Role of mineralocorticoid receptor in insulin resistance

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Purpose of review
Recent data suggest that mineralocorticoid receptor activation can affect insulin resistance independent of its effects on blood pressure. This review discusses new evidence linking mineralocorticoid receptor to insulin resistance and the underlying mechanisms of these effects.

Recent findings
Observational studies have shown mineralocorticoid activity to be associated with insulin resistance irrespective of race, blood pressure or body weight. Increased mineralocorticoid activity may be the common link between obesity, hypertension, dyslipidemia and insulin resistance, features that make up the metabolic syndrome. Treatment of primary aldosteronism is associated with a decrease in insulin resistance and provides one of the most convincing evidences in favor of the contribution of mineralocorticoid receptor to insulin resistance. Dietary salt restriction, which increases aldosterone levels, is also associated with an increase in insulin resistance. Potential mechanisms by which mineralocorticoid receptor may contribute to insulin resistance include a decreased transcription of the insulin receptor gene, increased degradation of insulin receptor substrates, interference with insulin signaling mechanisms, decreased adiponectin production and increased oxidative stress and inflammation. Advantages of mineralocorticoid receptor antagonists on insulin resistance have been demonstrated in animal models.

Summary
There may be a benefit of mineralocorticoid receptor antagonists in human insulin resistance states, but more clinical research is needed to explore these possibilities.

Keywords
aldosterone, insulin resistance, mineralocorticoid receptor, obesity

INTRODUCTION

Traditionally, mineralocorticoid effects have been linked to fluid and electrolyte balance with blockade of the mineralocorticoid receptor reducing blood pressure (BP) in individuals with hypertension. Recent studies have shown mineralocorticoid receptor antagonists to improve clinical outcomes in acute myocardial infarction with heart failure, chronic heart failure and diabetic nephropathy [1–5]. These effects of mineralocorticoid receptor blockade are not dependent on BP regulation, but involve beneficial effects of mineralocorticoid receptor blockade on vascular function/injury, inflammation, cardiac fibrosis and renal damage. Accumulating data also suggest a key role of the mineralocorticoid receptor in metabolic regulation. This article reviews scientific evidence linking mineralocorticoids to glucose metabolism and insulin resistance with special emphasis on the underlying mechanisms of these effects.

OBSERVATIONAL STUDIES LINKING MINERALOCORTICOIDS AND INSULIN RESISTANCE

Observational studies have linked mineralocorticoid receptor to insulin resistance in many different conditions including obesity, hypertension, metabolic syndrome, primary aldosteronism and also in normal healthy individuals.

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KEY POINTS

- High aldosterone levels are present in human insulin resistant states and correlate with measures of insulin resistance.
- Mineralocorticoid receptor activity may interfere with insulin signaling, directly or via an increase in oxidative stress and inflammation.
- Advantages of mineralocorticoid receptor antagonists have been demonstrated in animal models but remain to be proven in human insulin resistance states.

OBESITY, MINERALOCORTICOIDS AND INSULIN RESISTANCE

The relationship between mineralocorticoids and insulin resistance has been reported for almost 2 decades beginning with the observation that obese individuals often have high BP, activated renin angiotensin aldosterone system (RAAS) and insulin resistance [6]. Urinary aldosterone excretion and angiotensin II-stimulated aldosterone levels are higher in overweight individuals and aldosterone production correlates with insulin resistance suggesting a potential role for aldosterone in the pathophysiology of obesity-mediated insulin resistance [7]. Weight loss by low calorie diet leads to an improvement in insulin sensitivity as well as a decrease in BP [8], and these changes are associated with reversal of the RAAS overactivity [9]. Similarly, weight loss after gastric bypass surgery lowers RAAS activity and improves insulin resistance [10], whereas weight loss after gastric banding has been demonstrated to reduce aldosterone levels along with a reduction in BP and insulin resistance [11].

The mechanisms of increased mineralocorticoid activity in obesity are not established. According to one hypothesis, fatty acids from visceral adipocytes may induce hepatic formation of an adrenal secretagogue that leads to increased aldosterone production [12]. Alternatively, there may be a direct effect of lipids on aldosterone as a lipid infusion was shown to increase aldosterone along with an increase in insulin resistance [13▪]. Finally, adipocytes may produce factors that directly activate mineralocorticoid receptor [14▪▪].

