Mineralocorticoid Receptor Antagonists for the Treatment of Hypertension and the Metabolic Syndrome

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Editorial Commentary

Increasing evidence suggests a link between the metabolic syndrome and aldosterone. Patients with obesity and the metabolic syndrome have been found to have increased adrenal production of aldosterone and increased cortisol levels, whereas weight reduction is associated with a decrease in aldosterone. A high-fat diet has been shown to lead to an upregulation of mineralocorticoid expression, and adipocytes produce aldosterone through angiotensin II–mediated aldosterone synthase, which is regulated by calcineurin. Increased levels of aldosterone are associated with brown fat dysfunction and inflammation of white fat, as well as several other adverse cardiovascular and renal effects including mitochondrial dysfunction, an increase in reactive oxygen species, macrophage infiltration and inflammatory cytokine activation, myocardial and vascular fibrosis and hypertrophy, endothelial dysfunction, mesangial cell inflammation and fibrosis, podocyte loss, albuminuria, progressive renal dysfunction, insulin resistance, pancreatic β-cell dysfunction, sympathetic nervous system activation, ventricular and atrial arrhythmias, as well as sodium retention, potassium loss, and hypertension. Mineralocorticoid receptor antagonists (MRAs) have been shown to decrease inflammation and myocardial fibrosis in patients with obesity and the metabolic syndrome, as well as to provide target organ protection in patients with hypertension independent of a drop in blood pressure and to reduce total mortality and total hospitalizations in patients with chronic heart failure and a reduced left ventricular ejection fraction. One can therefore postulate that aldosterone and activation of the MR play a critical role in the cardiovascular and renal consequences of the metabolic syndrome and that MRAs would have a beneficial effect in preventing these consequences.

In this issue of Hypertension, Bugioni et al report on the measurement of plasma aldosterone levels in a random sample (n=1674, ≥45 years of age) of the general population from Olmsted county, MN. They noted that aldosterone levels were associated with hypertension, central obesity, chronic renal disease, the metabolic syndrome, as well as increased triglyceride levels, concentric left ventricular hypertrophy, and atrial fibrillation after adjusting for age and sex. Aldosterone levels in the highest tertile correlated with lower naturetic peptide levels and mortality. Although most of these associations remained significant after excluding patients with an aldosterone level above the normal range, the association with mortality did not remain significant. Of interest was the finding that aldosterone levels were significantly higher in those patients with hypertension treated with antihypertensive medications, likely reflecting aldosterone breakthrough or escape in those treated with a renin–angiotensin–aldosterone system inhibitor. The authors suggest that aldosterone levels within the normal range might be a biomarker of cardiorenal and metabolic disease and that MRAs and chronic naturetic peptide therapy might delay the onset or progression of cardiovascular and cardiorenal disease in high-risk subjects identified by determining plasma aldosterone levels.

Although high aldosterone levels within the normal range may correlate with the components of the metabolic syndrome and its cardiovascular and cardiorenal consequences, one should be skeptical of how useful and cost-effective this measurement might be for screening patients in the general population for the use of MRA or naturetic peptide administration. Measurement of plasma aldosterone levels has not been found to be particularly useful in selecting patients for the use of an MRA with chronic heart failure and a reduced left ventricular ejection fraction and heart failure and a reduced left ventricular ejection fraction early postmyocardial infarction in whom MRAs have been shown to be effective in reducing total mortality. In part, this may be related to the fact that the MR can be activated by both aldosterone and cortisol, as well as the fact that MR activation is in part determined by the level of sodium intake and oxidative stress. Furthermore, as pointed out above MR expression may vary depending on dietary fat intake. Given the association of high aldosterone and cortisol levels with the components of the metabolic syndrome and the recent finding that there is an increased sensitivity to activation of the MR with age, one might argue that it would be more efficient and cost-effective to consider treatment of patients with the metabolic syndrome with an MRA especially the aged, regardless of their baseline aldosterone level.

The finding by Bugioni et al that patients with hypertension treated with an antihypertensive agent had significantly elevated aldosterone levels along with the previous knowledge that treatment with a angiotensin-converting enzyme inhibitor or angiotensin receptor blocker leads to aldosterone breakthrough or escape in a relatively high percentage of patients would argue for earlier use of an MRA in patients with hypertension, especially those with the metabolic syndrome. The finding that patients with hypertension treated with a
angiotensin-converting enzyme inhibitor and the thiazide diuretic chlorthalidone have an increase in directly measured sympathetic nerve traffic and that the addition of an MRA but not a angiotensin receptor blocker significantly reduces sympathetic nerve traffic\textsuperscript{11} would also support consideration of an MRA in patients with hypertension. At the moment, MRAs are not widely used early in the therapy of hypertension and are often considered fourth line drugs in the treatment of patients with resistant hypertension already treated with a thiazide diuretic, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a calcium channel blocking agent at target or maximally tolerated doses. The increasing data linking aldosterone and activation of the MR to target organ damage along with the recent data suggesting an increased sensitivity to aldosterone in the elderly\textsuperscript{11} would, however, argue for the earlier and wider use of MRAs in patients with hypertension, especially the elderly, and those with the metabolic syndrome. The results of the study by Buglioni et al\textsuperscript{10} suggesting that MRA and natriuretic peptide administration might be of value in preventing the development of the metabolic syndrome, as well as its cardiovascular and cardiorenal consequences in the general population in conjunction with the increased understanding of the role of cortisol in activating the MR and the evidence for dysregulation of aldosterone in the aged,\textsuperscript{11} provide the basis for further efforts to detect those individuals in the general population at greatest risk of developing the metabolic syndrome, cardiovascular, and cardiorenal disease and to prevent their development with an MRA and natriuretic peptide. In the long run, it may be more effective to prevent rather than to treat the consequences of the metabolic syndrome, such as chronic kidney disease, atrial fibrillation, heart failure, and their consequences. However, before attempting to screen the general population for an increase in serum aldosterone levels and evidence of activation of the MR and to move the use of MRAs from fourth line therapy to an earlier stage in the treatment of patients with hypertension and to prevent the metabolic syndrome and its cardiovascular and renal consequences with an MRA or natriuretic peptide, we will need well-designed prospective randomized trials evaluating the efficacy and especially the safety and cost-effectiveness of such a strategy. Regardless, the study by Buglioni et al\textsuperscript{10} is of importance and helps to focus our attention on the potential benefits of the early use of an MRA and a natriuretic peptide to prevent the consequences of the metabolic syndrome and hypertensive heart disease.

Disclosures
None.

References
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