Aldosterone and the mineralocorticoid receptor in insulin resistance and diabetes

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ABSTRACT
Aldosterone is a key regulator of water and electrolyte metabolism, but recent evidence from multiple lines of research also identifies it as a major player in other chronic disorders, particularly diabetes and the metabolic syndrome. In this review, we summarize relevant aspects of aldosterone production, secretion, action, the way aldosterone and the mineralocorticoid receptor may impact energy metabolism, and useful take-home messages concerning mineralocorticoid antagonism in patients with type 2 diabetes mellitus. *(Rev ALAD. 2017;7:203-11)*

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RESUMEN
La aldosterona es un regulador clave del metabolismo del agua y los electrolitos, pero la evidencia reciente de múltiples líneas de investigación también la identifica como un actor principal en otros trastornos crónicos, en particular en la diabetes y el síndrome metabólico. En esta revisión se resumen los aspectos relevantes de la producción de aldosterona, así como su secreción, su acción y la forma en que la aldosterona y el receptor mineralocorticoide pueden afectar al metabolismo energético, además de aportar información útil sobre el antagonismo mineralocorticoide en pacientes con diabetes mellitus de tipo 2.

INTRODUCTION

The understanding of aldosterone has evolved a great deal since its discovery and crystallization in 1953 and the first description of hyperaldosteronism as a cause of hypertension and hypokalemia in 1955. Initially recognized as a hormone purely concerned with water and electrolyte metabolism (hence its original name electrocortin), aldosterone and the mineralocorticoid receptor (MCR) are now known to be major players in the pathogenesis of multiple disorders, including type 2 diabetes mellitus (T2DM) and insulin resistance.

ALDOSTERONE AND THE MCR

Aldosterone is produced in the zona glomerulosa, the outermost cell layer of the adrenal cortex. Being a steroid hormone, aldosterone is not stored but produced “on demand” under the influence of three regulators: Angiotensin II (AngII), plasma potassium, and adrenocorticotropic hormone, from the most to the least potent. Once in circulation, 50–70% of plasma aldosterone circulates bound to albumin or corticosteroid-binding globulin. After only 15–20 min, aldosterone is inactivated through conversion to tetrahydroaldosterone in the liver. The best-characterized effects of aldosterone in epithelia are: (i) To promote sodium and water transport from the luminal to the basal side, (ii) to promote movement of potassium from the basal to the luminal side, and (iii) to promote the movement of hydrogen ions from the basal to the luminal side. Consequently, clinically overt aldosterone excess is characterized by arterial hypertension (secondary to sodium and water retention), hypokalemia, and alkalosis.

Regulation of aldosterone secretion

As mentioned above, aldosterone production and secretion are regulated to a large extent by the renin-Ang system and by plasma potassium. When
aldosterone secretion. In the case of K+, glomerulosa cells are characterized by a high K+ conductance, so even minuscule changes in plasma K+ concentration depolarize their plasma membrane and cause opening of voltage-dependent Ca++ channels, Ca++ entry, and aldosterone secretion.\(^4\)

### Aldosterone action and the MCR

The very existence of an MCR was for a long time controversial until its cloning and characterization in 1987\(^9\), almost 35 years after the discovery of aldosterone. The MCR belongs to the 3C family of nuclear receptors, which also includes the cortisol, progesterone, and androgen receptors. In reality, the so-called MCR has an equal affinity for aldosterone and cortisol and binds many other 3-ketosteroids as well\(^10\). This has important implications. Given that cortisol concentrations in plasma are more than 100-fold higher than those of aldosterone, the specificity of aldosterone binding to the MCR in the kidney is achieved through the action of 11-beta-hydroxysteroid dehydrogenase Type II (11-beta-HSD-II), an enzyme that converts cortisol to inactive cortisone. Expression of 11-beta-HSD-II outside the kidney is virtually null. Hence, aldosterone is the primary ligand of the MCR in the kidney, but in extrarenal tissues the MCR is activated mostly by cortisol.

