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Induction of CYP3As in HepG2 Cells by Several Drugs. - Association between Induction of CYP3A4 and Expression of Glucocorticoid Receptor - .

T.Usui (臼井達洋) , Y.Saitoh (齋藤侑也) , F.Komada (駒田富佐夫) .

Department of Drug Informatics, Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama, 350-0295 Japan

The cytochrome P-450 3A (CYP3A) enzyme family is responsible for most of the drug metabolism in the human liver. In this study, we demonstrated the inductive effects of phenobarbital, rifampicin, carbamazepine, phenytoin, prednisolone, ciclosporin and clotrimazole on CYP3A4, CYP3A5 and CYP3A7 mRNA expression, and established the relationship between the expression of human glucocorticoid receptor α (hGR α mRNA and the induction of CYP3A4 mRNA in cultured HepG2 cells by reverse transcription polymerase chain reaction (RT-PCR).

Treatment with prednisolone, rifampicin and carbamazepine rapidly induced the level of CYP3A4 mRNA expression by 3- to 6-fold. However, phenytoin and phenobarbital gradually induced CYP3A4 mRNA level by 3 to 4-fold. The induction of CYP3A4 mRNA expression by clotrimazole and ciclosporin was negligible. Treatment with phenytoin, rifampicin, carbamazepine and ciclosporin induced approximately 2-fold increases in the expression of CYP3A5 mRNA, although prednisolone, phenytoin and clotrimazole had no effect. Treatment with rifampicin, phenytoin, clotrimazole and ciclosporin resulted in approximately a 2-fold induction of the CYP3A7 mRNA level. Treatment with rifampicin and ciclosporin induced the expression of hGR α mRNA significantly in comparison with controls, although the induction of hGR α mRNA following treatment with other drugs was negligible.

In cluster analysis, the induced level of CYP3A4, CYP3A5, CYP3A7 and hGR α mRNA by these drugs could be classified into four major clusters. This suggested that each cluster might be associated with different mechanism(s) of induction by these drugs.

Furthermore, we studied the associations between the expression of hGR α mRNA and the induced level of CYP3A4 mRNA by prednisolone and ciclosporin. Treatment with both prednisolone and ciclosporin showed synergistic effects on induction of CYP3A4 mRNA and, following treatment with both drugs, the expression level of CYP3A4 mRNA was 2-fold greater compared with prednisolone alone after the fifth day. Positive correlations were observed between the levels of hGR α mRNA expression and those of CYP3A4 mRNA. This observation shows that the regulation of CYP3A4 gene expression was hGR α -dependent and that ciclosporin may function as a regulator of expression via hGR α .