Structure-Dependent Induction of CYP2B by 3-Methylsulfonyl Metabolites of Polychlorinated Biphenyl Congeners in Rats

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1. Introduction

Methylsulfonyl ($MeSO_2$) metabolites of polychlorinated biphenyls (PCBs) were first identified in the blubber of grey seals in the Baltic.[1] Subsequently, the presence of $MeSO_2$-PCBs in the Yusho patients and the normal persons from the Japanese environment[2, 3] and in several mammalian species such as otters, polar bears, beluga whales and minks from the Canadian and Swedish environment[4, 5] was reported. Also in healthy Swedish women, $MeSO_2$ isomers were found in human milk sampled in Stockholm during 1972 - 1991.[6] The main $MeSO_2$-PCBs in Swedish human milk have been shown to be 3- and 4-$MeSO_2$ derivatives of PCBs with chlorine atoms in 2,5- or 2,3,6-positions, e.g. 3-$MeSO_2$- and 4-$MeSO_2$-2,2',3',4',5-pentachlorobiphenyls (3-$MeSO_2$- and 4-$MeSO_2$-2,2',3',4',5-pentaCBs), 3-$MeSO_2$- and 4-$MeSO_2$-2,2',4',5,5',6-hexachlorobiphenyls (3-$MeSO_2$- and 4-$MeSO_2$-2,2',4',5,5',6-hexaCBs).[6]

In our preceding paper,[7] we reported for the first time that 3-$MeSO_2$ derivatives of 2,3',4',5-tetrachlorobiphenyl (2,3',4',5-tetraCB) (IU-70), 2,2',3,4,5'-pentaCB (IU-87), 2,2',4,5,5'-pentaCB (IU-101) and 2,2',3,4,5,5'-hexaCB (IU-141), which were major methyl sulfones accumulated in the blubber of seals in the Baltic,[4] were inducers of microsomal drug-metabolizing enzymes, but 4-$MeSO_2$ derivatives of their PCB congeners had almost no effect on microsomal drug-metabolizing enzyme activities.

In this study, we investigated the inducing effects on the drug-metabolizing enzyme system of 3-$MeSO_2$ derivatives of eleven PCB congeners, which are reported to be retained in the Yusho patient tissues[2] and Swedish human milk,[6] and structurally similar 3-methyl sulfones. And we also compared with those of phenobarbital (PB) and 3-methylcholanthrene (3-MC). We consider that it is important to investigate 3-$MeSO_2$-PCBs regarding their chemical structure and potential abilities to induce hepatic microsomal drug-metabolizing enzymes.

2. Materials and methods

Chemicals. The $MeSO_2$-derivatives of 2,5-dichlorobiphenyl (2,5-diCB) (IU9), 2,2',5-trichlorobiphenyl (2,2',5-triCB) (IU18), 2,4',5-triCB (IU31), 2,2',3,4-tetraCB (IU41), 2,2',4,5'-tetraCB (IU49), 2,2',5,5'-tetraCB (IU-52), 2,3',4',5-tetraCB (IU-70), 2,2',3,4,5'-pentaCB (IU-87), 2,2',4,5,5'-pentaCB (IU-101), 2,3,3',4',6-pentaCB (IU110), 2,2',3,3',4,6'-hexaCB (IU-132), 2,2',3,4,5,5'-hexaCB (IU-141) and 2,2',3,4',5',6-hexaCB (IU-149) were synthesized as described

elsewhere.[8] The purity of these compounds was > 99% when analyzed by gas chromatography. 3-Hydroxybenzo[*a*]pyrene was the kind gift of Prof. Nadao Kinoshita of Kyushu University, Japan. The microsomal P450 standards and antibodies against purified cytochrome P450s were obtained from Daiichi Pure Chemicals Co., Ltd. (Tokyo, Japan). Other chemicals were obtained as commercial reagent grade.

Animal treatments. Male Wistar rats weighing about 200 g were used in the present study. They were housed in an air-conditioned room with free access to a commercial chow and tap water. Rats received an i.p. injection of 3-$MeSO_2$-PCBs. For control, the animals were treated with an equivalent volume of the vehicle. All rats were starved for about 18 hr prior to death and then killed by decapitation at 96 hr after the dosing.

Biochemical analyses. Microsomes were prepared according to the procedure described previously.[7] The protein content was determined by the method of Lowry *et al.*[9] Aminopyrine *N*-demethylase and aniline hydroxylase activities were assayed as reported previously.[10] Cytochromes P450 and b_5 contents were estimated according to the method of Omura and Sato.[11, 12] Benzo[*a*]pyrene hydroxylase activity was determined by the method of Nebert and Gelboin.[13] The immunoblotting and immunochemical quantitation were performed as described by Imaoka *et al.*[14]

3. Results and discussion

The administrations of 3-$MeSO_2$-2,5-diCB, 3-$MeSO_2$-2,4',5-triCB, 3-$MeSO_2$-2,2',4',5-tetraCB, 3-$MeSO_2$-2,2',5,5'-tetraCB, 3-$MeSO_2$-2,3',4',5-tetraCB, 3-$MeSO_2$-2,2',3',4',5-pentaCB, 3-$MeSO_2$-2,2',4',5,5'-pentaCB, 3-$MeSO_2$-2,2',3',4',5,5'-hexaCB, 3-$MeSO_2$-2,2',3',4',5,6-hexaCB, 3-$MeSO_2$-2,2',4',5,5',6-hexaCB (2 μmol/kg each) to rats resulted in characteristic increases in the contents of cytochromes P450 and b_5 and the activities of aminopyrine *N*-demethylase, aniline hydroxylase and benzo[*a*]pyrene hydroxylase. However, 3-$MeSO_2$-2,2',5-triCB, 3-$MeSO_2$-6,2',3',4'-tetraCB and 3-$MeSO_2$-2,3',4',5,6-pentaCB had no increasing effect on both cytochrome contents and the enzyme activities.

