Methylsulfonyl Metabolites Derived from 2,2',4',5,5'-PentaCB and 2,2',3,4',5',6-HexaCB in Rats

Koichi Haraguchi[A], Yoshihisa Kato[B], Ryohei Kimura[B] and Yoshito Masuda[A]

[A]Daiichi College of Pharmaceutical Sciences, Minami-Ku, 22-1 Tamagawa-Cho, Fukuoka 815, Japan.

[B]School of Pharmaceutical Sciences, University of Shizuoka, 52-1, Yada, Shizuoka 422, Japan.

INTRODUCTION

In the metabolism of PCB, formation of sulfur-containing metabolites such as the methyl sulfides and the methyl sulfones has been well documented [1, 2]. Among them, methylsulfonyl PCB ($MeSO_2$-CBs) are known as persistent and lipophilic compounds that have been shown to be selectively retained in tissues of animals [3]. In recent studies, a large number of $MeSO_2$-CBs have been detected and identified in several mammals [4]. To date, the only $MeSO_2$-CBs identified in wildlife are those originating from CBs with a 2,5-dichloro- or 2,3,6-trichloro-substituted phneyl ring [5]. For example, the most dominating congeners in seal blubber were identified as 3- and 4-$MeSO_2$-CBs derived from 2,2',4',5,5'-pentaCB (I-101) and 2,2',3,4',5',6-hexaCB (I-149) [5]. These parent CBs are major constituents in commercial PCB mixtures [6] and their metabolites have been also found in other species such as otter, mink, and polar bear [7].

In the present study, I-101 and I-149 were administered i.p. to rats in order to study if they can be metabolized to the methyl sulfones, which are subsequently accumulated in the tissues or excreted to the feces. The tissue distribution of the parent CBs and their metabolites in rats were examined in relation to the behavior of $MeSO_2$-CBs observed for wildlife. In addition, this study includes fecal excretion of the methylthio and hydroxylated products identified.

EXPERIMENTAL

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 were given i.p. I-101 and I-149 (342 μmol/kg, respectively) and were killed at various times afterwards. Liver, lung, kidney, adipose tissues and blood were removed. Feces were collected daily for eight days. Samples were analyzed for the parent CBs and their metabolites according to the conventional method [8].

RESULTS and DISCCUSION

2,2',4',5,5'-pentaCB (I-101)

The major metabolites in the extracts of feces from I-101 were identified as 3-hydroxy (OH)- and 4-methylthio (MeS)-2,2',4',5,5'-pentaCB. The maximum excretion of these metabolites occurred on 2 days or 3 days after the injection. The amounts of both 3-OH and 4-MeS metabolites during the first 8 days accounted for about 0.5% and 0.1% of the dose, respectively. Their isomeric 4-OH- and 3-MeS-pentaCB were present at much lower quantities. The corresponding 3- and 4-$MeSO_2$-pentaCBs were also detected, but the total levels were estimated to be less than 1/4 of those for the MeS-pentaCBs. The ratios of 3-MeS-/4-MeS-pentaCB and 3-$MeSO_2$-/4-$MeSO_2$-pentaCB in the feces were about 0.1 and 0.25, respectively.

During 42 days after the injection, 3- and 4-$MeSO_2$-2,2',4',5,5'-pentaCBs were retained in all tissues studied, together with the unmetabolized CB. There were no traces of other chlorinated components and hydroxylated metabolites in tissues, except for traces of MeS metabolites in adipose tissue. Time course of tissue concentration of both the parent CB and the metabolites showed that the CB was rapidly eliminated from tissues, whereas $MeSO_2$-CBs gave rise to high concentration during the first several days and continued to keep the level constant at least until 16 days after the injection. Tissue concentrations of the parent CB and the $MeSO_2$-pentaCB at 42 days after the injection are shown in Table 1. In adipose tissue, the parent CB level was still higher even after 42 days after the injection, and 3- and 4-$MeSO_2$-pentaCBs were also retained in the highest levels among the analyzed tissues. Liver and adipose tissue contained the 3- and 4-$MeSO_2$-CBs in a similar concentration range. In all tissues except for adipose tissue, the $MeSO_2$-CB levels exceeded the CB level. Lung and kidney were dominated by 4-$MeSO_2$-pentaCB. In particular, the concentration of 4-$MeSO_2$-CB in the lung nearly equalled that in the adipose tissue and was more than 10 times higher than the parent CB at 32 days and 42 days. Thus, the ratios of 3-$MeSO_2$-/4-$MeSO_2$-pentaCB in tissues were estimated as 0.01 for lung, 0.09 for kidney, 0.30 for blood, 0.85 for adipose tissue and 0.88 for liver. These results indicate that 3-$MeSO_2$-pentaCB tends to concentrate in liver and adipose tissue, whereas 4-$MeSO_2$-pentaCB shows a great affinity for lung and kidney.

2,2',3,4',5',6-hexaCB (I-149)

As in the case of I-101, the fecal metabolites of rats dosed with I-149 consisted mainly of hydroxy, methylthio and methylsulfonyl derivatives, major one being 4-MeS-2,2',3,4',5',6-hexaCB. The isomeric 3-MeS-hexaCB, and 3- and 4-$MeSO_2$-hexaCBs were also detected. Total amounts of the MeS-hexaCBs in feces during the first 8 days were about half of those for MeS-pentaCBs from I-101. 3- and 4-$MeSO_2$-2,2',4',5,5',6-hexaCBs were deteced in all tissues studied, at a concentration lower than $MeSO_2$-pentaCBs from I-101. The distribution pattern was similar to that obserbed for I-101, with marked uptake of 4-$MeSO_2$-hexaCB in lung and kidney.

In conclusion, 2,2',4',5,5'-pentaCB and 2,2',3,4',5',6-hexaCB were preferentially biotransformed to methylthio metabolites which are partly oxidized to the corresponding methyl sulfones in rats. The MeS-CB metabolites were largely excreted to feces, while the $MeSO_2$-CBs were retained in all the tissues. In spite of lower formation ratio of 3-$MeSO_2$-CB relatively to 4-$MeSO_2$-CB, the former isomer was favored for retention in liver and adipose, while the latter was selectively localized in lung and kidney. In this study, however, there was no significant difference in the distribution ratio of 3-$MeSO_2$-/4-$MeSO_2$-CB between liver and adpose tissue, which has been observed in mammals such as seal, otter and mink [7].

Table 1. Concentrations (ng/g) of the parent CB and the $MeSO_2$ metabolites in tissues of rats at 42 days after dosage of 2,5,2',4',5'-pentaCB.

Tissues	Parent CB	Metabolites		Ratio	
		3-$MeSO_2$	4-$MeSO_2$	3-$MeSO_2$/ 4-$MeSO_2$	Metabolites/ Parent CB
Adipose tissue	3736	447	526	0.85	0.3
Liver	73	43	49	0.88	1.3
Kidney	32	7	74	0.09	2.5
Lung	37	5	458	0.01	12.5
Blood	8	3	10	0.30	1.6

Each value is the mean from four rats.

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