When not occupied by a ligand, the MCR lies in the cytosol, bound to the chaperone HSP90. Binding of aldosterone or other ligand to the MCR induces its translocation to the nucleus and conformational change to the transcriptionally active state\(^11\). MCR activation augments membrane expression of the epithelial sodium transporter epithelial sodium channels (ENaC) by an indirect mechanism. MCR activation strongly induces expression of the serum- and glucocorticoid-regulated kinase 1 (sgk-1). Normally, ENaC is degraded in the proteasome after ubiquitination by the protein Nedd4-2\(^12\). Sgk-1 phosphorylates and inactivates Nedd2-4\(^3\), leading to prolonged residence of ENaC in the apical membrane and increased sodium transport from the tubular lumen to the cell cytoplasm. Activated MCR also increases expression of the gene for the Na+/K+ ATPase, leading to sodium transport from the cytoplasm to the intercellular space, and of K+ from the intercellular space to the cell cytoplasm and eventually (due to leakage) into the tubular lumen\(^14\) (Fig. 2).

Aldosterone also has many established effects beyond water and electrolyte transport. These “non-classic” effects of aldosterone include collagen synthesis, secretion of growth factors, secretion of plasminogen inhibitor activator-1 (PAi-1), and activation of proinflammatory genes\(^15\).

### Influence of Aldosterone/MCR Activation on Insulin Action and Glucose Metabolism

#### Aldosterone, MCR, and beta-cell function

It is well known that hyperaldosteronism-associated hypokalemia impairs insulin secretion\(^16,17\) and that this...
defect is only partially reversible after reestablishment of normal plasma K⁺. Induction of hyperaldosteronism in mouse models of diabetes leads to worsening of glucose tolerance, decreased beta-cell mass, and increased oxidative stress markers. Interestingly, MCR antagonism with spironolactone only partially antagonizes these effects, while diet supplementation with the antioxidant N-acetylcysteine (NAC) completely abolishes them. Taken together, these results suggest the existence of MCR-independent mechanisms that mediate aldosterone-induced beta-cell dysfunction, probably involving the generation of oxidative stress.

**Aldosterone, MCR, and peripheral insulin action**

Activation of the MCR in blood vessels, skeletal muscle, and adipose tissue elicits relevant metabolic effects. Adequate peripheral glucose uptake is determined by tissue perfusion, glucose diffusion through cellular membranes, and patent insulin signaling pathways. In the endothelium, MCR activation reduces nitric oxide production and increases reactive oxygen species (ROS) production through induction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. These actions initially cause endothelial dysfunction and ultimately impair insulin action at the target tissue. In addition, MCR activation in vascular smooth muscle cells reduces the expression of insulin receptor substrate-1 (IRS-1) and downstream Akt signaling, directly inducing insulin resistance. In the same cell type, MCR activation induces anomalous formation of insulin receptor/insulin-like growth factor-1 receptor dimers in the plasma membrane, further impeding insulin signaling. Skeletal muscle as the quantitatively dominant target of insulin action is also affected by aldosterone and MCR activation. In Wistar rats, systemic administration of aldosterone reduces skeletal muscle glucose uptake, along with depleted insulin receptors and reduced expression and phosphorylation of signaling molecules IRS-1 and Akt. Likewise, when MCR were blocked in the Ren2 rat (a model of secondary hyperaldosteronism and insulin resistance) insulin sensitivity and insulin receptor signaling improved markedly, while NADPH oxidase activity and ROS production declined.
The other major target of insulin action is adipose tissue. In vitro studies have revealed a negative impact of aldosterone administration on insulin response by cultured 3T3 adipocytes, accompanied by a drop in IRS-1 and IRS-2 expression, Akt-1 phosphorylation, and 2-deoxyglucose uptake. In the same cell culture model, supplementation of the medium with aldosterone greatly reduced adiponectin mRNA synthesis while enhancing PAi-1 expression in a dose-dependent fashion. Both changes are known to be related with worsened adipocyte insulin sensitivity. In vivo models have confirmed that MCR antagonism (eplerenone) improves tissue expression of the adipocyte health markers adiponectin and peroxisome-proliferator-activated receptor-gamma.

