血中グルコースの調節に関わる ホスホエノールピルビン酸カルボキシキナーゼは RORα 核内受容体の標的である

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Phosphoenolpyruvate carboxykinase, a key enzyme that controls blood glucose, is a target of retinoic acid receptor-related orphan receptor α

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ABSTRACT: Phosphoenolpyruvate carboxykinase (PEPCK) catalyzes a committed and rate-limiting step in hepatic gluconeogenesis, and its activity is tightly regulated to maintain blood glucose levels within normal limits. PEPCK activity is primarily regulated through hormonal control of gene transcription. Transcription is additionally regulated via a cAMP response unit, which includes a cAMP response element and four binding sites for CCAAT/enhancer-binding protein (C/EBP). Notably, the cAMP response unit also contains a putative response element for retinoic acid receptor-related orphan receptor α (RORα). In this paper, we characterize the effect of the RORα response element on cAMP-induced transcription. Electrophoresis mobility shift assay indicates that RORα binds this response element in a sequence-specific manner. Furthermore, luciferase reporter assays indicate that RORα interacts with C/EBP at the PEPCK promoter to synergistically enhance transcription. We also found that cAMP-induced transcription depends in part on RORα and its response element. In addition, we show that suppression of RORα by siRNA significantly decreased PEPCK transcription. Finally, we found that a RORα antagonist inhibits hepatic gluconeogenesis in an in vitro glucose production assay. Taken together, the data strongly suggest that PEPCK is a direct RORα target. These results define possible new roles for RORα in hepatic gluconeogenesis.

抄録　ホスホエノールピルビン酸カルボキシキナーゼ（PEPCK）は肝糖新生の律速酵素であり，その活性は血中グルコース量の調節に関与している。PEPCK 活性は、主に遺伝子転写の段階で調節されている。本論文では，PEPCK 遺伝子のプロモーター領域内の cAMP 応答配列へ相乗的作用を及ぼす RORα 応答配列の存在を明らかにした。方法は、ゲルシフト解析およびルシフェラーゼレポーター解析により、RORα 応答配列への RORα 核内受容体の作用を評価した。さらに、siRNA ノックダウン法および RORα アンタゴニストにより、RORα の発現減少に伴うグルコース生産量の減少を評価した。これらの解析の結果、RORα が PEPCK の発現亢進に直接的に作用することで肝糖新生を増加させることをはじめて明らかにした。