target-organ dysfunction in hypertensive or diabetic patients. As detailed in recent reviews (4-6), these include stimulation of plasminogen activator inhibitor, transforming growth factor β_1, and ROS. Several lines of evidence (56) have focused on aldosterone's effects on the glomerular podocyte. Aldosterone promotes loss of glomerular podocytes and a consequent decrease in slit–pore membrane integrity, with consequent proteinuria (4,54-56). In addition, aldosterone increases renal tubular and interstitial oxidative stress and inflammation, processes that promote salt-induced tubuloglomerular injury, by means of rapid nongenomic effects (4).

Conclusion

The important role of aldosterone in the pathogenesis of the metabolic syndrome, resistant hypertension, and associated cardiovascular and chronic kidney disease is increasingly recognized. Overweight and obesity are conditions that stimulate adrenal production of aldosterone, which in turn is associated with insulin resistance, the metabolic syndrome, and an increased propensity for type 2 diabetes. Many of these adverse effects of aldosterone are mediated through rapid-membrane actions of this hormone. Accumulating evidence shows that therapy with mineralocorticoid receptor antagonists has considerable clinical utility in treating resistant hypertension and preventing cardiovascular and chronic kidney disease in patients with the metabolic syndrome and diabetes. Future investigative efforts should focus on further delineation of the role of mineralocorticoid receptor blockade in the management of the metabolic syndrome and resistant hypertension.

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References

1. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110:1245–50. PMID: 15326067. [PubMed: 15326067]
2. Manrique C, Lastra G, Whaley-Connell A, Sowers JR. Hypertension and the cardiometabolic syndrome. J Clin Hypertens (Greenwich) 2005;7:471–6. PMID: 16103758. [PubMed: 16103758]
3. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006;444:875–80. PMID: 17167476. [PubMed: 17167476]
4. Sowers JR. Metabolic risk factors and renal disease. Kidney Int 2007;71:719–20. PMID: 17429418. [PubMed: 17429418]
5. Cooper SA, Whaley-Connell A, Habibi J, Wei Y, Lastra G, Manrique C, et al. Renin-angiotensin-aldosterone system and oxidative stress in cardiovascular insulin resistance. Am J Physiol Heart Circ Physiol 2007;293:H2009–23. PMID: 17586614. [PubMed: 17586614]
6. Epstein M. Aldosterone blockade: an emerging strategy for abrogating progressive renal disease. Am J Med 2006;119:912–9. PMID: 17071154. [PubMed: 17071154]
7. Simpson SA, Tait JF, Wettstein A, Neher R, Von Euw J, Schindler O, et al. Constitution of aldosterone, a new mineralocorticoid. Experientia 1954;10:132–3. PMID: 13161890. [PubMed: 13161890]
8. Williams JS, Williams GH. 50th anniversary of aldosterone. J Clin Endocrinol Metab 2003;88:2364–72. PMID: 12788829. [PubMed: 12788829]
9. Brown NJ. Aldosterone and vascular inflammation. Hypertension 2008;51:161–7. PMID: 18172061. [PubMed: 18172061]
10. Wehling M, Christ M, Theisen K. Membrane receptors for aldosterone: a novel pathway for mineralocorticoid action. Am J Physiol 1992;263:E974–9. PMID: 1443130. [PubMed: 1443130]
11. Schiffrin EL. Effects of aldosterone on the vasculature. Hypertension 2006;47:312–8. PMID: 16432039. [PubMed: 16432039]
12. de Gasparo M, Joss U, Ramjoué HP, Whitebread SE, Haenni H, Schenkel L, et al. Three new epoxy-spirolactone derivatives: characterization in vivo and in vitro. J Pharmacol Exp Ther 1987;240:650–6. PMID: 2949071. [PubMed: 2949071]
13. Epstein M, Williams GH, Weinberger M, Lewin A, Krause S, Mukherjee R, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol 2006;1:940–51. PMID: 17699311. [PubMed: 17699311]
14. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17. PMID: 10471456. [PubMed: 10471456]
15. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21. PMID: 12668699. [PubMed: 12668699]
16. Goodfriend TL. Treating resistant hypertension with a neglected old drug [Editorial]. Hypertension 2007;49:763–4. PMID: 17309945. [PubMed: 17309945]
17. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, Pimenta E, Aban I, Oparil S, et al. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. Arch Intern Med 2008;168:1159–64. PMID: 18541823. [PubMed: 18541823]
18. Pimenta E, Gaddam KK, Pratt-Ubunama MN, Nishizaka MK, Aban I, Oparil S, et al. Relation of dietary salt and aldosterone to urinary protein excretion in subjects with resistant hypertension. Hypertension 2008;51:339–44. PMID: 18086955. [PubMed: 18086955]
19. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a

scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117:e510–26. PMID: 18574054. [PubMed: 18574054]

20. Gallay BJ, Ahmad S, Xu L, Toivola B, Davidson RC. Screening for primary aldosteronism without discontinuing hypertensive medications: plasma aldosterone-renin ratio. Am J Kidney Dis 2001;37:699–705. PMID: 11273868. [PubMed: 11273868]
21. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 2002;40:892–6. PMID: 12468575. [PubMed: 12468575]
22. Strauch B, Zelinka T, Hampf M, Bernhardt R, Widimsky J Jr. Prevalence of primary hyperaldosteronism in moderate to severe hypertension in the Central Europe region. J Hum Hypertens 2003;17:349–52. PMID: 12756408. [PubMed: 12756408]
23. Eide IK, Torjesen PA, Drolsum A, Babovic A, Lilledahl NP. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. J Hypertens 2004;22:2217–26. PMID: 15480108. [PubMed: 15480108]
24. Kidambi S, Kotchen JM, Grim CE, Raff H, Mao J, Singh RJ, et al. Association of adrenal steroids with hypertension and the metabolic syndrome in blacks. Hypertension 2007;49:704–11. PMID: 17159085. [PubMed: 17159085]
25. Fletcher EC, Orolinova N, Bader M. Blood pressure response to chronic episodic hypoxia: the renin-angiotensin system. J Appl Physiol 2002;92:627–33. PMID: 11796674. [PubMed: 11796674]
26. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, Langenbach J, Willenberg HS, Barthel A, et al. Human adipocytes secrete mineralocorticoid-releasing factors. Proc Natl Acad Sci U S A 2003;100:14211–6. PMID: 14614137. [PubMed: 14614137]
27. Freel EM, Ingram M, Friel EC, Fraser R, Brown M, Samani NJ, et al. Phenotypic consequences of variation across the aldosterone synthase and 11-beta hydroxylase locus in a hypertensive cohort: data from the MRC BRIGHT Study. Clin Endocrinol (Oxf) 2007;67:832–8. PMID: 17651452. [PubMed: 17651452]
28. Stowasser M, Gordon RD. Aldosterone excess, hypertension, and chromosome 7p22: evidence continues to mount [Editorial]. Hypertension 2007;49:761–2. PMID: 17339541. [PubMed: 17339541]
29. Makhanova N, Hagaman J, Kim HS, Smithies O. Salt-sensitive blood pressure in mice with increased expression of aldosterone synthase. Hypertension 2008;51:134–40. PMID: 18039983. [PubMed: 18039983]
30. Lastra G, Whaley-Connell A, Manrique C, Habibi J, Gutweiler AA, Appesh L, et al. Low-dose spironolactone reduces reactive oxygen species generation and improves insulin-stimulated glucose transport in skeletal muscle in the TG(mRen2)27 rat. Am J Physiol Endocrinol Metab 2008;295:E110–6. PMID: 18445755. [PubMed: 18445755]
31. Liu SL, Schmuck S, Chorazcyzewski JZ, Gros R, Feldman RD. Aldosterone regulates vascular reactivity: short-term effects mediated by phosphatidylinositol 3-kinase-dependent nitric oxide synthase activation. Circulation 2003;108:2400–6. PMID: 14557368. [PubMed: 14557368]
32. Callera GE, Touyz RM, Tostes RC, Yogi A, He Y, Malkinson S, et al. Aldosterone activates vascular p38MAP kinase and NADPH oxidase via c-Src. Hypertension 2005;45:773–9. PMID: 15699470. [PubMed: 15699470]
33. Min LJ, Mogi M, Iwanami J, Li JM, Sakata A, Fujita T, et al. Cross-talk between aldosterone and angiotensin II in vascular smooth muscle cell senescence. Cardiovasc Res 2007;76:506–16. PMID: 17706954. [PubMed: 17706954]
34. Conn JW. Hypertension, the potassium ion and impaired carbohydrate tolerance. N Engl J Med 1965;273:1135–43. PMID: 5841677. [PubMed: 5841677]
35. Bochud M, Nussberger J, Bovet P, Maillard MR, Elston RC, Paccaud F, et al. Plasma aldosterone is independently associated with the metabolic syndrome. Hypertension 2006;48:239–45. PMID: 16785327. [PubMed: 16785327]
36. Fallo F, Veglio F, Bertello C, Sonino N, Della Mea P, Ermani M, et al. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. J Clin Endocrinol Metab 2006;91:454–9. PMID: 16291704. [PubMed: 16291704]

