Difference in transcriptional activity of two homologous CYP21A genes

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Abstract

Steroid 21-hydroxylase (CYP21) deficiency is the major cause of congenital adrenal hyperplasia, a common genetic disease due to steroid imbalance. The main cause for the mutation of the CYP21A2 (c21B) gene is conversion of its nucleotide sequence to the neighboring homologous but nonfunctional c21A gene. In this report the transcriptional activities of the c21A and c21B genes have been analyzed. Transient transfection assays showed that transcription derived from the c21A gene was about 5-fold lower in strength than that of the c21B gene, although both sequences responded to cAMP normally in two adrenocortical cell lines. The normal response to cAMP could probably be attributed to equal activation of both genes by a transcription factor Nur77. The lower transcriptional activity of the c21A gene was attributed to sequence changes within 167 base pairs of the 5'-flanking region, which differs from the c21B gene by only four nucleotides at positions around -100. These four nucleotide changes render the c21A sequence to bind proteins less tightly than the -100 region of the c21B sequence, which binds proteins such as transcription factor Sp1 in electrophoretic mobility shift assays. The reduced transcription due to nucleotide changes at the regulatory region of the c21A gene, in combination with other mutations in the coding region, could play important roles in 21-hydroxylase deficiency.