HYPERTENSION, MINERALOCORTICOIDS AND INSULIN RESISTANCE

Patients with essential hypertension have higher aldosterone levels than normotensive patients and aldosterone may be one of the mediators of increased insulin resistance and dyslipidemia in these patients as suggested by a positive correlation between plasma aldosterone and measures of insulin resistance [15,16]. Thus, aldosterone may contribute to not only the maintenance of high BP but also insulin resistance and increased cardiovascular risk in patients with essential hypertension [17,18].

MINERALOCORTICOIDS AND INSULIN RESISTANCE IN HEALTHY INDIVIDUALS

Aldosterone production is also a predictor of insulin sensitivity in normal healthy individuals. This was demonstrated in a well controlled physiological study wherein angiotensin II-stimulated aldosterone predicted 8% of the variance in insulin sensitivity, which is almost one-third of that predicted by age, BMI and diastolic BP together (23%) [19▪]. In a recent study involving 483 African–Americans without any cardiovascular or renal disease, aldosterone levels were predictive of homeostatic model assessment (HOMA)-insulin resistance independent of all other variables [20]. In another recent study of 1088 individuals plasma aldosterone levels predicted insulin resistance [21▪▪]. Further, when 564 of these individuals were followed for 10 years, insulin resistance developed more often in individuals with high baseline plasma aldosterone than in those with low baseline plasma aldosterone [21▪▪].

MINERALOCORTICOIDS AND THE METABOLIC SYNDROME

Thus, increased aldosterone is observed in obesity and in hypertension. In both conditions, as well as in healthy individuals, aldosterone is associated with insulin resistance. On the basis of these observations and on cellular and animal studies described below, the hypothesis has been proposed that aldosterone is a pathological link between obesity, insulin resistance, hypertension and dyslipidemia, features that make up the metabolic syndrome (MetS) [22,23]. This concept is supported by data from the Framingham Offspring Study that showed high circulating aldosterone levels to be associated with the development of MetS, in a predominately white population [24]. Further, African–American hypertensive men with MetS had high plasma aldosterone that was predictive of HOMA-insulin resistance [25,26]. These data suggest that aldosterone has a role in the causation of insulin resistance irrespective of race, body weight and BP.

GENE POLYMORPHISMS, MINERALOCORTICOIDS AND INSULIN RESISTANCE

Gene polymorphism studies provide another way of exploring the relationship between aldosterone and

insulin resistance. Genetic variations in aldosterone synthase gene (CYP11B2) that are associated with increased aldosterone are predictive of high plasma glucose levels and insulin resistance [27,28]. These gene polymorphisms are also associated with increased risk of type 2 diabetes, hypertension and the MetS [29]. Similarly, an angiotensinogen gene polymorphism that is associated with increased RAAS activity is associated with high fetal total glycated hemoglobin, a surrogate of fetal insulin resistance at birth [30]. Another relation between insulin activity and mineralocorticoids is shown by the hepatic nuclear factor (HNF)1A gene mutation that causes type 3 maturity-onset diabetes of the young, the most common single gene mutation causing type 2 diabetes mellitus. HNF1A-null mice show an overactive adrenal gland with increased aldosterone levels [31].

PRIMARY ALDOSTERONISM AND INSULIN RESISTANCE

Studies on patients with primary aldosteronism provide the most compelling evidence about the role of aldosterone in insulin resistance in humans. Patients with primary aldosteronism have increased insulin resistance and impaired glucose metabolism [32] and serum aldosterone levels correlate with insulin resistance [33]. Removal of aldosterone excess by surgery or by medical therapy improves insulin sensitivity, implicating aldosterone as a main determinant of the alteration in insulin sensitivity [33–35]. Low adiponectin levels have also been described in primary aldosteronism and seem to be the result of aldosterone excess because therapeutic interventions to correct the aldosterone effect reverse these changes [36]. Also, patients with primary aldosteronism in the presence of specific adiponectin gene polymorphisms are more prone to develop MetS [37]. Recently, nonalcoholic fatty liver disease (NAFLD), a known complication of insulin resistance, was found to be more frequent in patients with primary aldosteronism, further indicating a role for aldosterone in inducing insulin resistance [38]. A small study showed that treatment with spironolactone decreases insulin levels and improves insulin sensitivity in NAFLD [39▪].

