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Pathogenic Mechanism of Salt-Sensitive Hypertension Caused by Renal Tubular Cell-Specific NFAT5 Deficiency

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Summary

Nuclear factor of activated T-cells 5 (NFAT5) is a transcription factor that is expressed in various tissues including Kidney. NFAT5 is activated by hypertonic conditions as observed in the renal medulla. The role of NFAT5 in the kidney and the regulation of blood pressure (BP) remains obscure. We have found that inducible and renal tubular cell-specific NFAT5 knockout (KO) mice exhibit high BP, hypernatremia, polyuria, and low urinary sodium excretion.

In the present study, we examined measurement of BP for KO mice and wild type (WT) mice using radiotelemetry method. To investigate salt-sensitive hypertension of KO mice, the expression of epithelial sodium channel (ENaC) in the kidney was examined. To assess body fluid volume, plasma renin activity (PRA), plasma aldosterone concentration (PAC), antidiuretic hormone (AVP: arginine vasopressin), and hematocrit (Ht) were measured.

As the results, mean BP was significantly higher in dark period, but not in light period, in KO mice. While high salt diet (HSD) enhanced the increase in the BP, treatment with amiloride significantly decreased the BP in KO mice to the level of WT mice in dark period, but not in light period.

The expression of ENaC was increased in membrane fraction of the renal medulla, not cortex, in KO mice both with RSD ad HSD.

PRA and PAC are not significantly different between in WT mice and KO mice with regular salt diet (RSD) (basal condition), although PAC tended to be low in KO mice compared to WT mice. HSD suppressed PRA and PAC both in WT mice and KO mice. AVP level was not different between WT mice and KO mice with RSD. HSD tended to increase AVP level both in WT mice and KO mice. AVP level was significantly higher in KO mice with HSD than in WT mice with RSD. Ht level was lower in KO mice than in WT mice both with RSD and HSD.

In summary, deficit of renal tubular NFAT5 increases the expression of ENaC and urinary sodium reabsorption, leading to the increase in BP by gaining of body fluid. HSD enhances the phenotype and exhibits salt-sensitive hypertension. Therefore, the BP is increased in dark period (eating time for mice), not in light period in KO mice. Because KO mice exhibit polyuria, body fluid volume could be decreased in light period (sleep period).

In conclusion, renal tubular NFAT5 should play and important role in regulating sodium reabsorption through ENaC under high-salt condition, thereby preventing salt-dependent hypertension.