

Basic Study for Investigating Novel Regulatory Effects of BMP-6 on Salt-Sensitive Hypertension

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Summary

Aldosterone is synthesized in the zona glomerulosa of the adrenal cortex. We previously reported the presence of a functional BMP system including BMP-6 in human adrenocortical cells. BMP-6 contributes to Ang II-induced aldosterone production by activating Smad signaling, in which endogenous BMP-6 action is negatively controlled by Ang II *in vitro*. In the present study, we examined the *in vivo* role of BMP-6 in regulation of aldosterone by neutralizing endogenous BMP-6 in rats treated with immunization against BMP-6. Three-week-old male rats were actively immunized with rat mature BMP-6 antigen conjugated with keyhole limpet hemocyanin (KLH). The immunization treatment had no effect on bilateral adrenal weight or its ratio to body weight. Urinary aldosterone excretion was time-dependently increased during the 8-week observation period in the control group. Of note, the level of urinary aldosterone excretion in BMP-6-KLH-immunized rats was significantly reduced compared to that in the control group, suggesting that endogenous BMP-6 contributes to the induction of aldosterone production *in vivo*. Moreover, the level of urinary aldosterone / creatinine after 8-week treatment was significantly lowered by treatment with BMP-6-KLH. In contrast, with chronic Ang II treatment, urinary aldosterone and creatinine-corrected values at 8 weeks were not significantly different between the two groups, suggesting that the effects of BMP-6-KLH were impaired under the condition of chronic treatment with Ang II. The mRNA levels of *Cyp11b2*, but not those of *Star*, *P450scc* and *3 β hsd2*, were significantly decreased in adrenal tissues isolated from BMP-6-KLH-immunized rats after 8-week treatment. Furthermore, the ratio of plasma aldosterone level to corticosterone was significantly decreased by immunization with BMP-6-KLH. Collectively, the results indicate that endogenous BMP-6 is functionally linked to aldosterone synthesis by the zona glomerulosa in the adrenal cortex *in vivo*.