LOW SALT DIET AND INSULIN RESISTANCE

Additional evidence in favor of aldosterone as a mediator of insulin resistance comes from studies involving manipulations of dietary sodium intake. It is well known that as individuals transition from a liberal to a low salt diet there is activation of RAAS activity. Recent studies demonstrated an increase in insulin resistance in individuals on a low salt diet as compared with a liberal salt diet [40▪,41]. Further, salt sensitivity of BP, due to insufficient suppression of aldosterone production on a liberal salt diet is strongly associated with insulin resistance, which again suggests a role for aldosterone in insulin resistance [42].

Fasting insulin, triglycerides, inflammatory markers and the insulin response to oral glucose, all rise significantly after dietary salt restriction raising the possibility of an effect of RAAS activation on these metabolic parameters [43–45]. Adiponectin levels are lower on lower salt diet as compared with high salt diet [46,47]. In this context, recent studies showing increased mortality in association with low salt intake [48–51] present an interesting argument against the prevailing views about the benefits of low salt diet [52].

POTENTIAL MECHANISMS OF MINERALOCORTICOID INDUCED INSULIN RESISTANCE

A number of in-vitro and in-vivo studies have explored the mechanisms of mineralocorticoid-mediated insulin resistance. These mechanisms are summarized in Fig. 1.

MINERALOCORTICOIDS AND INSULIN RECEPTOR LEVELS

Treatment of human promonocytic cells with aldosterone leads to decreases in glucose uptake and reductions in insulin receptor mRNA levels due to a decrease in insulin receptor gene transcription [53,54]. Addition of a mineralocorticoid receptor antagonist prevents these changes in insulin receptor mRNA levels [53,54]. Further, incubation of 3T3-L1 adipocytes with aldosterone leads to increased degradation of insulin receptor substrate (IRS) 1 and IRS2 [55]. These data suggest an effect of mineralocorticoid receptor on gene transcription and stability of factors involved in the insulin signaling pathways.

MINERALOCORTICOIDS AND OXIDATIVE STRESS

Another suggested mechanism underlying the interaction between mineralocorticoid receptor and insulin signaling may involve reactive oxygen species (ROS). Aldosterone inhibits expression of uncoupling protein-1 (UCP-1) [56] and decreases in UCP-1 are associated with increased production of ROS. In 3T3-L1 adipocytes, activation of

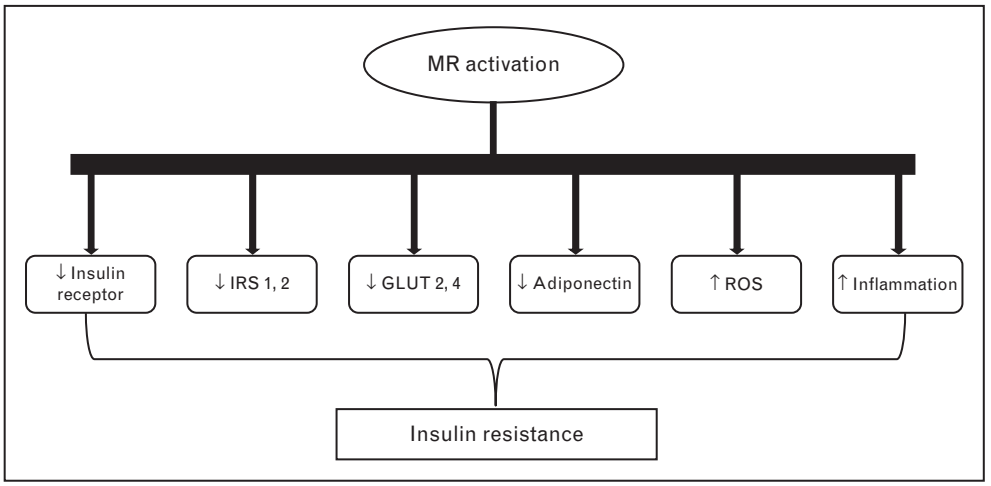

FIGURE 1. Potential mechanisms of mineralocorticoid receptor induced insulin resistance. GLUT, glucose transported; IRS, insulin receptor substrate; MR, mineralocorticoid receptor; ROS, reactive oxygen species.

mineralocorticoid receptor by aldosterone increases intracellular ROS levels [57] and these increases in ROS contribute to the degradation of IRS protein [55,58]. Obesity is a state of oxidative stress due to increased ROS generation by circulating leukocytes as well as adipocytes [59]. Treatment of obese ob/ob and db/db mice with the mineralocorticoid antagonist, eplerenone reduces insulin resistance along with suppression in adipose tissue of macrophage infiltration and ROS production [57]. These results suggest that mineralocorticoid receptor-mediated insulin resistance is the result at least in part of activation of oxidative stress.

