HYDROXYLATED POLYCHLORINATED BIPHENYLS (OH-PCBs) AND THEIR PRECURSORS (TOTAL PCBs) IN HUMAN SERUM AND CEREBROSPINAL FLUID (CSF) SAMPLES

Watanabe Kiyohiko[1], Takumi Takasuga[1], Senthilkumar Kurunthachalam[1], Hiroaki Takemori[1], Takaaki Shoda[2], Yoichiro Kuroda[3]

[1]Shimadzu Techno Research Inc.,
[2]Dept. Medicine, Ehime Univ., Medic. Res. Ehime
[3]Tokyo Met. Ins.

Introduction

Polychlorinated biphenyls (PCBs) have great potential for bioaccumulation and consecutive biological adverse effects. In humans and wildlife, PCBs taken in to the body and were metabolized into hydroxylated (OH-) forms. Particularly, metabolism of the individual components of PCBs proceeds via CYP450-mediated formation of arene oxide intermediates, which results in OH- products. Although ample evidence suggests toxicity of the dioxin-like PCBs (DLPCBs), information regarding toxicity of PCB metabolites are meager. Especially, metabolites are likely to affect thyroid hormone, and it has already demonstrated that some OH-PCBs act as endocrine disrupters[1]. The study confirms that when thyroxin is added to the cultured neuron of the cerebellum it grows normally[2], however the growth is strongly obstructed when OH-PCB added[3]. Therefore, OH-PCBs attributed to impact the biochemical process of the brain is likely[4,5]. Earlier, we established pretreatment and high sensitivity analytical method of polychlorinated biphenyls (PCBs) and their hydroxylated metabolites (OH-PCBs) in serum and cerebrospinal fluid (CSF) of humans for the first time. In this study, we analyzed additional serum and CSF samples in order to confirm that CSF plays any additional bioaccumulation of OH-PCBs. Particularly, total PCBs and OH-PCBs in the CSF and serum were extracted by specialized developed method[6,7].

Materials and Methods

Samples and Cleanup: Cerebrospinal fluid (CSF) and serum was collected from eight individual volunteers from Ehime University Hospital by specialized surgeon. Furthermore, only CSF were collected from 17 individuals. The brief cleanup and analytical procedure of the PCBs and OH-PCBs analysis has been reported elsewhere[6,7]. Two laboratory blank also conducted in order to see any glass wares and solvents contamination. Blank contains <1 pg/g wet concentration for any PCB congener (except HxCB-153 at 0.32 pg/g).

Results and Discussion

Total PCBs and OH-PCBs in Human Serum and CSF

Among 8 serum and 25 CSF samples analyzed, total PCBs were greater in serum (100-3200 pg/g wet wt) (Table 1). Particularly, 8 congeners were detected in serum with HpCB-180 was predominant congener followed by HxCB-153. Concentrations of total PCBs in CSF were ND to 10 pg/g wet wt. Only HxCB-153, HpCB-180 and HpCB-182/187 were noticed. Similarly concentrations of OH-PCBs in serum were comparatively higher in serum (68-630 pg/g wet wt). Interestingly OH-PCBs were slightly higher in CSF (ND-41 pg/g wet wt.) when compare to total PCBs. The predominant OH-PCBs was 4-OH-HpCB-187, 4-OH-HxCB-146 and 4-OH-PeCB-107 in serum and 4-OH-HpCB-187 and 4-OH-HxCB-165 in CSF. Similar accumulation trend are also reported in excreta of gray seal, common murre, intralumina uterine fluid of mice. Parent PCB congeners for 4-OH- HpCB-187 was HpCB-187/183 which is not predominant contaminants in biological samples and thus metabolism of HpCB-187/183 to 4-OH-HpCB-187 seem to have specific protein binding activity after metabolism. Specific protein binding of hydroxylated tail of PCB with CSF could be another possible explanation. Hydroxylated PCBs found in serum and CSF have two structural elements in common; either a 4-hydroxy-3,5-dichlorophenyl ring (or more chlorine atoms in the ring) or a 3-hydroxy-2,4-dichlorophenyl ring (or more chlorine atoms in the ring) and chlorine atoms in at least 3- and 4-positions in the other phenyl ring. Occurrence of OH-PCBs in CSF suggests they enter into the brain through blood-brain barrier.

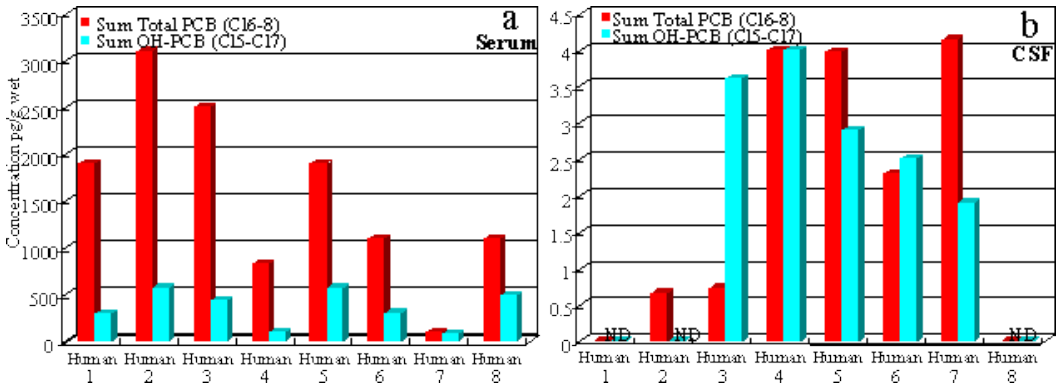

Figure 1. Concentrations of total PCBs and OH-PCBs in serum and CSF of 8 humans.

