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Role of Natriuretic Peptides in Renal and Bone Homeostasis and Its Application to Translational Research

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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 recently generated transgenic mice that overproduce BNP in the liver to the circulation (BNP-Tg mice), which showed low blood pressure. Although tissue-protective role of natriuretic peptides has been suggested in cardiac and vascular remodeling, effects on renal pathophysiology are still unclarified. Therefore we investigated the effects of chronic excess of BNP and CNP on renal injury using various nephropathy models in mice.

We first examined the effect on glomerular injury and proteinuria in streptozotocin-induced diabetic nephropathy model. We found that glomerular hypertrophy and mesangial expansion as well as progressive albuminuria were significantly ameliorated in BNP-Tg mice. Lower serum creatinine levels, less renal expression of transforming growth factor-β (TGF-β) and monocyte chemoattractant protein-1 (MCP-1), and less renal activation of ERK/MAP kinase were also observed in diabetic BNP-Tg mice. Next we examined the effect of CNP on renal interstitial fibrosis in unilateral ureteral obstruction (UUO) model. CNP-Tg mice that were established using the BNP-Tg mice strategy, revealed less fibrosis after UUO with significant inhibition in macrophage infiltration compared with control non-Tg mice. Furthermore, continuous i.p. administration of CNP after ureteral obstruction ameliorated renal fibrotic process in control mice, suggesting a therapeutic potential.

We have already demonstrated that overexpression of CNP in chondrocytres rescues bone phenotypes in a mouse model of achondroplasia. CNP-Tg mice with excess plasma levels of CNP prepared above, also reveal augmented long bone growth. Furthermore, crosses between CNP-Tg mice with CNP-deficient mice rescued the bone phenotype of CNP-knockouts.

These results indicate that the chronic excess of circulating BNP and CNP in mice ameliorates histological and functional alterations in various nephropathy models. Furthermore, excess plasma CNP 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 should be therapeutically useful in various renal and bone diseases.