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Multiple enhancer units mediate drug induction of CYP2H1 by xenobiotic-sensing orphan nuclear receptor chicken xenobiotic receptor

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Binding of nuclear receptors to drug-responsive enhancer units mediates transcriptional activation of cytochromes P-450 (P-450) by drugs and xenobiotics. In previous studies, a 264-base-pair (bp) phenobarbital-responsive enhancer unit (PBRU) located at -1671 to -1408 upstream of the chicken CYP2H1 transcriptional start-site increased gene expression when activated by the chicken xenobiotic-sensing orphan nuclear receptor CXR. In extension of these studies, we now have functionally analyzed a second distal drug-responsive element and delimited a 643- and a 240-bp PBRU located between 5 and 6 kilobases upstream of the transcriptional start site of CYP2H1. Both PBRUs were activated by CXR after treatment with different drugs. A nuclear receptor binding site, a direct repeat-4 (DR-4) hexamer repeat, was identified on the 240-bp PBRU. Site-directed mutagenesis of this DR-4 abolished activity in reporter gene assays in the chicken hepatoma cells leghorn male hepatoma as well as transactivation of the 240-bp PBRU by CXR in CV-1 cells. CXR bound to this PBRU in electromobility shift assays and the complex remained unaffected by unlabeled 240-bp PBRU with a mutated DR-4. In cross-species experiments, both the human xenobiotic-sensing nuclear receptors pregnane X receptor and constitutive androstane receptor bound to this element, suggesting sequence conservation between chicken and mammalian PBRUs and between the DNA binding domains of these receptors. Of two orphan nuclear receptors involved in cholesterol and bile acid homeostasis, only chicken liver X receptor (LXR) but not chicken farnesoid X receptor bound to the 240-bp PBRU. These results suggest that CYP2H1 induction is explained by the combined effect of multiple distal enhancer elements interacting with multiple transcription factors, including CXR and LXR.
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