In vivo metabolism of 3,3',5,5'-tetrachlorobiphenyl in rats

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Introduction

The environmental contaminants, PCBs, are known to be biotransformed mainly to hydroxylated metabolites. Detection of hydroxylated metabolites of individual PCB congeners in feces has been reported. Hydroxylated metabolites of PCBs are considered to be normally excreted in feces and urine. However, specific retention of hydroxylated PCB metabolites in blood of some mammals including human have been recently demonstrated [1]. These metabolites are substituted with hydroxy group in the 4- or 3-position and chlorine atoms adjacent to the hydroxy group. Furthermore we have found that hydroxylated metabolites of PCDFs are also retained selectively in the blood of rats administered PCDFs [2]. The retention of hydroxylated metabolites of PCBs and PCDFs in blood is probably due to a binding of these metabolites to a thyroxin transporting proteins (e.g. transthyretin, TTR) [3]. In addition, the possibility has been reported that the hydroxylated metabolites of PCBs might play an important role in the mechanism of PCB toxicity. Brouwer et al. have demonstrated that 4-hydroxy-3,3',4',5-tetraCB, a metabolite of 3,3',4,4'-tetraCB, exhibits strong binding affinity with TTR, causing a decrease of blood level of thyroxin and vitamin A [4].

We have shown that 3,3',5,5'-tetraCB, one of the coplanar PCB congeners, was metabolized to 4-hydroxy-3,3',5,5'-tetraCB with liver microsomes of rats treated with 3-methylcholanthrene (MC) and 3,3',4,4',5-pentaCB [5]. However, the hydroxylated metabolite was not produced with those of rats treated with phenobarbital (PB) or untreated [5]. It is of interest that the structure of the hydroxylated metabolite, 4-hydroxy- 3,3',5,5'-tetraCB, fits to the structural requirements for binding of hydroxylated PCBs with TTR. Therefore, study on the distribution of 4-hydroxy-3,3',5,5'-tetraCB in rat, especially in rat blood, is of interest.

This paper reports the in vivo metabolism of 3,3',5,5'-tetraCB in the rat pretreated with MC, PB and untreated.

Experimental

Male Wistar rats (ca.200g) were treated i.p. with 3,3',5,5'-tetraCB dissolved in corn oil at a single dose of 100 mg / kg and were killed 5 days after the injection. Liver, adipose tissue, kidney and blood were taken out for analysis of hydroxylated metabolites. PB and MC pretreatments were performed before the injection of 3,3',5,5'-tetraCB for 3 days as described elsewhere [5]. Each of untreated and PB- and MC-treated groups consists of 4 rats.The hydroxylated metabolites were extracted, purified and analyzed as methylated derivatives by GC (ECD) and GC/MS as described elsewhere [2].

Results and Discussion

In the serum of untreated rats , a hydroxylated metabolite of tetraCB was detected and the structure of this metabolite was identified as 4-hydroxy-3,3',5,5'-tetraCB by comparison with authentic standard on GC and GC/MS (Fig. 1). This metabolite was also observed in the serum of rats pretreated with MC and PB. However the content of this metabolite in the serum varied. The concentrations (ng/g serum) of this metabolite in the serum from the untreated, PB-treated and MC- treated rats were 11.4±1.5, 39.1±9.3 and 18.9±1.7, respectively. Unmetabolized 3,3',5,5'-tetraCB was determined at high concentrations of 252.3±20.2 ng/g and 249.0±34.5 ng/g in the serum of rats untreated and pretreated with PB , respectively. On the other hand, the concentration of unmetabolized 3,3',5,5'-tetraCB in MC-pretreated rat serum was 48.0±37.6 ng/g, indicating a rapid biotransformation of 3,3',5,5'-tetraCB compared to the PB treatment and untreatment.

These results were different from those obtained from in vitro study. Formation of 4-OH-3,3',5,5'-tetraCB in vitro was observed only after incubation with liver microsomes derived from the MC-treated rat [5]. However, 4-OH-3,3',5,5'-tetraCB was detected in vivo in all the rats treated with MC, PB and untreated, indicating more complicated situation of in vivo 3,3',5,5'-tetraCB metabolism. As mentioned above, accelerated metabolism of 3,3',5,5',-tetraCB was expected in the MC-treated rat, but the concentration of 4-OH-3,3',5,5'-tetraCB in serum was not so high. To understand the reason of lower level of 4-OH-3,3',5,5'-tetraCB in MC-treated rat serum, the studies on the excretion of the hydroxylated metabolite in feces and the distribution of the hydroxylated metabolite in other tissues are now under investigation.

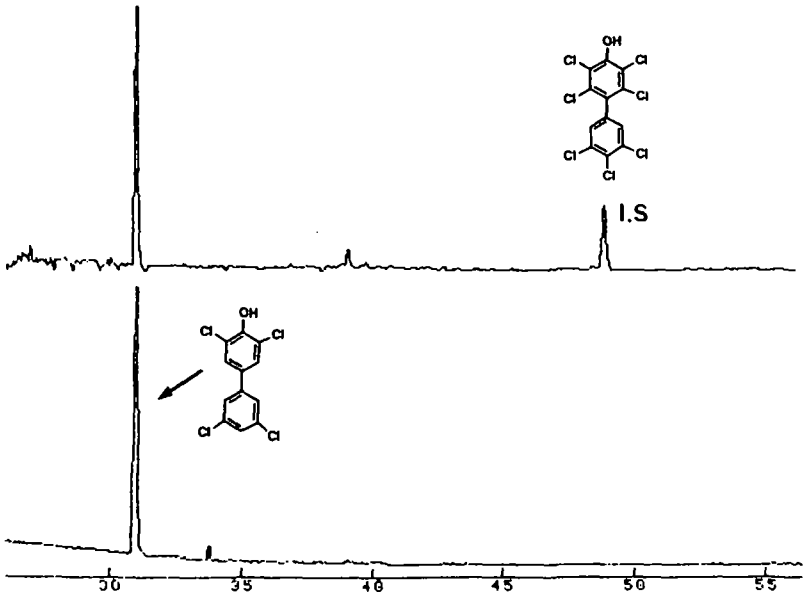

Fig. 1. Gas chomatograms of methylated metabolite of 3,3',5,5'-tetraCB in rat serum (upper) and of 4-OH-3,3',5,5'-tetraCB standard (lower).

References

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