INDUCTION OF CYP3AS BY GLUCOCORTICOIDS IN HUMAN FETAL HEPATOCYTES
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Cytochrome P450s (CYPs) play a critical role in the oxidative metabolism of drugs. The CYP3As gene expression is modulated by a large variety of endogenous and exogenous substances, including drugs. We have reported that CYP3A4 and CYP3A7 mRNA expressions in human fetal hepatocytes were markedly increased by dexamethasone (DEX) [1]. However, rifampicin and phenobarbital, both of which are highly effective inducers of CYP3A enzymes in primary cultures of human adult hepatocytes, did not appreciably induce CYP3A4 mRNA in human fetal hepatocytes. In the present study, we investigated the effects of various glucocorticoids on the expression of genes encoding CYP3A enzymes in human fetal hepatocytes. The hepatocytes (gestation average 16 weeks) were obtained from Applied Cell Biology Research Institute (Kirkland, WA). The expression of CYP3A4 and CYP3A7 mRNAs was induced by fludrocortisone, methylprednisolone, betamethasone and DEX (10 nM or 1 µM), but not cortisone and hydrocortisone. The inducibility of glucocorticoids on CYP3A4 and CYP3A7 showed a correlation with the intensity of anti-inflammatory effect. CYP3A5 mRNA expression level showed no significant changes following addition of the glucocorticoids used in this study. The induction of the DEX-mediated CYP3A4 and CYP3A7 mRNAs was suppressed by glucocorticoid receptor antagonist, RU-486. These results suggest that the induction mechanism of CYP3As by glucocorticoid in human fetal hepatocytes is different from that in human adult hepatocytes and is mediated directly by the glucocorticoid receptor (NR3C1), not pregnane X receptor (NR1I2).