ASSOCIATION BETWEEN ALDOSTERONE/MCR ACTIVATION AND GLUCOSE METABOLISM IN HUMANS

Separate studies have found cross-sectional associations between plasma concentrations of aldosterone and insulin resistance measured by the homeostasis model assessment - insulin resistance (HOMA-IR) or hyperinsulinemic-euglycemic clamp in participants with obesity, essential hypertension, heart failure (HF), or primary hyperaldosteronism. Nevertheless, only one prospective study has found high plasma aldosterone levels to be predictive of future development of insulin resistance in initially non-diabetic subjects after a 10-year follow-up. Of note, patients with primary hyperaldosteronism who underwent adrenalectomy and were followed for 5.2 years showed a significantly lower incidence of T2DM compared to controls with essential hypertension (Hazard Ratio [HR] = 0.60, P < 0.01). Patients with primary hyperaldosteronism treated with adrenalectomy or MCR blockers and followed for 6 months demonstrated improvements in insulin resistance measured as HOMA-IR or area under the insulin curve in an oral glucose tolerance test. Even though these findings suggest that aldosterone blockage or inhibition could have positive repercussions in insulin sensitivity and prevention of T2DM, current evidence is insufficient and randomized trials will have to be undertaken to address this particular hypothesis.

CLINICAL IMPLICATIONS OF MCR ACTIVATION IN PATIENTS WITH DIABETES, PREDIABETES, OR THE METABOLIC SYNDROME

Screen for mineralocorticoid excess in patients with T2DM

Up to 70% of patients with T2DM are hypertensive, and up to 15% of patients with hypertension have some degree of hyperaldosteronism. However, the possibility of primary aldosteronism in patients with T2DM and hypertension is often overlooked, in part because hypertension is often attributed to other risk factors commonly encountered in T2DM patients. The prevalence of primary hyperaldosteronism in subjects with T2DM and uncontrolled or resistant hypertension ranges from 11% to 24% in different populations. This evidence highlights the relevance of screening for hyperaldosteronism in T2DM, especially when there is resistant hypertension, mild or overt hypokalemia or family history of hyperaldosteronism. The screening test recommended by current guidelines is the plasma aldosterone concentration/plasma renin activity ratio.

When needed, select the best MCR antagonist for your patient with T2DM

Since the first description of an orally bioavailable MCR antagonist (spironolactone) by Cella and
collaborators in 1957, there have been major developments in this drug family. Current available MCR antagonists might be roughly classified into steroidal (spironolactone, eplerenone) and non-steroidal (finerenone, esaxerenone) compounds, but so far only steroidal compounds have been approved for use in humans. Differences between these two drug subfamilies lie in their potency and MCR selectivity. Spironolactone is a potent, competitive antagonist of the MCR that also has significant antagonist activities at the androgen and progesterone receptor. This causes undesirable side effects such as gynecomastia, sexual impotence, and menstrual irregularities in a fraction of patients. For this reason, later generations of MCR antagonists have been aimed primarily at the improvement of MCR selectivity and the reduction of side effects. In 1989, eplerenone emerged as a more selective MCR antagonist but with a much lower potency (about 40-fold lower) and affinity for the MCR compared to spironolactone. Thus, eplerenone is a less potent yet better-tolerated alternative to spironolactone. Due to its anti-androgen effect, spironolactone treatment may slightly worsen glycemic control in patients with T2DM, while eplerenone may have a mildly positive effect on glycemic control. Meanwhile, finerenone is a heterobicyclic analog of naphthyridine derivatives. Finerenone is at least as potent as spironolactone but has a much better selectivity toward the MCR than eplerenone (about 500-fold greater). Evidence on the clinical benefits of finerenone in T2DM patients with various comorbidities is growing fast (please see below).

