EFFECTS OF 2,2',4,5,5'-PENTACHLOROBIPHENYL AND 2,2',3,3',4,6'-HEXACHLOROBIPHENYL ON SERUM HORMONE LEVELS IN RATS AND MICE

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Introduction

A number of the methylsulfonyl ($MeSO_2$) metabolites of polychlorinated biphenyls (PCBs) have been found in several species of animals in Canada and Sweden [1-4] and in healthy humans [5-8].

We previously showed that the 3-$MeSO_2$ metabolites derived from 2,2',4,5,5'-pentachlorobiphenyl (PentaCB) and 2,2',3,3',4,6'-hexachlorobiphenyl (HexaCB) induced hepatic drug-metabolizing enzymes [9]. We also showed that the 3- and 4-$MeSO_2$ metabolites of PentaCB and HexaCB reduced the level of serum thyroxine (T_4) [10-12], suggesting that the metabolites may be ultimate endocrine-disrupters. Furthermore, we suggested that the reduction of serum T_4 level is dependent on increase in the hepatic T_4 glucuronidation through $MeSO_2$ metabolites-mediated induction of both UGT1A1 and UGT1A6 [13]. Recently, we reported that there are marked differences in the hepatic concentration of the $MeSO_2$ metabolites of PentaCB and HexaCB, and in induction pattern of phase I microsomal drug-metabolizing enzymes by PentaCB and HexaCB between rats and mice [14, 15].

In the present study, therefore, we investigated the effects of PentaCB and HexaCB on serum testosterone and thyroid hormone levels in rats and mice.

Materials and Methods

Chemicals. PentaCB and HexaCB were synthesized by using the Cadogan coupling reactions [16]. The purity of these compounds was >99% when analyzed by gas chromatography. All other chemicals used in the present experiments were commercially obtained.

Animal treatments. Male Wistar rats, weighing 150-210 g, and male ddy mice, weighing 27-39 g, were housed three or four per cage with free access to commercial chow and tap water, and maintained on a 12-hr dark/light cycle (8:00 a.m.-8:00 p.m. light) in a room with controlled temperature (24.5 ± 1°C) and humidity (55 ± 5%). Rats and mice received an intraperitoneal injection of PentaCB or HexaCB (342 μmol/kg) dissolved in Panacete 810 (5 ml/kg). Control animals were treated with a vehicle alone (5 ml/kg). All animals were starved for 18 hr prior to killing by decapitation at days 1, 2, 4 and 8 after the dosing. Blood was collected from animals between 10:30 and 11:30 a.m. After clotting at room temperature, serum was separated by centrifugation and stored at -50°C prior to determination of the levels of total testosterone, total thyroxine (T_4), total triiodothyronine (T_3) and thyroid stimulating hormone (TSH) by radioimmunoassay using Coat A Count Total Testosterone Kit (Diagnostic Products Corporation; Los Angeles, U.S.A.), Amerlex-MT4, Amerlex-MT3

(Ortho-Clinical Diagnostics Co.; Amersham, UK) and Biotrak rTSH [^{125}I] assay system (Amersham Life Science Ltd.; Little Chalfont, UK), respectively.

Preparation of hepatic microsomes and the microsomal enzyme assays. Hepatic microsomes were prepared according to the procedure described previously [17]. The protein content was determined by the method of Lowry *et al.* [18] with bovine serum albumin as a standard. The microsomal activities of UDP-glucuronosyltransferase (UDP-GT) toward 4-nitrophenol and chloramphenicol were determined as described by Isselbacher *et al.* [19] and Ishii *et al.* [20], respectively.

Results and Discussion

No change was observed in the serum concentration of testosterone after the administration of PentaCB or HexaCB in rats and mice (Fig. 1). On the other hand, the serum concentrations of total T_4 were reduced by both PCB treatments in rats and mice. Total T_4 level was reduced by PentaCB from day 1 (40-60%), and the depression continued through day 8 in rats and mice (Fig. 2). HexaCB significantly reduced serum total T_4 levels by 40-60% at days 2 and 4 in rats and mice (Fig. 2). The serum concentration of total T_3 was decreased at day 1 (42% decrease) by PentaCB treatment in rats, and decreased at day 4 (53-63% decrease) by HexaCB in rats and mice. The serum concentrations of TSH were decreased at day 1 by HexaCB, while no change was found in the serum TSH level after the administration of PentaCB.