37. Giacchetti G, Ronconi V, Turchi F, Agostinelli L, Mantero F, Rilli S, et al. Aldosterone as a key mediator of the cardiometabolic syndrome in primary aldosteronism: an observational study. J Hypertens 2007;25:177–86. PMID: 17143190. [PubMed: 17143190]
38. Catena C, Lapenna R, Baroselli S, Nadalini E, Colussi G, Novello M, et al. Insulin sensitivity in patients with primary aldosteronism: a follow-up study. J Clin Endocrinol Metab 2006;91:3457–63. PMID: 16822818. [PubMed: 16822818]
39. Ehrhart-Bornstein M, Arakelyan K, Krug AW, Scherbaum WA, Bornstein SR. Fat cells may be the obesity-hypertension link: human adipogenic factors stimulate aldosterone secretion from adrenocortical cells. Endocr Res 2004;30:865–70. PMID: 15666838. [PubMed: 15666838]
40. Rondinone CM, Rodbard D, Baker ME. Aldosterone stimulated differentiation of mouse 3T3-L1 cells into adipocytes. Endocrinology 1993;132:2421–6. PMID: 8504747. [PubMed: 8504747]
41. Caprio M, Fève B, Claës A, Viengchareun S, Lombès M, Zennaro MC. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. FASEB J 2007;21:2185–94. PMID: 17384139. [PubMed: 17384139]
42. Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, et al. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. Circulation 2008;117:2253–61. PMID: 18427128. [PubMed: 18427128]
43. Lamounier-Zepter V, Ehrhart-Bornstein M. Fat tissue metabolism and adrenal steroid secretion. Curr Hypertens Rep 2006;8:30–4. PMID: 16600157. [PubMed: 16600157]
44. Goodfriend TL, Ball DL, Egan BM, Campbell WB, Nithipatikom K. Epoxy-keto derivative of linoleic acid stimulates aldosterone secretion. Hypertension 2004;43:358–63. PMID: 14718355. [PubMed: 14718355]
45. Fallo F, Della Mea P, Sonino N, Bertello C, Ermani M, Vettor R, et al. Adiponectin and insulin sensitivity in primary aldosteronism. Am J Hypertens 2007;20:855–61. PMID: 17679033. [PubMed: 17679033]
46. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. N Engl J Med 1981;304:930–3. PMID: 7010165. [PubMed: 7010165]
47. Dall'Asta C, Vedani P, Manunta P, Pizzocri P, Marchi M, Paganelli M, et al. Effect of weight loss through laparoscopic gastric banding on blood pressure, plasma renin activity and aldosterone levels in morbid obesity. Nutr Metab Cardiovasc Dis 2009;19:110–4. PMID: 18718746. [PubMed: 18718746]
48. Hitomi H, Kiyomoto H, Nishiyama A, Hara T, Moriwaki K, Kaifu K, et al. Aldosterone suppresses insulin signaling via the downregulation of insulin receptor substrate-1 in vascular smooth muscle cells. Hypertension 2007;50:750–5. PMID: 17646573. [PubMed: 17646573]
49. Mosso LM, Carvajal CA, Maiz A, Ortiz EH, Castillo CR, Artigas RA, et al. A possible association between primary aldosteronism and a lower beta-cell function. J Hypertens 2007;25:2125–30. PMID: 17885557. [PubMed: 17885557]
50. Hayden MR, Sowers JR. Pancreatic renin-angiotensin-aldosterone system in the cardiometabolic syndrome and type 2 diabetes mellitus [Editorial]. J Cardiometab Syndr 2008;3:129–31. PMID: 18983326. [PubMed: 18983326]
51. Wei Y, Whaley-Connell AT, Habibi J, Rehmer J, Rehmer N, Patel K, et al. Mineralocorticoid receptor antagonism attenuates vascular apoptosis and injury via rescuing protein kinase B activation. Hypertension 2009;53:158–65. PMID: 19114643. [PubMed: 19114643]
52. Stas S, Whaley-Connell A, Habibi J, Appesh L, Hayden MR, Karuparthi PR, et al. Mineralocorticoid receptor blockade attenuates chronic overexpression of the renin-angiotensin-aldosterone system stimulation of reduced nicotinamide adenine dinucleotide phosphate oxidase and cardiac remodeling. Endocrinology 2007;148:3773–80. PMID: 17494996. [PubMed: 17494996]
53. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. Circ Res 2008;102:401–14. PMID: 18309108. [PubMed: 18309108]
54. Nagase M, Yoshida S, Shibata S, Nagase T, Gotoda T, Ando K, et al. Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. J Am Soc Nephrol 2006;17:3438–46. PMID: 17082236. [PubMed: 17082236]