**MCR antagonists reduce mortality in patients with T2DM and HF**

Use of mineralocorticoid antagonists reduces mortality in patients with T2DM and HF in different clinical settings. A recent meta-analysis of four randomized clinical trials estimated the mortality impact of MCR antagonists in these patients at 22% (95% confidence interval [CI]: 12-31%). Khosraviani et al. compared the mortality impact of MCR antagonism in patients with or without T2DM. In this observational study of 3160 patients with systolic HF (left ventricle ejection fraction < 35%) concomitantly receiving a beta-blocker plus an ACE inhibitor or angiotensin-receptor blocker, 2-year all-cause mortality was reduced by an absolute 5.2% (relative risk [RR]: 0.70, 95% CI 0.54-0.91) among spironolactone users with T2DM. Remarkably, this effect did not exist in HF patients without T2DM (RR: 0.89, 95% CI: 0.67-1.19).

In the EPHESUS trial, treatment of patients with T2DM and HF with eplerenone following an acute myocardial infarction reduced the risk of cardiovascular death or cardiovascular hospitalization by 17%. Similarly, subgroup analyses of the EMPHASIS-HF study found a 46% reduction in the primary composite endpoint of hospitalization for HF or death from cardiovascular causes for patients with T2DM who received eplerenone (HR 0.54, 95% CI: 0.42-0.70). Supported by this evidence, the 2016 ACC/AHA/HFS HF guidelines update recommends the use of MCR blockers in patients with diabetes and HF with reduced ejection fraction, additional to inhibition of the renin-Ang system. The efficacy and safety of finerenone in the context of HF was evaluated in the Mineralocorticoid Receptor antagonist Tolerability Study-HF. This study compared the use of different doses of finerenone versus eplerenone for 90 days in patients with worsening HF and chronic kidney disease and/or diabetes mellitus. The primary endpoint of a 30% or greater reduction in N-terminal pro-B-type natriuretic peptide occurred at similar rates in all study groups. However, a secondary composite outcome of death from any cause, cardiovascular hospitalization, or emergency presentation to hospital occurred at the lowest rate in the finerenone 10 mg group (HR vs. eplerenone: 0.56; 95% CI: 0.35-0.90).
MCR antagonists may provide renal benefits in patients with T2DM

MR blockers also have shown to improve surrogate markers of renal dysfunction in patients with T2DM\(^8\),\(^9\). In patients with diagnosed diabetic nephropathy, the addition of finerenone to an AngII-receptor blocker or ACE inhibitor resulted in improvements in the urinary albumin/creatinine ratio compared with placebo\(^8\). Likewise, a second study in Japanese patients with diabetic nephropathy found an anti-albuminuric effect of finerenone addition to inhibition of renin-Ang system, without increases in serum potassium or deterioration of glomerular filtration\(^8\).

MCR antagonists are indicated, yet seldom used, in patients with T2DM and resistant hypertension

Multiple studies have addressed the role of MR antagonists in the management of hypertensive patients with T2DM\(^8\)–\(^10\). A recent meta-analysis comprising eight randomized trials and one prospective observational study concluded that MCR blockers provide a 9.4 mmHg reduction (95% CI: 12.9-5.9) in systolic blood pressure and a 3.8 mmHg (95% CI: 5.5-2.2) reduction in diastolic blood pressure compared with placebo\(^9\). The effect was even greater in patients already receiving an ACE inhibitor or AngII receptor antagonist and was accompanied by only mild increases in plasma potassium (0.4 mEq/L, 95% CI: 0.3-0.5 mEq/L). Urinary albumin excretion was also systematically reduced across studies. Despite all the available evidence demonstrating morbidity and mortality advantages for selected patients treated with MCR antagonists, they are underutilized in clinical practice\(^9\). It has been estimated that only 32% of patients eligible for an MCR antagonist are actually prescribed one\(^9\).

CONCLUSION

Aldosterone and the MCR are relevant players in the pathogenesis and management of diabetes and its complications. Clinicians should bear in mind the potential advantages of blocking MCR in patients with T2DM who may benefit from such therapy.

REFERENCES