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## Development of New Therapy for Renal Disorders and Investigation of the Molecular Mechanism by Natriuretic Peptides and a Novel Endocrine Factor Ngal

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### Summary

The Natriuretic Peptide Superfamily consists of atrial, brain, and C-type natriuretic peptides (ANP, BNP, and CNP). ANP and BNP possess potent hypotensive and natriuretic activities. Circulating ANP and BNP levels are increased in various renal disorders, but their role in the progression of renal damage remains elusive. In our department, we have established transgenic mice overexpressing BNP specifically in the liver (BNP-Tg mice), and reported that chronic excess of BNP in the circulation ameliorates renal damage caused by subtotal nephrectomy and autoimmune-mediated glomerulonephritis. In the present study, we investigated the effects of BNP upon diabetic nephropathy using BNP-Tg mice. Furthermore, we examined the effects of neutrophil gelatinase-associated lipocalin (Ngal), which is a novel kidney differentiation factor. The molecular mechanism of BNP and Ngal actions was also studied.

Induction of diabetes by streptozotocin in wild-type mice resulted in glomerular hypertrophy, expansion of mesangial area, and increased albuminuria. These changes were diminished in BNP-Tg mice. In cultured rat mesangial cells, high glucose stimulated gene expression of matrix protein fibronectin and its potent inducer transforming growth factor- $\beta$ , which were all cancelled with co-treatment with BNP. Renal ischemia-reperfusion injury causes histological injury of the kidney, concomitantly with functional impairment shown by accumulation of creatinine in the blood. Pretreatment of mice with Ngal potently suppressed these damages. Both BNP and Ngal inhibited phosphorylation of extracellular signal-regulated kinase *in vitro*, suggesting the involvement of mitogen-activated kinases in the subcellular actions of BNP and Ngal.

The present study opens a possibility for the development of new tools for the treatment of renal disorders.