The induction profiles of the drug-metabolizing enzymes and two PB-inducible forms of cytochrome P450, CYP2B1 and CYP2B2, in hepatic microsomes of rats treated with nine 3-$MeSO_2$ derivatives, namely 3-$MeSO_2$-2,4',5-triCB, 3-$MeSO_2$-2,2',4',5-tetraCB, 3-$MeSO_2$-2,2',5,5'-tetraCB, 3-$MeSO_2$-2,3',4',5-tetraCB, 3-$MeSO_2$-2,2',3',4',5-pentaCB, 3-$MeSO_2$-2,2',4',5,5'-pentaCB, 3-$MeSO_2$-2,2',3',4',5,5'-hexaCB, 3-$MeSO_2$-2,2',3',4',5,6-hexaCB and 3-$MeSO_2$-2,2',4',5,5',6-hexaCB were similar to those of rats treated with PB, but were different from those of rats treated with 3-MC. These findings indicate that 3-$MeSO_2$ metabolites derived from nine PCBs are PB-type inducers of microsomal drug-metabolizing enzymes.

The most potent inducers were 3-$MeSO_2$-2,2',4',5-tetraCB, 3-$MeSO_2$-2,2',3',4',5-pentaCB and 3-$MeSO_2$-2,2',4',5,5'-pentaCB. The inducers of a second place were 3-$MeSO_2$-2,2',3',4',5,5'-hexaCB and 3-$MeSO_2$-2,4',5-triCB. 3-$MeSO_2$-2,2',4',5,5',6-hexaCB, 3-$MeSO_2$-2,2',3',4',5,6-hexaCB, 3-$MeSO_2$-2,3',4',5-tetraCB and 3-$MeSO_2$-2,2',5,5'-tetraCB were relatively weak PB-type inducers. As shown in Figure, the compounds with a chlorine atom at 4'-position of 3-$MeSO_2$-2,5-diCB derivatives had the increasing effects of CYP2B1 and CYP2B2. The compounds with a chlorine atom at 2'-position of 3-$MeSO_2$-2,4',5-triCB derivatives became more active inducers of CYP2B. The compounds with a chlorine atom at 2- or 3'-position of 3-$MeSO_2$-2,4',5-triCB derivatives became lower inducers.

In conclusion, the results of the present study showed that the structure-CYP2B induction relationships for the 3-$MeSO_2$ derivatives studied.

META (po)

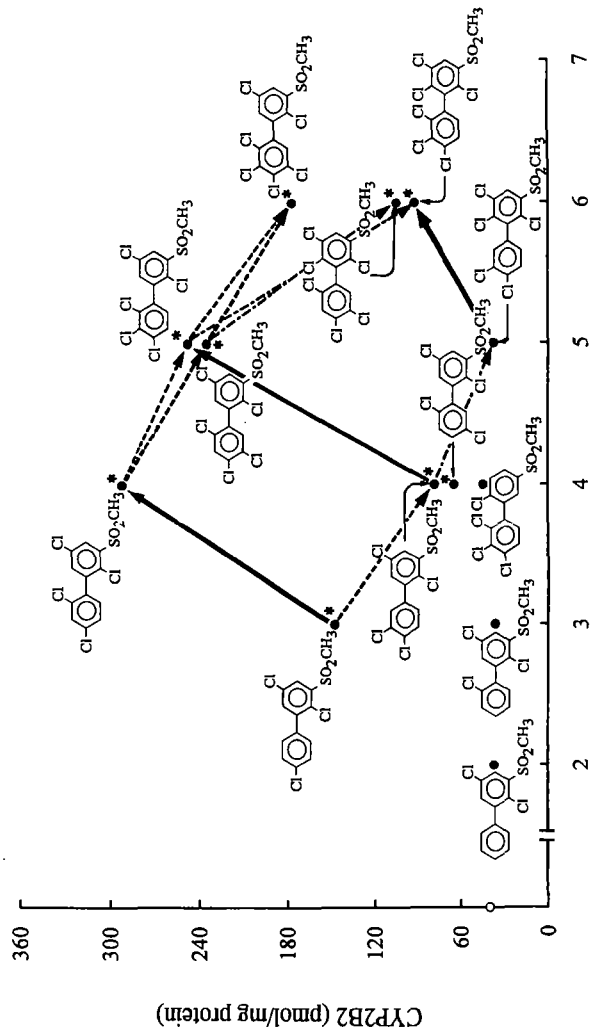

Figure. Relationship between number of chlorine atoms of 3-MeSO2-PCBs and induction of CYP2B2 of rat hepatic microsomes

Rats were given i.p. 3-MeSO2-PCBs (2 μmol/kg) and killed 96 hr after the administration.
Each point represents the mean for 5-6 animals.
O: control (40 ± 2 pmol/mg protein),
——▶: Addition of a chlorine atom at 2'-position,
- - - -▶: Addition of a chlorine atom at 3'-position,
——▶: Addition of a chlorine atom at 2-position.
* $P<0.05$, significantly different from the control.

4. References

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