Effects of Methylsulfonyl Metabolites of PCBs Accumulated in Tissues of Mammals on Activities of Hepatic Microsomal Drug-Metabolizing Enzymes in Rats

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Introduction

A number of methylsulfonyl (MeSO₂) derivatives of polychlorinated biphenyls (PCBs) have been demonstrated in tissues of such mammals as seals, otters, minks and polar bears. The main substances in the seal blubber have been identified as 3- and 4-MeSO₂ PCB isomers chlorinated at 2- and 5-positions of at least one of the phenyl rings. Even in healthy people, MeSO₂-PCB isomers were found in adipose tissue at concentrations as high as those of PCB. However, the biological activities and toxicologic effects of MeSO₂-PCB metabolites on animals has been studied little. Thus, we investigated the effects of 2,3',4',5'-tetrachlorobiphenyl (tetraCB) (IU-70), 2,2',4',5',5'-pentaCB (IU-101) and 2,2',3',4',5',5'-hexachlorobiphenyl (hexaCB) (IU-141) and their 3- and 4-MeSO₂-PCBs on the drug-metabolizing enzyme system.

Methods

Male rats received an i.p. injection of PCBs or their MeSO₂-derivatives. For control, the animals were treated with an equivalent volume of the vehicle. All rats were starved for about 18 h prior to the experiment and killed by decapitation at 96 h after the dosing.

Results and Discussion

The 3- and 4-methyl sulfoxides and 3- and 4-MeSO₂ metabolites were detected in blood, tissues and feces of rats dosed with the three kinds of PCB. We determined that 3- and 4-MeSO₂ metabolites were formed from these three PCBs chlorinated at 2- and 5-positions of the phenyl ring, and these metabolites remained for a long period of time with parent PCB in the body.

The three PCB congeners and their 3-MeSO₂-

derivatives increased to the same degree the contents of cytochromes P-450 and b₅, and the aminopyrine, 7-ethoxycoumarin and benzo[*a*]-pyrene metabolizing activities, while their 4-MeSO₂-derivatives did not. No change was observed in aniline hydroxylase activity after the administration of these PCB congeners and their MeSO₂ derivatives. The induction profiles of the hepatic microsomal drug-metabolizing enzymes of rats treated with the PCBs and their 3-MeSO₂-derivatives were similar to those of rats treated with phenobarbital (PB) but different from those of rats treated with 3-methylcholanthrene. 3-MeSO₂-2,2',4',5,5'-pentaCB (0.2–5 μmol/kg) produced nearly a dose-related increase in microsomal drug-metabolizing enzyme activities. At 2 μmol/kg these inducing abilities on all of the parameters corresponded to those of PB (431 μmol/kg twice with a 24 h interval). Major PB-inducible forms, CYP2B1, 2B2, 2C6 and 3A2 were strongly induced by the three PCB congeners and their 3-MeSO₂-PCB isomers, while their 4-MeSO₂-PCB isomers had little increase effect on these P-450 forms.

In this study, we found that 3-MeSO₂-PCB metabolites derived from the three PCBs tested were strong PB-type inducers of hepatic drug-metabolizing enzymes, 3-MeSO₂-2,2',4',5,5'-pentaCB was a particularly strong inducer, while 4-MeSO₂-PCB metabolites showed little effect.

Our conclusion is that the 3-MeSO₂-PCB metabolites play an important role in the induction which parent PCB congeners are reported to cause on the hepatic drug-metabolizing enzyme system.