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COMMENT

Effects of esaxerenone, a nonsteroidal mineralocorticoid receptor blocker, independent of urinary sodium/potassium ratio and salt intake

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Mineralocorticoid receptors (MR) are expressed in epithelial and non-epithelial tissues, including the kidney, colon, brain, heart, vasculature, and adipose tissue. MR activation in the kidney induces sodium reabsorption, accompanied by potassium ion excretion, leading to elevated blood pressure (BP). The broader effects of MR activation include sympathetic nervous system activation and increased oxidative stress, which contribute to inflammation, remodeling, apoptosis, and fibrosis in the cardiovascular tissues. Consequently, MR activation has been implicated in the etiology of hypertension and cardiovascular diseases. High salt intake enhances MR activity independent of aldosterone through the small guanosine triphosphatase (GTPase) Ras-related C3 botulinum toxin substrate 1 (Rac1), thereby contributing to salt-sensitive hypertension and organ damage [1, 2].

Therefore, MR blockers (MRBs) are expected to be crucial in treating patients with MR activation, including those with excessive salt intake. The ability to predict endogenous MR activity and, consequently, the degree of antihypertensive effects of MRBs is important; however, such methods have not yet been established.

In this issue of *Hypertension Research*, Katsuya et al. [3] investigated whether the baseline sodium/potassium ratio, an indirect indicator of salt intake and MR activity, and baseline estimated 24-h urinary sodium excretion, an indicator of salt intake, could predict the antihypertensive effect of esaxerenone, a nonsteroidal MRB. This exploratory open-label interventional study (ENaK Study) involved patients with essential hypertension inadequately controlled with an angiotensin receptor blocker (ARB) or a calcium channel blocker (CCB). Esaxerenone significantly reduced morning home BP, bedtime home BP, and office BP, along with a notable decrease in the urinary albumin-to-creatinine ratio (UACR), a risk factor for cardiac and renal events [4] and N-terminal pro-brain natriuretic peptide (NT-proBNP), a predictor of cardiovascular risk and kidney damage [5] (Fig. 1). These effects were consistent irrespective of the concomitant use of antihypertensive drugs (ARB and CCB) and were achieved without clinically relevant serum potassium elevation or novel safety concerns.

The antihypertensive effect of esaxerenone was independent of the baseline urinary sodium/potassium ratio. This result is unexpected as a previous substudy of a long-term phase 3 study showed that the antihypertensive effect of esaxerenone monotherapy was stronger in patients with higher than lower sodium excretion at baseline [6]. The discrepancy was speculated to be attributable to the lower estimated 24-h urinary sodium excretion at baseline (169.2 ± 44.2 mEq/day) in the present study compared to that in the phase 3 substudy (212.8 ± 97.4 mEq/day). However, the reason for this remains unknown, and future studies are required to address this issue. Furthermore, the urinary sodium/potassium ratio is not a suitable indicator of MR activity because of its susceptibility to the influence of numerous factors [7]. Therefore, predicting the antihypertensive effect of esaxerenone based on the urinary sodium/potassium ratio is challenging in some patients. Additionally, the antihypertensive effect of esaxerenone was independent of the estimated 24-h urinary sodium excretion at baseline. This observation demonstrates that esaxerenone is effective not only in patients with essential hypertension who have a high salt intake but also in those

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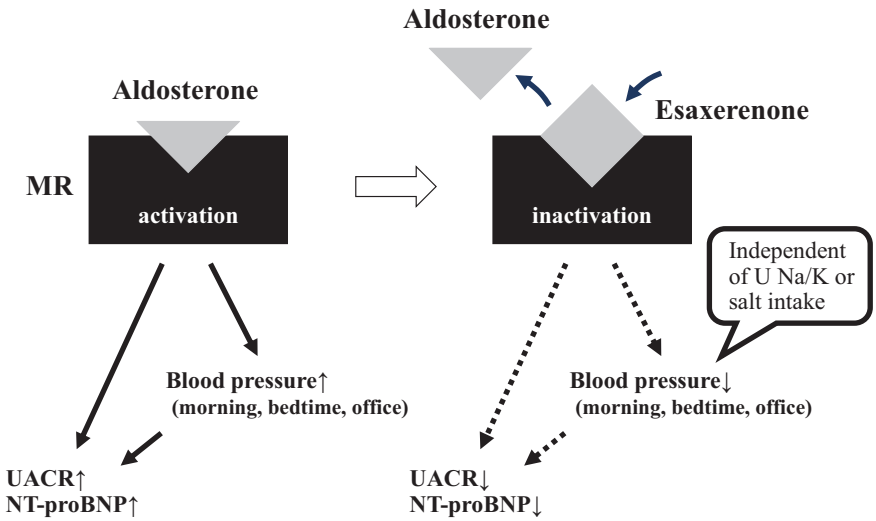

Fig. 1 Effects of esaxerenone in patients with hypertension inadequately controlled with an ARB or a CCB. MR mineralocorticoid receptor, UACR urinary albumin-to-creatinine ratio, NT-proBNP N-terminal pro-brain natriuretic peptide, UNa/K urinary sodium/potassium ratio

with a low salt intake, suggesting the existence of patients with hypertension and MR activation due to mechanisms other than Rac1 activation.

In this study, esaxerenone reduced morning home BP, bedtime home BP, and office BP in patients with hypertension inadequately controlled with either an ARB or CCB. ARBs decrease the plasma aldosterone concentration (PAC) by suppressing aldosterone secretion from the adrenal cortex through antagonistic action on the angiotensin II type 1 receptor. In this study, the ARB subcohort tended toward a lower baseline PAC than the CCB subcohort, although the difference was not statistically significant. Despite this observation, the BP reduction achieved with esaxerenone was substantial in both subcohorts, suggesting that the antihypertensive effect of esaxerenone may involve inhibiting MR activation independently of aldosterone.

Here, esaxerenone significantly reduced the UACR and NT-proBNP levels in the ARB and CCB cohorts. It is anticipated that the ARB treatment had already exhibited renoprotective and cardioprotective effects. However, esaxerenone treatment reduced these parameters further. Thus, esaxerenone may be a therapeutic option capable of reducing the risk of cardiovascular and renal events in patients with hypertension.

Compliance with ethical standards

Conflict of interest SM and AI received honorariums from Daiichi Sankyo Company Limited as a lecture fee.

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