GENDER-RELATED DIFFERENCES IN EXPRESSION AND FUNCTION OF HEPATIC P-GLYCOPROTEIN AND MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN (Mrp2) IN RATS

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To clarify whether gender-related differences exist in the function of hepatic P-glycoprotein (P-gp)- and/or multidrug resistance-associated protein (Mrp2)-mediated hepatobiliary transport and their expression, we measured the hepatobiliary excretion ability of doxorubicin, a substrate for P-gp and Mrp2, and their protein levels in male and female rats. When rats received a single intravenous injection of doxorubicin, a delay in the disappearance of doxorubicin from plasma was observed in male rats. When rats received a constant-rate infusion of doxorubicin, no significant gender-related differences in the apparent hepatobiliary clearance of doxorubicin based on the steady-state plasma concentration were observed between male and female rats. However, the biliary clearance of doxorubicin based on the liver concentration, which represents the actual function of P-gp and/or Mrp2, in female rats was larger than that in male rats. These results suggest that the actual function of the hepatobiliary transport of doxorubicin is higher in female rats than in male rats. Western blot analysis revealed that the expression of P-gp and Mrp2 in the liver of female rats was significantly higher than that in male rats, which corresponded with results of the hepatobiliary excretion experiments. The expression of hepatic cytochrome P450 (CYP) 2B1, which involved in metabolism of doxorubicin, was significantly higher in male rats than in female rats. By pretreatment with testosterone, the actual biliary clearance of doxorubicin in female rats was near to that in male rats. The protein levels of P-gp and Mrp2 in female rats was also dropped by treatment with testosterone nearer to those in male rats. These results suggest that gender-related differences exist in P-gp- and Mrp2-mediated hepatobiliary transport and that these two transporters may be regulated by sex hormone.