Comparative metabolism of polychlorinated biphenyls (Kanechlor-500) in rats, hamsters and guinea pigs

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Introduction

In animals, metabolism of polychlorinated biphenyls (PCBs) proceeds via cytochrome P450 (CYP450)-mediated formation of arene oxide intermediate, which results in both hydroxylated (OH) and methylsulfonyl ($MeSO_2$) metabolites [1]. Some of these metabolites are persistent and show a specific retention in blood or tissues of laboratory animals as well as environmental mammals [2, 3]. Recent studies have demonstrated that some OH metabolites of PCBs can cause alteration in the thyroid hormone metabolism [4, 5], whereas $MeSO_2$ metabolites can cause induction of several CYP450 isozymes [6] and reduction of thyroid hormone levels in rats [7].

Commercially produced PCB mixtures, e.g. Kanechlor-500, are the ultimate source of PCBs in the environment. However, the patterns of residual PCBs in tissues have been shown to vary among animal species. To our knowledge, only limited data are available on the species difference in metabolism of PCB mixtures. In this study, metabolism, excretion and tissue distribution of Kanechlor-500 were compared among rats, hamsters and guinea pigs in relation to the tissue affinity of persistent metabolites such as OH- and $MeSO_2$-PCBs.

Materials and Methods

Reference compounds such as methoxy-, methylthio- (MeS-) and $MeSO_2$-PCBs were

synthesized as described previously [8, 9]. Kanechlor-500 was injected i.p. to male Wistar rats, male Hartley guinea pigs and male Golden syrian hamsters at a single dose of 100 mg/kg. Feces were collected daily for 5 days. These animals were killed 5 days after the injection and liver, lung and blood were removed and stored at –20 ºC until analysis.

The extraction and sample clean-up procedures are described elsewhere [10]. The analysis of individual PCBs and their metabolites was carried out on GC/MS system (AOC-17, GC-17A, QP-5000, Shimadzu) with a DB-5 capillary column (60 m x 0.25 mm, i.d.). Temperature program: 100 ºC, 2 min, 100-250 ºC at 20 ºC/min, 250-280 ºC at 2 ºC/min. The quantification of $MeSO_2$ and OH metabolites was performed on GC/ECD (GC-14A, Shimadzu) with column conditions analogous to those described for GC/MS.

Results and Discussion

The major PCB components in Kanechlor-500 were CB-52 (5.6%), CB-95 (6.6%), CB-101 (10.0%), CB-110 (7.4%), CB-118 (7.7%), CB-138 (5.3%) and CB-153 (5.4%). The actual CB patterns in tissue after 5 days of exposure were different among species. The dominating congener in liver was CB-138 (13.7% of total PCBs) for rats, CB-153 (17.0%) for hamsters and CB-118 (32.2%) for guinea pigs. Comparison of relative contribution of PCB constituents in liver indicated that rats retained non-coplanar PCBs with 2,4- or 2,3,4-chlorine substitution (e.g. CB-85, CB-99 and CB-128), whereas hamsters retained more highly chlorinated PCBs (e.g. CB-180). In contrast, guinea pigs retained preferably coplanar PCBs (e.g. CB-37, CB-81, and CB-77). For example, CB-77 was a minor component (0.03%) of Kanechlor-500 but was present in guinea pig liver at a much higher concentration (1.8% of total PCBs).

All the species metabolized Kanechlor-500 to MeS metabolites as well as OH metabolites in feces. The excretion of MeS metabolites during the first 5 days of exposure was estimated to be similar to that of unchanged PCBs for all the species. Major MeS metabolites were

identified as 3- and 4-MeS metabolites from CB101 in rats, whereas those from CB-87 and CB-132 in guinea pigs.

All the species exhibited the tissue retention of $MeSO_2$ metabolites. Total concentrations of $MeSO_2$-PCBs were higher in the order of guinea pigs > rats > hamsters. Most of persistent $MeSO_2$ metabolites were those originated from CBs with 2,5- or 2,3,6-chlorine substitution, although the metabolites from CB-52, CB-95 and CB-110 were minor. Rat liver accumulated preferably 3- and 4-$MeSO_2$ metabolites of CB-101. For the retention profile, hamsters resembled rats. In contrast, guinea pigs retained selectively 3-$MeSO_2$ metabolites derived from CB-87 and CB-132 in the liver.

Although a large amount of OH metabolites were excreted in feces, some of them were selectively retained in blood, liver and lung of each species. Rats and hamsters exhibited a specific retention of 4-OH-2,3,5,3',4'-pentaCB (90% of total OH-PCBs) derived from CB-118 (or CB-105) in both blood and liver. In contrast, guinea pig showed a specific retention of 3-OH-2,4,5,3',4'-pentaCB derived from CB118 in blood, and also an additional metabolite 3-OH-2,4,5,2',4'-pentaCB (60%) derived from CB-99 in liver.

The selective retention of OH metabolites in blood has also been observed for rats exposed to Arochlor-1254 and individual congeners (e.g. CB-77, CB-105, CB-118 and CB-156) as well as in seal and human blood [3, 10]. The retained OH-PCBs all demonstrated the structural similarity of an OH-group at the 3- or 4-position together with two adjacent chlorine atoms. These affinity would be due to binding to transthyretin concomitant with a reduction in levels of circulating thyroid hormone and vitamin A in the blood [5]. Interestingly, the species difference was observed in the hydroxylation of CB-118, which could be explained by the catalytic activity of each P450 isozyme. Koga *et al*. [11-13] reported that guinea pig CYP2B18 can catalyze only 3-hydroxylation for CB-52 and CB-70, whereas rat CYP1A1 and hamster CYP2A8 are involved in the 4-hydroxylation.

In conclusion, the three species showed a marked difference in toxicokinetics and metabolism of Kanechlor-500. In particular, guinea pigs are resistant to metabolize coplanar PCBs and have the unique P450-dependent monooxygenase systems [14]. Thus, the contribution of PCB metabolites in species-dependent toxicity may be important for developing schemes for congener-specific risk assessment of PCBs.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research (C) (no.10672116) from the Ministry of Education, Science, Sports and Culture of Japan.

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