REGIOSELECTIVE SEX AND SPECIES DIFFERENCES IN IMIPRAMINE METABOLISM

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The regioselective P450– and FMO-mediated imipramine metabolism (2–hydroxylation, N-demethylation and N-oxidation) was studied using liver microsomes from both sexes of various strains of mice, guinea pigs and hamsters. Regioselective sex differences were observed in Imipramine metabolism. These sex differences were species- and strain-dependent. inhibition studied using P450–specific or FMO-specific inhibitors showed that P450 was mainly responsible for imipramine N-oxidation and N-demethylation were male-dominant reactions. According to a recent paper, imipramine N-oxidation is catalyzed mainly by FMO1 in rats. Our results indicated that FMO1 might exist male-dominantly in rats. By contrast, imipramine N-oxidation occurred female-dominantly in all the strains of mice examined. These result coincide with a previous report that FMO1 was a female-dominant isoform in mice. In Hartley guinea pigs and Syrian Golden hamsters, significant sex differences of N-oxidation were not observed. Therefore, FMO1 may exist female dominantly in Hartley guinea pigs and not in Strain 2 guinea pigs. Hamsters had especially high activities of imipramine 2–hydroxylase and N-oxidase. We did not determine which isoform of P450 or FMO catalyze those metabolic pathways. Rates of imipramine metabolism in hamsters and guinea pigs were high among all species examined. In rats and mice, significant sex differences were observed. In all species examined, the activity of imipramine N-oxidation was higher than that of 2–hydroxylation or N-demetylation.