Induction of Hepatic Microsomal Drug-Metabolizing Enzymes by 3-Methylsulfonyl-2,2',4',5,5'-Pentachlorobiphenyl in Female Rats

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Introduction

Several reports have shown methylsulfonyl (MeSO₂) metabolites of polychlorinated biphenyls (PCBs) to be present in liver, adipose tissue and milk of human subjects and in tissues of mammals such as seals, otters, minks and polar bears. We previously reported that some 3-MeSO₂ metabolites of PCBs were potent inducers of CYP2B1, CYP2B2, CYP3A2 and CYP2C6 in male rat liver, and that the structure-CYP2B1/2 induction relationship existed for the 3-MeSO₂ derivatives studied. In the present study, we investigated in detail the effect of 3-MeSO₂-2,2',4',5,5'-pentachlorobiphenyl (3-MeSO₂-2,2',4',5,5'-pentaCB) on the drug-metabolizing enzyme system on female rats, and compared their activities with those after administration to male rats.

Methods

Female Wistar rats were given i.p. 2,2',4,5,5'-pentaCB or its MeSO₂ derivatives. For control, the animals were treated with an equivalent volume of the vehicle. All rats were starved for 18 h prior to death and then killed by decapitation at a designated time after dosing.

Results and Discussion

Significant increases in cytochrome P450 content, aminopyrine and benzo[*a*]pyrene metabolizing activities were observed at 48–144 h after a single injection of 3-MeSO₂-2,2',4',5,5'-pentaCB (2 μmol/kg) to female rats. 3-MeSO₂-2,2',4',5,5'-pentaCB produced dose-related increases in its hepatic concentration, in

the content of cytochrome P450 and in the extent of aminopyrine and benzo[*a*]pyrene metabolizing activities of liver microsomes in the range of 0.5–5 μmol/kg. The ratios (male/female) of the contents of cytochromes P450 and *b*₅ and of the activities of aminopyrine *N*-demethylase and benzo[*a*]pyrene hydroxylase in liver microsomes from each sex after administration of the vehicle were almost the same as those of the 3-MeSO₂ derivative. Major phenobarbital (PB)-inducible forms, CYP2B1, CYP2B2, CYP3A2 and CYP2C6 were potently induced by the 3-MeSO₂ derivative, but major 3-methylcholanthrene (3-MC)-inducible forms, CYP1A1 and CYP1A2 were not. The induction profiles of the drug-metabolizing enzymes and the cytochrome P450 isozymes in hepatic microsomes of female rats treated with the 3-MeSO₂ derivative were similar to those of rats treated with PB, but were different from those of rats treated with 3-MC. The 4-MeSO₂ isomer had no increasing effect on the enzyme activities or the cytochrome P450 forms.

The results of the present study show that 3-MeSO₂-2,2',4',5,5'-pentaCB is a potent PB-type inducer of hepatic drug-metabolizing enzymes in female rats and that there is no sex difference in the induction of the drug-metabolizing activities by treatment with 3-MeSO₂-2,2',4',5,5'-pentaCB. The 4-MeSO₂ isomer had little effect in both male and female rats. Our results also suggest that 3-MeSO₂-2,2',4',5,5'-pentaCB plays an important role in the induction brought about by 2,2',4,5,5'-pentaCB on the hepatic drug-metabolizing enzyme system in both rat sexes.