Expression mechanism of human renal sodium dependent phosphate transporter (NaPi-3 and NPT-1) genes

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Summary

Human X-linked hypohpsphatemic vitamin D-resistant rickets (XLH) is characterized by impaired renal tubule reabsorption of phosphate. Recent report suggest that a humoral factor that affects gene expression of the Na^+/Pi cotransporter is the abnormality underlying murine Hyp (an animal model of XLH). To identify factors that may mediate this transcriptional repression of the cotransporter gene, we characterized the genomic structure of human Na^+/Pi cotransporter (NaPi-3, NPT-1) genes.

Human genomic libraries Lambda EMBL3 were screened with human NaPi-3 and NPT-1 cDNA fragments as probes. Isolated lambda DNA were sequenced. Sequence analysis of NaPi-3 gene encompassing 2.4kb upstream from exon 1 indicated a TATA box-like sequence about 30 bp upstream of the corresponding mRNA cap site. We also identified a cAMP-responsive element, AP-1 binding site, Pho-4 binding site and three direct repeat motifs. The 5' flanking region of NPT-1 gene contains a octamer motif, two CCAAT boxes and several VDRE half-sites, but TATA-like sequence was not observed.

Transient transfection study with COS-7 cells demonstrated that luciferase gene expression driven by the NaPi-3 or NPT-1 gene promoter was induced by 1,25-dihydroxyvitamin D_3[1,25$(OH)_2D_3$] in a vitamin D receptor-dependent manner. Dexamethasone or 12-*O*-tetradecanoyl phorbol-13-acetate (TPA), which is protein kinase C inhibitor, markedly inhibited promoter activity induced by 1,25$(OH)_2D_3$. Functional analysis of NaPi-3 and NPT-1 gene promoters indicated that vitamin D may play an important role in transactivation of both genes.

These data raise the possibility that abnormal metabolism in XLH is closely related with the underexpression of phosphate transporter genes.