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Role of Natriuretic Peptide System in Metabolic Syndrome-Related Renal Disease and Bone Homeostasis and Its Application to Translational Research

Masashi Mukoyama, Akihiro Yasoda, Tetsuro Yoshioka, and Kazutomo Sawai

Department of Medicine and Clinical Science,
Kyoto University Graduate School of Medicine

Summary

Natriuretic peptides are a family of structurally related hormones/paracrine factors that regulate blood pressure, body fluid homeostasis, cardiorenal function, vascular growth, and bone growth. We already reported that cardiac secretion of brain natriuretic peptide (BNP), a potent natriuretic and vasorelaxing peptide, is markedly increased in heart failure, hypertension and renal failure. We already generated transgenic mice that overproduce BNP in the liver to the circulation (BNP-Tg mice), and demonstrated that the chronic excess of BNP exerts renal protective activities in various nephropathy models, including subtotal nephrectomy, proliferative glomerulonephritis, and diabetic nephropathy. Although a tissue-protective role of CNP, another natriuretic peptide, has been suggested in cardiac and vascular remodeling, effects on renal pathophysiology are still unclarified. Therefore we investigated the effects of CNP on renal injury using nephropathy models in mice.

We first established CNP-transgenic mice (SAP-CNP-Tg mice) with excess of circulating CNP, and examined the effect of CNP on glomerular injury and proteinuria in streptozotocin-induced diabetic nephropathy model. We found that mesangial expansion and progressive albuminuria were significantly ameliorated in CNP-Tg mice. Less renal expression of monocyte chemoattractant protein-1 (MCP-1) and transforming growth factor- β (TGF- β) was also observed in diabetic CNP-Tg mice. Next we examined the effect of CNP on renal interstitial fibrosis in unilateral ureteral obstruction (UUO) model. CNP-Tg mice revealed less fibrosis after UUO with significant inhibition in macrophage infiltration and MCP-1 expression compared with control non-Tg mice. Furthermore, continuous i.p. administration of CNP after ureteral ligation ameliorated renal fibrotic process in control mice, suggesting a therapeutic potential.

We have already demonstrated that overexpression of CNP in chondrocytes rescues bone phenotypes in a mouse model of achondroplasia. SAP-CNP-Tg mice with excess plasma levels of CNP also reveal augmented long bone growth. Crosses between CNP-Tg mice with achondroplasia model mice (Ach mice) rescued the bone phenotype of Ach mice. Furthermore, continuous i.v. infusion of CNP in young control as well as Ach mice resulted in significant bone growth.

These results indicate that the chronic excess of circulating CNP in mice exerts renoprotective actions in various nephropathy models. Furthermore, excess of CNP in plasma can activate the receptor in the bone tissue. These data will open up the possibility of translational research that the infusion of the ligands or augmentation of the endogenous natriuretic peptide system, especially CNP system, should be therapeutically useful in various renal and bone diseases.