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STRAIN DIFFERENCES OF ALDEHYDE OXIDASE AND CYTOCHROME P450 ACTIVITIES IN MOUSE LIVER
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Aldehyde oxidase, a molybdo-flavoenzyme, is involved in drug metabolism. It catalyzes the oxidation of methotrexate, acyclovir and phthalazine, and the reduction of zonisamide, sulindac and many other drugs. Nevertheless, the biological role of aldehyde oxidase is obscure. In the previous study, we demonstrated significant strain differences of aldehyde oxidase activity in rats, though the substrate specificities were consistent. In this study, we examined the strain and sex differences of aldehyde oxidase and cytochrome P450 (CYP) activities in mouse liver. Four strains of mice (C57BL/6J Jcl, DBA/2J Jcl, BALB/c Cr Slc and C3H/He Slc) were investigated. It had been reported that aldehyde oxidase (AOX1) and AOH1, which is a homolog of AOX1, are expressed in mouse liver, and that AOH1 is the major isozyme in mice, but DBA/2 mice expressed little AOH1. C57BL/6J showed the highest activity towards benzaldehyde and N1-methyl nicotinamide as oxidative substrates, followed by C3H/He and BALB/c. The lowest activity was observed in DBA/2. The activities of males were significantly higher than those of females in C57BL/6J, whereas DBA/2 showed little sex difference. We examined the substrate specificities of AOX1 and AOH1 using DBA/2 mice and norharmane, which is a potent inhibitor of AOX1. These isozymes had similar substrate specificity. AOH1 showed strong quinoline 2-hydroxylase activity. Sex differences of CYP activities were observed in C3H/He mice. The CYP activities of C3H male mice were greater than those of females. The mechanisms of the strain and sex differences are under investigation.

31PE-80

GENETIC POLYMORPHISMS OF DRUG TRANSPORTERS IN PATIENTS WITH HEPATITIS C VIRUS (HCV)-ASSOCIATED HEPATOCELLULAR CARCINOMA (HCC)
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Hepatocellular carcinoma (HCC) is one of the major causes of cancer-related death worldwide. Approximately 90% of HCC are derived from infection with hepatitis B or C virus (HBV or HCV), and progress through several stages such as liver cirrhosis (LC), but the detailed mechanism has not yet been elucidated. In development of HCC, many risk factors have been reported; age, sex, alcohol consumption and tobacco smoking, etc. However, the individual variability of development of HCC might not be explained by these risk factors. In this study, we focused on the role of drug transporters in the liver. To investigate this hypothesis, we conducted polymorphism analysis of drug transporter genes (4 uptake transporters; OATP1B1, IB2, B1 and OCT1, and 6 efflux transporters; MDR1, MRP1, MRP2, MRP3, BSEP and BCRP) with 58 HCV-HCC patients and 61 healthy volunteers. As a result, although no significant differences were observed in the frequency of any single nucleotide polymorphisms (ie, SNP based analysis), frequencies of haplotype patterns of the MRP1 and BSEP gene variants were significantly different between patients and healthy volunteers. Besides, the combinations of several gene polymorphisms such as MDR1 3435>C>T, MRp 825T>C, and BSEP -1528I>-15278 CTCT>delete gave significant associations with HCV-HCC. Interestingly, genetic variants detected in this study as candidate factors for HCV-HCC belong to the efflux transporters. Further clinical studies with greater number of patients are necessary to confirm these observations.