MINERALOCORTICOIDS AND INFLAMMATION

Inflammatory pathways are known to affect insulin signaling and induce insulin resistance. It is well established from in-vivo studies, that activation of mineralocorticoid receptor increases inflammation, and mineralocorticoid receptor blockade reduces inflammation, in the vasculature, heart, kidney and adipose tissue [22,60]. There appear to be direct effects of mineralocorticoid receptor on inflammatory molecules, as incubation of 3T3-L1 preadipocytes and adipocytes with aldosterone increases mRNA expression of multiple inflammatory factors including monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor (TNF) α and plasminogen activator inhibitor [61]. By analogy to the effects of TNF-α on inflammation and insulin resistance, some investigators have suggested that induction of inflammation may be the underlying mechanism linking aldosterone to insulin resistance [62]. Consistent with this hypothesis, treatment of obese mice with eplerenone reduces expression of proinflammatory and prothrombotic factors in adipose tissue and increases expression of adiponectin in heart and adipose tissue [61]. These effects of mineralocorticoid receptor blockade on adiponectin and adipokine gene expression may influence insulin resistance.

The relationship between mineralocorticoid receptor, inflammation, oxidative stress and insulin resistance has been studied in the deoxycorticosterone acetate (DOCA) and salt hypertensive rat model. These animals have mineralocorticoid receptor activation resulting in increased oxidative stress, inflammation and insulin resistance; treatment with hemin reduces oxidative stress and inflammation and improves insulin sensitivity [63▪]. Further, treatment of Zucker diabetic-fatty rat with hemeoxygenase-1 reduces aldosterone, reduces markers of oxidative stress and inflammation (e.g. nuclear factor-κB, AP-1, and AP-2), increases AMP-activated protein kinase and increases glucose transported (GLUT4) expression [64].

MINERALOCORTICOIDS AND OTHER INSULIN SIGNALING PATHWAYS

The transgenic Ren2 rat manifests increased tissue RAAS with elevated serum aldosterone and is both hypertensive and insulin resistant with reduced muscle IRS-1 tyrosine phosphorylation, Akt phosphorylation/activation, and GLUT4 expression [65]. These findings suggest that aldosterone contributes to insulin resistance in the transgenic Ren2 rats by interfering with insulin signaling pathways [65]. Similarly, rats injected with aldosterone daily for 15 days showed decreased transcription of GLUT2 and GLUT4 genes and decreased translocation of GLUT4 to the plasma membrane in liver and

skeletal muscle [66]. In DOCA implanted hypertensive rats, GLUT4 levels were depressed several-fold in aortae and carotid arteries compared with sham-treated normotensive rats and uptake of the glucose analog, 2-deoxyglucose (2-DOG), was reduced by 53% [67].

Another mechanism that may involve overlap between mineralocorticoid receptor and insulin receptor signaling is related to RAS-related C3 botulinum substrate 1 (RAC1) pathways. RAC1 is able to directly activate mineralocorticoid receptor even in the absence of mineralocorticoids or glucocorticoids. Overexpression of circulating peptide coupling factor 6 (CF6) in mice increases renal RAC-1 leading to activation of renal mineralocorticoid receptor [68]. These mice also have defects in insulin signaling mechanisms in the skeletal muscle and the liver resulting in a decrease of plasma membrane-bound GLUT4 leading to insulin resistance [68].

MINERALOCORTICOIDS AND ADIPOCYTE DIFFERENTIATION

Aldosterone and mineralocorticoid receptor may also be involved in adipocyte biology at the more basic level. Differentiation of 3T3-L1 preadipoctyes into adipocytes is dependent on the presence of mineralocorticoid receptor. Using siRNA technology to reduce mineralocorticoid receptor and glucocorticoid receptor levels and pharmacological inhibition of mineralocorticoid receptor and glucocorticoid receptor, investigators demonstrated that this differentiation is dependent on activation of the mineralocorticoid receptor by either glucocorticoids or mineralocorticoids [69]. Further, the aldosterone effect on adipose maturation is accompanied by induction of PPAR-γ expression [69]. These results suggest that mineralocorticoid receptor may be an important proadipogenic transcription factor that may mediate both aldosterone and glucocorticoid effects on adipose tissue development [69]. These studies provide further mechanistic support for the concept that mineralocorticoid receptor may be involved in the pathophysiology of obesity and MetS.

