Editorial Commentary

Specific Aldosterone Synthase Inhibition
A Potential Improvement Over Mineralocorticoid Receptor Antagonism?

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We have come to appreciate the many physiological and pathophysiological functions of adrenal steroid hormones in health and disease and the benefits and adverse effects of therapeutic manipulations. Glucocorticoids are an indispensable component in the treatment of inflammatory conditions. Blockade of the mineralocorticoid receptor (MR) with spironolactone is a long-established diuretic therapy in states of volume overload. In patients with heart failure, MR blockade prolongs survival because of beneficial effects on the heart. In patients with treatment-resistant arterial hypertension, MR blockade has been found to provide superior blood pressure–lowering effects compared with α-blockers and β-blockers.1 Even in patients on hemodialysis, MR blockade seems to prolong survival.2

Much work has been invested in deciphering the molecular pathways involved in steroid hormone function. On ligand binding, steroid hormone receptors translocate to the nucleus to activate or repress target genes. It has been proposed, however, that some of the effects of steroid hormones, including aldosterone, are not mediated by the known MR but rather by nongenomic effects that do not involve gene translation and, therefore, produce a faster response. In contrast to the classical genomic effects, such nongenomic effects are less well understood on a molecular level. In humans, the existence of nongenomic effects has been difficult to prove. Experimental studies suggest that GPR30 may mediate some of the postulated MR-independent effects of aldosterone.

Aldosterone-synthase inhibition has been developed as a novel alternative strategy to MR blockade. In contrast to MR blockade, aldosterone-synthase inhibition would be able to attenuate both genomic and nongenomic effects. On the contrary, there is evidence that in many species, cortisol (or a related glucocorticoid) is the main activator of the MR. In fact, in evolutionary terms, the MR seems to have developed even before aldosterone, suggesting that it was not designed as a specific receptor for aldosterone. Aldosterone synthesis by CYB11B2 and the specificity of the MR for aldosterone through the activity of 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) seem to have been developed later in evolution. In epithelial tissues, such as colon and distal kidney tubules, 11β-HSD2 converts cortisol to cortisone. Cortisone, as opposed to cortisol, does not activate the MR, and thus, 11β-HSD2 protects the MR from cortisol-induced activation. However, when activity of 11β-HSD2 is reduced (eg, by oxidant stress), or in nonepithelial tissues where 11β-HSD2 is absent (such as in the heart), cortisol potently activates the MR. There is also evidence that the MR can be activated aldosterone-independently, for example, via rac1.3 Compared with MR blockade, a disadvantage of aldosterone-synthese inhibition could thus, be unchecked activation of the MR by cortisol or by other, aldosterone-independent mechanisms, such as rac1 activation.

One of the first available aldosterone-synthese inhibitors was LCI699, an orally active compound initially developed as a new treatment for arterial hypertension. In patients with primary hyperaldosteronism and hypertension, it indeed safely lowered plasma aldosterone levels, but was found to have only moderate blood pressure–lowering effects.4 In patients with essential hypertension, LCI699 did not seem to be as effective as the MR blocker eplerenone in its blood pressure–lowering effects.5 In the end, the main issue with LCI699 was its insufficient selectivity because it not only inhibited aldosterone synthase (CYP11B2) but also inhibited cortisol synthase (CYP11B1) at lower doses.6 As a result, LCI699 is now under development as a treatment for hypercortisolism.

In this issue of Hypertension, the article by Bogman et al7 provides preclinical and early clinical data on RO6836191, a compound developed by the pharmaceutical company Hoffmann-La Roche. In vitro, RO6836191 inhibited CYP11B2 versus CYP11B1 at 1:100-fold lower concentrations, a specificity ratio much improved from the 1:3.6 reported for LCI699. A histological changes of the adrenal gland as well as hormonal responses after adrenocorticotropic hormone challenge were then investigated in cynomolgus monkeys treated with RO6836191 at doses from 0 to 40 mg/kg. In the adrenals, increased expression of CYP11B2 and expansion of the zona glomerulosa were found, consistent with potent CYP11B2 inhibition after RO6836191 treatment. Even at the lowest dose, RO6836191 treatment blunted aldosterone release. Only at higher doses of ≥30 mg/kg, the aldosterone precursor 11-deoxycorticosterone (11-DOC) and the cortisol precursor 11-deoxycorticisol increased. Cortisol and corticosterone levels, however, decreased only at the maximum dose of 40 mg/kg.
Finally, the authors report on short-term hormonal effects of RO6836191 at doses of 1 to 360 mg in humans. RO6836191 decreased plasma aldosterone levels dose-dependently, with a maximum suppressive effect on aldosterone levels being observed already at a dose of 10 mg. Urinary sodium to potassium excretion ratio increased at doses of 3 mg or higher, in line with expected diuretic effects. Increases of 11-DOC and 11-deoxycorticisol were found at doses above 90 mg. Plasma cortisol levels were unchanged at all doses tested. In addition, cortisol release after adrenocorticotropic hormone challenge (either via direct adrenocorticotropic hormone infusion or by postural stimulation) was not affected.

In previous studies with LCI699, the lowest dose that produced a decrease in aldosterone already led to an increase of 11-DOC.14 This seems to be different in the current study with RO6836191: while aldosterone already decreases at 10 mg, 11-DOC rises only at 90 mg. Of note, the dose–response effect on the cortisol precursor 11-deoxycortisol is remarkably similar to that on the aldosterone precursor 11-DOC. Would one not expect a much smaller 11-deoxycortisol increase, compared with 11-DOC, if cortisol synthesis were not affected? Can these results be explained simply by the longer half-life of cortisol versus aldosterone (66 minutes versus <20 minutes)?26 We think that more studies are required to rule out clinically significant suppression of cortisol with RO6836191.

In addition to the effects on cortisol, the increase of 11-DOC could be a further obstacle for the clinical use of aldosterone-synthase inhibition in cardiovascular and renal medicine. Contrary to the traditional impression that 11-DOC is simply a mostly inactive intermediate in the pathway to aldosterone and corticosterone synthesis, there is substantial evidence that 11-DOC itself activates both the MR and the GR,8 and this may have contributed to the relatively weak anti-hypertensive effects observed with LCI699.4,5 Furthermore, it was recently discovered that the enzyme ARK1C3 (aldo-keto-reductase 1C3) protects the MR from activation by 11-DOC, similar to 11β-HSD2 affording protection of the MR from cortisol-induced activation.10 To date, little is known on the distribution and regulation of ARK1C3.

In the present study by Bogman et al.,2 blood pressure was not affected. Perhaps this is not a surprise because the included subjects were healthy and normotensive. But even in the case that future studies in hypertensive patients show effective blood pressure lowering with this compound, will aldosterone-synthase inhibition, as a principle, provide more protection from target-organ damage than MR blockade? This was indeed suggested by a small experimental study in transgenic animals.6 One remains slightly doubtful considering the substantial body of evidence pointing at the MR rather than aldosterone as a key mediator of cardiovascular and renal injury.11 More research is required ideally including head-to-head comparisons of these 2 treatment principles (even noninferiority-designed clinical studies would be welcome!). Perhaps, aldosterone-synthase inhibition can be developed to an effective treatment option for cardiovascular and renal disease.

Disclosures

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