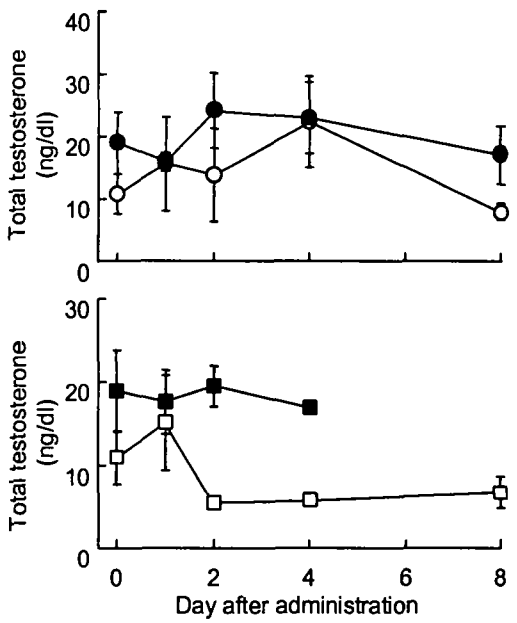

Fig. 1. Effects of PentaCB and HexaCB on serum total testosterone concentration in rats and mice. Animals were given i.p. PentaCB and HexaCB (342 μmol/kg each) and killed at the appropriate times after the administration. Each point represents the mean ± S.E. (vertical bars) for three to eight animals. —○— PentaCB (rat); —●—, PentaCB (mouse); —□—, HexaCB (rat); —■—, HexaCB (mouse).

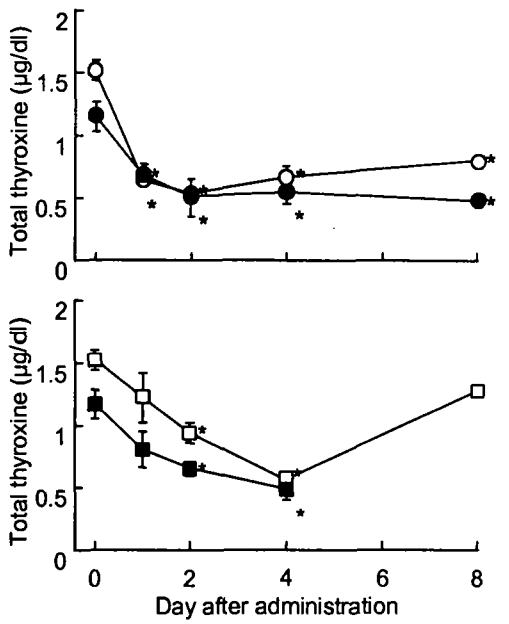

Fig. 2. Effects of PentaCB and HexaCB on serum total thyroxine concentration in rats and mice. The experimental conditions were the same as described in the legend to Fig. 1. Each point represents the mean ± S.E. (vertical bars) for three to eight animals. *P<0.05, significantly different from the control (0 hr). —○—, PentaCB (rat); —●—, PentaCB (mouse); —□—, HexaCB (rat); —■—, HexaCB (mouse).

PentaCB or HexaCB increase little UDP-GT (UGT1A6) activity toward 4-nitrophenol in both species. On the other hand, PentaCB and HexaCB treatments extensively increased the UDP-GT (UGT2B1) activity toward chloramphenicol in rats but not in mice.

In conclusion, PentaCB and HexaCB possess the ability to reduce the serum total T_4 and T_3 concentrations in rats and mice. Since PentaCB and HexaCB influence hardly UGT1A6 responsible for the glucuronidation of T_4 in rats and mice, the reduction of serum T_4 levels was not necessarily correlate with increase in hepatic T_4 glucuronidation activity. Further studies are needed to reveal the details of the reduction mechanisms.

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