55. Bomback AS, Klemmer PJ. Renal injury in extreme obesity: the important role of aldosterone [Letter]. Kidney Int 2008;74:1216. author reply 1216-7. PMID: 18854852. [PubMed: 18854852]

56. Whaley-Connell A, Habibi J, Wei Y, Gutweiler A, Jellison J, Wiedmeyer CE, et al. Mineralocorticoid receptor antagonism attenuates kidney reninangiotensin-aldosterone system mediated filtration barrier remodeling in the transgenic ren2 rat. Am J Physiol Renal Physiol. 2009 in press.

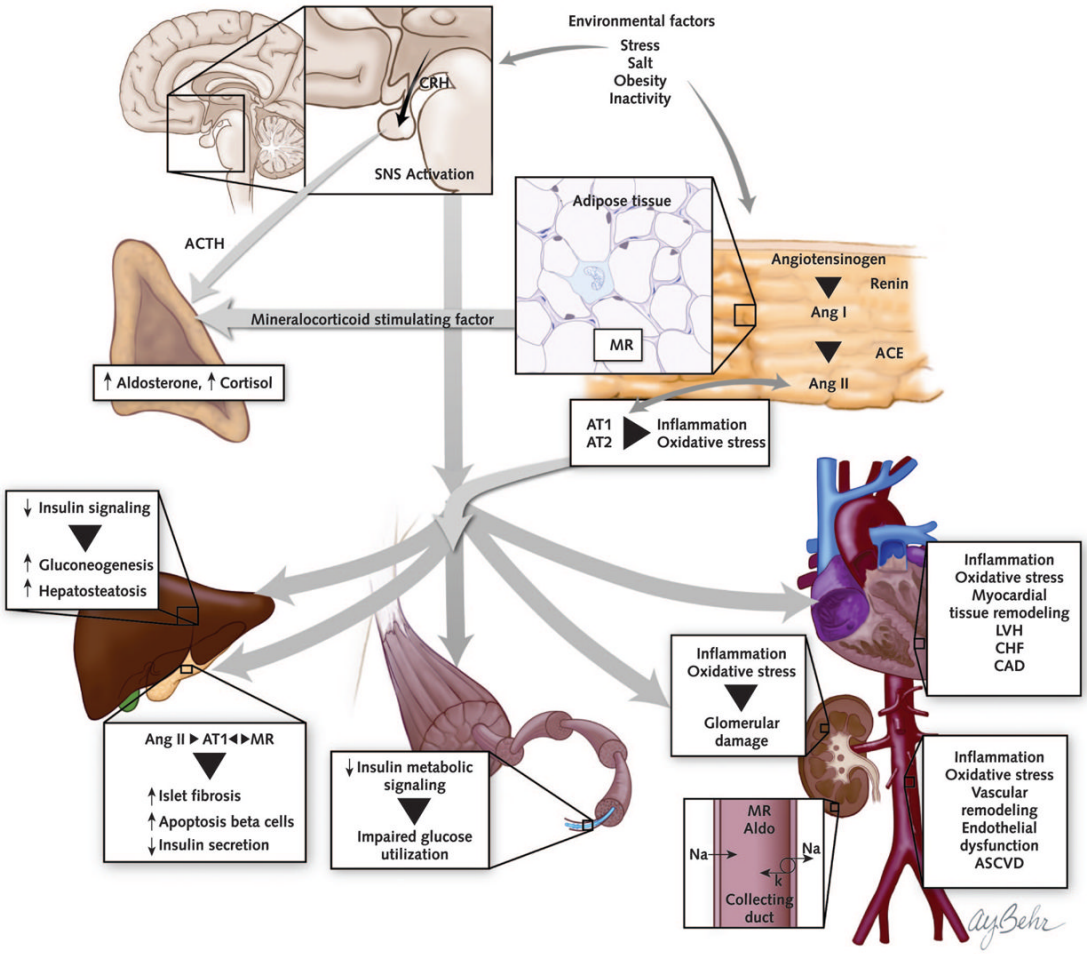

Figure 1. Systemic effects of aldosterone on insulin sensitivity and hypertension

High salt intake, obesity, inactivity, and other environmental factors interact to activate the renin–angiotensin–aldosterone system, with subsequent inflammation and oxidative stress that drive maladaptive tissue responses. ACE = angiotensin-converting enzyme; ACTH = adrenocorticotropic hormone; Aldo = aldosterone; Ang I = angiotensin I; Ang II = angiotensin II; ASCVD = atherosclerotic cardiovascular disease; AT1 = angiotensin type 1 receptor; AT2 = angiotensin type 2 receptor; CAD = coronary artery disease; CHF = congestive heart failure; CRH = corticotropin-releasing hormone; LVH = left ventricular hypertrophy; MR = mineralocorticoid receptor; SNS = sympathetic nervous system.

