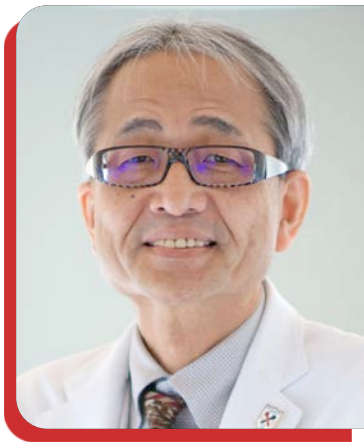
FOCUS ON ALDOSTERONE

Mineralocorticoid Receptor (MR)-associated Hypertension: Over-activation of MR by 'Greedy Kidney and Guts' for salt and sugar



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Significantly wider roles of mineralocorticoid receptors (MR)

Evolutionally, MR had been developed long before the emergence of aldosterone and possesses high binding affinity to steroid hormones other than aldosterone, including glucocorticoid. MR is activated by high aldosterone, a typical example of which is primary aldosteronism. The activation of MR by glucocorticoid, escaped from degradation by 11β hydroxysteroid dehydorgenase (HSD) type2 through the defect of HSD11B2 is known to cause hypertension (apparent mineral corticoid excess syndrome; AME).[1]

Thus, it is postulated that MR has wider biological activity not restricted to salt retention in the body through the kidney (sodium re-absorption) or the colon (sodium absorption). MR are expressed in the heart, blood vessels, the brain, the skin and macrophages. Significant roles of MR in several organs have been demonstrated in many clinical trials. Spironolactone has been used for more than 60 years. In 1957, the first human trial using spironolactone was performed, and in 1999, the epoch-making trial, the randomized aldactone evaluation study (RALES) study to show the effectiveness of spironolactone for life-saving for heart failure patients was reported. Eplerenone was developed as MR-specific MRB, and again life-saving effect for patients with left ventricular dysfunction after myocardial infarction was reported in eplerenone in post-myocardial infarct heart failure (EPHESUS) trial in 2003. Recent meta-analyses demonstrate the effectiveness of MRB for patients with chronic kidney diseases (CKD) or diabetes mellitus (DM).[2]

MR-associated hypertension

In 2012, we proposed the concept of "MR-associated hypertension", that is, the hypertension caused by over-activation of MR with wide range of plasma aldosterone level.[3] Primary aldosteronism with high plasma aldosterone level is the typical example of MR-associated hypertension but it is not only the cause of MR-associated hypertension. Even in low plasma aldosterone concentration states, MR can be over-activated and MR-associated hypertension occurs. MR blockers (MRB) are quite effective for MR-associated hypertension.

MR-associated hypertension is categorized into hypertension with elevated plasma aldosterone level and with normal or low aldosterone level. In the former category, the plasma aldosterone level usually exceeds 150pg/ml. Primary aldosteronism and aldosterone-associated hypertension exhibit low renin and high aldosterone level and in aldosterone breakthrough phenomenon during

ACE inhibitor or ARB administration plasma renin activity is high. In obesity, obstructive sleep apnea or sleep disorders, plasma renin and plasma aldosterone are in proportion high. In the latter category, in obesity, chronic kidney disease (CKD), polycystic ovary disease, high serum or tissue cortisol level, MR is over-activated in spite of normal aldosterone level.

There are several postulated mechanisms of over-activation of MR. Increased expression of MR, increased sensitivity of MR and we focus upon MR protein stabilization. Other investigators revealed MR over-stimulation through Rac1 by excessive salt intake.[4]

Therefore, several risk factors including left ventricular hypertrophy, diabetes, obesity, metabolic syndrome, salt and stress could activate MR via aldosterone dependent and independent pathways.

We are interested in the activation of MR by salt and sugar themselves. We focus on the significance of MR expressed in the intestines for sodium absorption. Administration of deoxycorticosteroid acetate (DOCA) and high salt induced the up-regulation of epithelial sodium channel (ENaC) β, the target molecule of MR in the intestines. Intestine specific MR knock-out mice exhibited blunted increase of blood pressure by DOCA and high salt loading, indicating the significant role of intestinal MR for sodium absorption and blood pressure regulation. High salt induces up-regulation of intestinal MR activity which is involved in sodium absorption and blood pressure regulation.[5]

We also demonstrated that high sugar induces MR protein stabilization by PKC β activation, O-N-acetylglucosamine (GlcNac) modification or EGF receptor-ERK activation.[6,7,8]

Greedy Organ hypothesis for salt and sugar

In 2021, in relation to excessive salt and sugar intake and occurrence of non-communicable diseases (NCDs), including hypertension, we have proposed "Greedy Organ Hypothesis".[9] Excessive intake of salt and sugar are sensed by the kidney and the intestines. And then, these organs up-regulate sodium-glucose co-transporters, SGLTs and come to absorb salt and sugar greedily. Excessive salt intake through SGLT2 makes the kidney greedy to induce hypertension/CKD. Excessive food intake through SGLT1 make the intestines greedy to induce obesity/DM. Furthermore, there is a "crossing" relationship between "greedy organs" and NCDs, that is, "greedy kidney" can cause obesity/DM and "greedy intestines" can cause hypertension/CKD.

