Abstract

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Synergistic activation of the prolactin promoter by vitamin D receptor and GHF-1: role of the coactivators, CREB-binding protein and steroid hormone receptor coactivator-1 (SRC-1).

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BACKGROUND: PRL gene expression is dependent on the presence of the pituitary-specific transcription factor GHF-1/Pit-1, which is transcribed in a highly restricted manner in cells of the anterior pituitary. In pituitary GH3 cells, vitamin D increases the levels of PRL transcripts and stimulates the PRL promoter.

METHODS: We have analyzed the role of GHF-1 and of the vitamin D receptor (VDR) to confer vitamin D responsiveness to the PRL promoter. For this purpose we have used nonpituitary HeLa cells, which do not express GHF-1.

RESULTS: We found that VDR activates the PRL promoter both in a ligand-dependent and -independent manner through a sequence located between positions -45/-27 in the proximal 5'-flanking region. This sequence also confers VDR and vitamin D responsiveness to a heterologous promoter. In the context of the PRL gene, VDR requires the presence of GHF-1 to activate the promoter. Truncation of the last 12 C-terminal amino acids of VDR, which contain the ligand-dependent activation function (AF2), abolishes regulation by vitamin D, suggesting that binding of coactivators to this region mediates ligand-dependent stimulation of the PRL promoter by the receptor.

CONCLUSION: Indeed, expression of the coactivators, steroid hormone receptor coactivator-1 (SRC-1) and CREB-binding protein (CBP), significantly enhances the stimulatory effect of vitamin D mediated by the wild-type VDR but not by the AF2 mutant receptor. Furthermore, CBP also increases the activation of the PRL promoter by GHF-1 and the ligand-independent activation by both wild-type and mutant VDR.

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