Differential effect of liver dysfunction on CYP3A1 and CYP3A2 expression in rats with carbon tetrachloride-induced cirrhosis.

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Irrespective of etiology, liver cirrhosis causes dysregulation of most drug-metabolizing enzymes, especially cytochromes P450 (CYPs), leading to a decrease in hepatic drug elimination which requires a substantial drug dosage adjustment in patients with severe liver dysfunction. Since carbon tetrachloride (CCl_4)-induced liver cirrhosis models have been widely employed to mimic human cirrhosis, a precise understanding of CCl_4-induced dysregulation of CYP expression is needed. Few and conflicting data are available on the effect of liver cirrhosis on CYP3A expression in rats, probably because available studies either investigated animals with different severity of liver dysfunction or used different experimental models of cirrhosis. Moreover, different methods have been used to ascertain CYP expression.

This study assessed the effect of liver dysfunction on CYP3A1 and CYP3A2 expression in rats with compensated or decompensated cirrhosis, depending on the length of exposure to CCl_4. The expression of the two CYP enzymes was measured by means of three different techniques: 1) determination of CYP3A1 and CYP3A2 mRNA levels by means of quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR); 2) measurement of protein expression of CYP3A enzymes by means of Western blot analysis; c) determination of the kinetic parameters of CYP3A1 and CYP3A2 enzymatic activity by means of kinetic analysis, using two validated marker reactions of CYP3A enzymes: midazolam (MDZ) 4-hydroxilation and testosterone (TST) 6β-hydroxilation.

Our data indicate that mRNA level and protein expression of CYP3A1 tended to decrease as liver function worsened, although differences were not statistically significant. In contrast, gene and protein expression of CYP3A2 significantly increased in rats with compensated cirrhosis, and to a lesser, not significant, extent in rats with decompensated cirrhosis. In accordance with data on CYP3A2 expression, we observed a significant increase in TST 6β-hydroxilation in rats with compensated cirrhosis, whereas the increase was not statistically significant in rats with decompensated cirrhosis (1253±516, 1583±77, 1458±502 pmol/mg/min in healthy, compensated and decompensated cirrhotic rats, respectively). In contrast, Vmax of MDZ 4-hydroxilation increased significantly in rats with both mild and severe cirrhosis (1000±438, 1750±340 and 1644±862 pmol/mg/min in healthy, compensated and decompensated rats, respectively). In conclusion, at variance with previous results, our data clearly indicate an increase in CYP3A2 gene and protein expression, and activity in CCl_4-treated compensated cirrhotic rats. With the exception of 4-OH-MDZ formation, increases are not significant In decompensated rats. Further studies are in progress in our laboratory to elucidate the mechanism by which liver cirrhosis induces CYP3A2 expression.