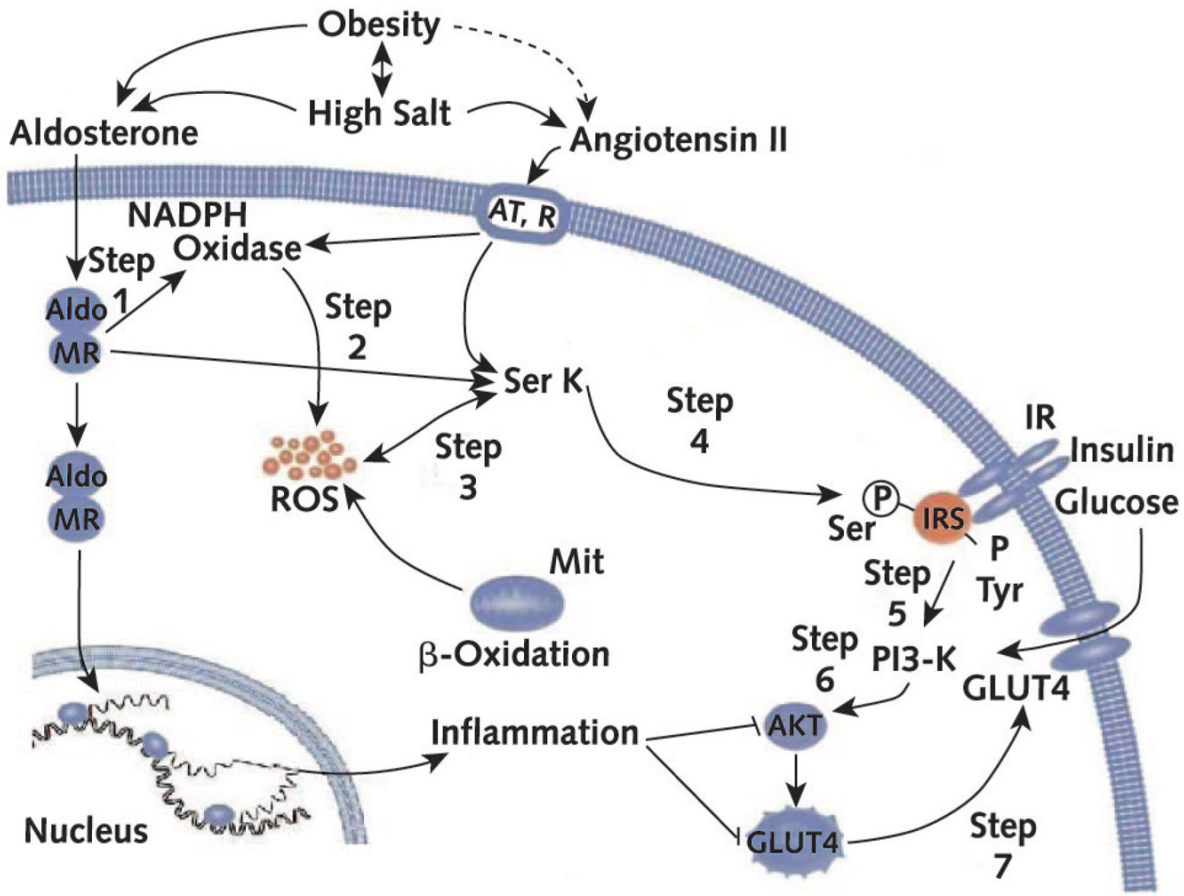

Figure 2. Inhibitory actions of aldosterone and angiotensin II on insulin metabolic signaling in skeletal muscle

Aldosterone and angiotensin II mediate increases in inflammation and ROS that activate redox-sensitive serine kinases and contribute to impaired insulin metabolic signaling. Aldosterone and angiotensin II induce rapid maladaptive responses by stimulation of NADPH oxidase (*step 1*), thus generating ROS (*step 2*). An increase in ROS activates redox-sensitive serine kinase–signaling molecules (*step 3*) (5,20-23). Reactive oxygen species–induced activation of these serine kinases induces phosphorylation of the serine moities of the IRS-1 docking protein (*step 4*). This serine phosphorylation of IRS-1 lessens its engagement with phosphatidylinositol 3-kinase (*step 5*), which leads to decreased activation of protein kinase B (*step 6*) and downstream metabolic effects, such as impaired glucose transport (*step 7*). AKT = protein kinase B; Aldo = aldosterone; AT = angiotensin; AT1R = angiotensin type 1 receptor; GLUT4 = glucose transport 4; IR = insulin receptor; MR = mineralocorticoid receptor; Mit = mitochondria; NADPH = nicotinamide ademine dinucleotide phosphate; P = phosphorus; PI3-K = phosphatidylinositol 3-kinase; R = renin; ROS = reactive oxygen species; Ser K = serine kinase; Tyr = tyrosine.