We reported that renal proximal tubular cells sense high glucose levels at their basolateral side and increase uptake of glucose by upregulating SGLT2 expression. Furthermore, high glucose upregulates the expression of gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK) and Glucose 6-phosphatase and induces gluconeogenesis. We think that these responses of renal tubular cells to high glucose are "greedy".[10]

The intestinal epithelial cells similarly behave to the renal tubular cells. Guts sense high sugar level by T1R3 ("Sweet Receptor") and up-regulate the expression of SGLT1. Recently, we reported that the intestines are also greedy to salt for upregulation of SGLT1. Transient administration of high salt to spontaneously-hypertensive rats (SHR) induced up-regulation of not only sodium hydrogen exchanger 3 (NHE3), but also SGLT1 and this effect persisted after returning to normal salt diet. We elucidated that this effect of transient high salt is caused by overactivation of intestinal renin-angiotensin system.[11]

Greedy Genes and MR-associated hypertension

Greedy kidney and intestines induced by high salt and sugar over-activate MR and induce MR-associated hypertension.

We call the genes to be activated by high salt and sugar and to make organs greedy are "greedy genes". In addition to SGLT1 and 2, the genes for MR and its target molecules, such as epithelial sodium channel (ENAC) can be the greedy genes. Therefore, MRB are effective to alleviate greedy organs to suppress NCDs, including hypertension.

Development of Non-steroidal MRB and their clinical potencies

Recently, esaxerenone was developed with non-steroidal structure which possesses high affinity and specificity to MR and exhibits long elimination half-life. In vitro binding experiment, esaxerenone exhibits around one-order of magnitude higher than spironolactone and two order of magnitude higher than eplerenone binding affinity to MR.[12]

We conducted a double-blind phase III study of esaxerenone compared with eplerenone in patients with essential hypertension in 2020.[13] Esaxerenone 2.5mg elicited comparable hypotensive effect to eplerenone 50mg both in systolic and diastolic blood pressure. Esaxerenone 5mg exhibited significantly a stronger effect than 2.5mg and eplerenone 50mg. 5mg esaxerenone caused 17mmHg in systolic and 8mmHg in diastolic blood pressure reduction. We analyzed the differential effect of esaxerenone on dipper, non-dipper, extreme dipper and riser blood pressure variation patterns. To dippers, it exerted similar hypotensive effect throughout the day.[14]

We also investigated the efficacy and safety of dosage-escalation of esaxerenone from 1.25 to 5mg added to a renin-angiotensin system (RAS) inhibitor in hypertensive patients with type 2 diabetes and albuminuria in a single-arm, open-label study.[15] Five mg esaxerenone induced 20/8mmHg blood pressure reduction in hypertensive patients with diabetes and significantly reduced albumin excretion with no apparent adverse effect, including elevation of serum K level.

We further investigated antihypertensive effects and safety of esaxerenone in patients with moderate kidney dysfunction with eGFR between 30 to 60, as monotherapy or add-on therapy with RAS inhibitors.[16] In both studies, blood pressure was significantly reduced by 18mmHg in systolic and 8-9mmHg in diastolic. Esaxerenone exhibited no serious effect on the elevation of serum K level or the increase of creatinine or decrease of eGFR.

Interestingly, esaxerenone exerted similar hypotensive action in the patients with RAS inhibitors, compared to other groups. This observation indicates that MR can be activatedbeing independent of renin-angiotensin-aldosterone cascade. This clinical observation indicates the existence of MR-associated hypertension.[17]

The effectiveness of another non-steroidal MRB, finerenone was reported in diabetic kidney disease patients around 2020.[18,19] It was demonstrated to exert weak effect on blood pressure but elicit significant suppressive action on inflammation and fibrosis. In FIDELIO-DKD, FIGARO-DKD and the combination analysis of these two studies, FIDELITY demonstrated that albumiuric diabetic CKD patients with median eGFR of 58ml/min and albumin excretion of 515mg/day, taking RAS inhibitors significantly inhibited cardiovascular or renal events with HR of 0.82 or 0.87.[20]

The reason and mechanism of differential action on blood pressure between two non-steroidal MRBs, esaxerenone and finerenone has not been fully known yet.

Positioning of MRB in world guidelines

In the 2020 ISH Guidelines, MRB are recommended as secondary medication. They are preferred for resistant hypertension or hypertension with HFrEF. 2017 ACC/AHA recommended MRB to hypertension with stable ischemic heart disease and HFpEF. 2018 ESC/ESH recommended MRB to hypertension with coronary artery disease, chronic kidney disease, HFrEF, and left ventricular hypertrophy. Our Japanese guideline states that MRB are effective for low renin hypertension and hypertension with chronic heart failure or after myocardial infarction. Only our guideline mentions esaxerenone as follows; Esaxerenone could be carefully administered to diabetics with albuminuria/proteinuria and patients with moderate renal dysfunction, based upon our evidence.

MRB could exert significant effect to suppress over-activation of MR and alleviate greedy organs for salt and sugar, therefore, they should be used more widely in NCDs in the future.

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