

## Mechanistic Analyses of Circadian Blood Pressure Regulation via Renal Magnesium Transporting Molecules

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### Summary

TRPM6 is a  $Mg^{2+}$  permeable channel strongly expresses at the renal distal convoluted tubule, and participates in magnesium reabsorption. We have previously revealed the novel role of TRPM6 as a regulatory molecule of circadian blood pressure variation; renal specific ablation of TRPM6 in mice not just show deficiency in magnesium reabsorption, but also showed suppressed circadian blood pressure variation. Moreover, we have found that the secretion of renin, the hormone involved in blood pressure control, is suppressed, and thus in this study we sought to clarify the detail of this impaired secretion.

First, to confirm and quantitatively evaluate the impaired renin secretion from the renal juxtaglomerular cells by TRPM6-deficiency, found from kidney slice culture experiments, we administered isoproterenol, a beta-adrenergic agonist, to mice and examined the amount of renin secreted into the blood. Expectedly, we found that unlike control mice, renal-specific TRPM6 knockout mice showed limited increase in blood renin activity after intraperitoneal isoproterenol administration. Next, we analyzed the expression level of adrenergic  $\beta 1$  receptor at the juxtaglomerular cells by immunofluorescence analyses of kidney sections and western blotting analyses of isolated juxtaglomerular cells. The results show that renal-specific knockout of TRPM6 in mice results in decreased expression of adrenergic  $\beta 1$  receptors in juxtaglomerular cells, which should lead to impaired response to sympathetic nerve stimulation and renin secretion. Consistently, administration of renin inhibitors or renal denervation to wild-type mice suppressed circadian variation of blood pressure, as in kidney-specific TRPM6 knockout mice. We also examined the effect of magnesium administration on circadian blood pressure variation. In wild-type mice fed a high-magnesium diet, TRPM6 expression in distal convoluted tubule was markedly decreased, and the circadian blood pressure variation was suppressed. Collectively, these results demonstrate that the importance of renal TRPM6 in circadian variation of blood pressure, and that it can be controlled by magnesium administration.