MINERALOCORTICOIDS AND INSULIN SECRETION

There is also a school of thought that mineralocorticoids impair insulin secretion, an effect that has been attributed to aldosterone induced hypokalemia. Recently, aldosterone was shown to suppress insulin secretion via activation of ROS [70]. This effect of aldosterone was independent of potassium and angiotensin II and was not mediated through mineralocorticoid receptor [70]. This effect in addition to aldosterone mediated increases in insulin resistance will further impair glucose metabolism.

MINERALOCORTICOID RECEPTOR ANTAGONISTS IN ANIMAL MODELS OF INSULIN RESISTANCE AND METABOLIC SYNDROME

Mineralocorticoid receptor antagonists reverse many of the changes associated with insulin resistance and metabolic syndrome. In a mouse model of diet-induced diabetes and NAFLD, the mineralocorticoid receptor blocker, spironolactone treatment improved glucose tolerance and hepatic mRNA expression of proinflammatory cytokines (TNFα, IL-6, and MCP-1) without any effect on calorie intake or body weight [71▪▪]. In a rat model of RAAS activation, low-dose spironolactone improved IRS-1/Akt phosphorylation in renal cortical tissue and reduced albuminuria [72]. mineralocorticoid receptor blockade reduces renal injury in rodent models of type 1 and 2 diabetes [73] and reduces aortic superoxide production and improves endothelium-dependent vasorelaxation in rodent models of type 1 diabetes [74]. Treatment with mineralocorticoid receptor antagonist also improved muscle insulin signaling parameters and systemic insulin sensitivity in association with reductions in NADPH oxidize activity and ROS production in transgenic Ren2 rats [65]. These results indicate that inhibition of the mineralocorticoid effect might be a beneficial therapeutic approach for multiple phenotypes of insulin resistance.

THERAPEUTIC CONSIDERATIONS

Metabolic dysregulation is common in conditions like diabetes, obesity, polycystic ovarian syndrome (PCOS), hypertension, and heart failure and when present contributes to the pathophysiology of these disorders. Given our increasing understanding of the relevance of aldosterone to the pathophysiology of hypertension, vascular and target organ damage, mineralocorticoid receptor blockade is being used with increasing frequency in the treatment of patients with hypertension and heart failure. With new data implicating the mineralocorticoid receptor in adipocyte biology and glucose metabolism, it may be worth considering the use of mineralocorticoid receptor antagonists in treatment of disorders with metabolic dysregulation.

High aldosterone levels along with high androgen levels are present in women with PCOS [75] and

treatment of PCOS with metformin improves insulin sensitivity along with a reduction in aldosterone and androgen levels [76]. Chlorthalidone, which tends to activate the RAAS, causes an increase in insulin resistance in hypertensive patients that is avoided by addition of spironolactone [77]. Treatment with spironolactone was recently demonstrated to decrease insulin levels in NAFLD [39▪]. Multiple studies have suggested that interruption of the RAAS with angiotensin inhibition can improve insulin sensitivity and potentially reduce the incidence of diabetes [78]. As aldosterone escape is a known phenomenon in patients treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, there may be a role for the use of mineralocorticoid receptor antagonists in addition to these drugs. The largest clinical trials with the use of mineralocorticoid receptor antagonists have been conducted in heart failure [1,2,4], but we were unable to find any literature related to insulin resistance in these trials.

CONCLUSION

Thus, available data suggest a role of mineralocorticoid receptor in the pathophysiology of insulin resistance. Although clinical data show a reduction in insulin resistance after treatment of primary aldosteronism, there is very little available data on the use of mineralocorticoid receptor antagonists for prevention or amelioration of insulin resistance in other clinical conditions. Given the increasing evidence for inappropriately elevated aldosterone levels in many common disorders associated with insulin resistance, for example, obesity and hypertension, this is an important area of future research that could lead to new therapies to prevent complications of insulin resistance like diabetes and cardiovascular disease.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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