

Functional Studies on the Role of Natriuretic Peptides in the Regulation and Maintenance of Renal Homeostasis —Protective Role in Renal Injury and Remodeling—

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Summary

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), which showed low blood pressure. Although tissue-protective role of natriuretic peptides has been suggested in cardiac and vascular remodeling, effects on renal histology and function are still unclarified. Therefore we investigated the effects of chronic excess of BNP on renal injury using various nephropathy models in mice.

We first examined the effect on glomerular injury following subtotal nephrectomy using surgical excision method. We found that glomerular hypertrophy with mesangial expansion was significantly ameliorated in BNP-Tg mice. Next we examined the effect on renal injury in the anti-GBM glomerulonephritis model. BNP-Tg revealed much less proteinuria with significant inhibition in mesangial proliferation and in interstitial fibrosis compared with control non-Tg mice. Lower BUN levels and less renal expression of transforming growth factor- β (TGF- β) and monocyte chemoattractant protein-1 (MCP-1) were also observed in nephritic BNP-Tg. Furthermore, BNP-Tg ameliorated tubulointerstitial injury following unilateral ureteral obstruction. After ureteral ligation, tubular damages with interstitial fibrosis were marked in non-Tg but significantly suppressed in BNP-Tg. Interstitial expression of TGF- β was also suppressed. In addition, the blood flow of the peritubular capillary was significantly maintained, suggesting the mechanism by which BNP exerts the protective effects against interstitial fibrosis. Finally, BNP-Tg showed significant amelioration in renal injury and proteinuria following streptozotocin-induced diabetes. These beneficial effects of BNP in nephropathy models were not reproduced by systemic hypotension with chronic hydralazine treatment. In cultured mesangial cells, natriuretic peptides abolished angiotensin II-induced TGF- β and fibronectin expression with inhibited ERK/MAP kinase activation.

These results indicate that the chronic excess of BNP in mice ameliorates histological and functional alterations in various nephropathy models. The results also suggest that the renoprotective effects of natriuretic peptides on renal injury, not due merely to systemic blood pressure reduction, may be therapeutically applicable in various renal diseases.