Total PCBs and OH-PCBs were also determined in serum and CSF of same volunteer (Figure 1a,b). Serum concentrations of hexa through octa PCBs were orders of magnitude greater than OH-PCBs (Figure 1a). On the other hand in CSF concentrations of OH PCBs were greater than total PCBs in two individuals (Figure 1b). Other 3 individuals showed more or less similar OH-PCBs and total PCBs (Figure 1b). Less significant correlation have been noticed for total PCBs and HO-PCBs (Figure 2). No good correlation between PCBs or OH-PCBs and age of human (Figure 3).

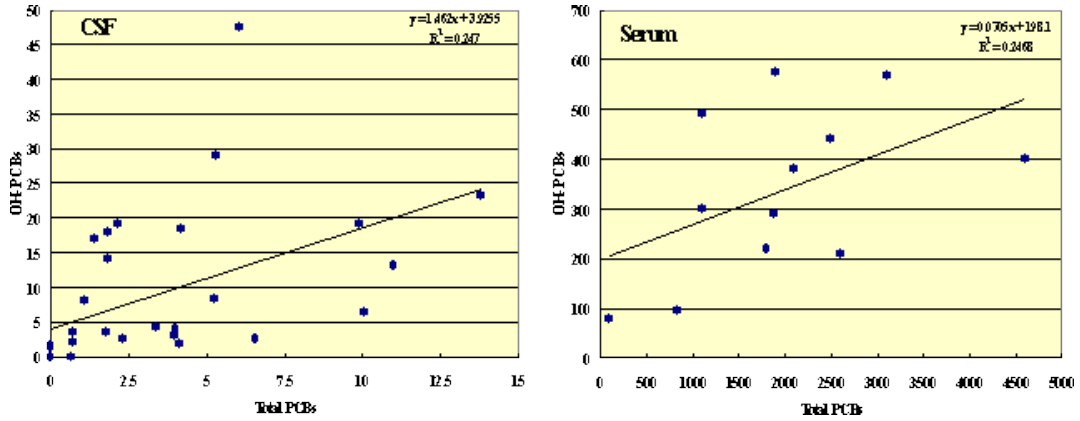

Figure 2. Correlation between age and total PCBs/OH-PCBs.

In general, total PCBs (DiCBs through DeCB) average concentrations (n=156) in blood of Japanese adults were 210,000 pg/g fat weight. The average dioxin-like PCBs were (25,000 fat weight) in same group of humans in which mono-ortho PCBs such as PeCB-118, 105 and HxCB-156 contributed to greater amount of total dioxin-like PCBs. Occurrence of OH-PCB-118 in human samples is of greater concern as it produce multitude of toxic effects.

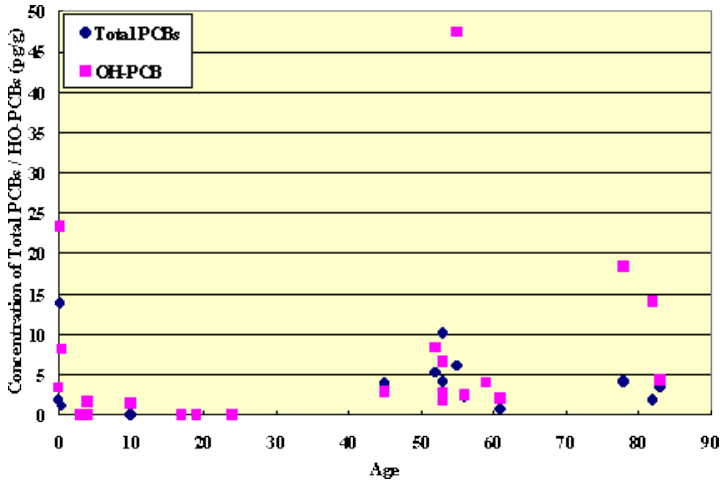

Figure 3. Correlation between Total PCBs / OH-PCBs and age.

OH-PCBs have been identified and quantified in blood from wildlife (5,900-33,000) and human blood plasma (238-1,750), breast milk (<1-5.0), maternal blood plasma (82-328), umbilical cord (103-788), cord blood plasma (35-271) on pg/g wet basis[8,9]. These studies reported that concentrations of OH-PCBs were greater or similar than the results obtained in our study. According to Sandau[10], OH-PCB was detected from whole blood with the total concentration were in the range of 0.117-11.6, and 0.161 on ng/g whole blood wet weight basis for the Inuit samples and southern population pool, respectively. Consequently, the magnitude of PCBs concentrations in humans reflects the local pollution sources.

The retention of OH-PCB congeners may be influenced by the exposure profile of PCBs, metabolism rate, and protein binding specificity. In general, metabolites of PCB are considered to be less toxic than their parent compounds. However, hydroxylated metabolites of 3,3',4,4'-TeCB(77) have a marked structural resemblance to thyroxine, the natural ligand for TTR and, therefore, competitively bind to TTR and can cause reductions in plasma tetraidothyroxine (T_4) levels and serum transport of vitamin A in rodents. Hydroxylated metabolites of PCBs have been shown *in vitro* to have binding affinities that are 10 times greater than TTR than for T_4. These results in persistent retention of these metabolites in blood of both humans exposed environmentally to PCBs. In addition, occurrence of OH-PCBs in CSF is of major concern as it can alter and modulate any signal that originated from brain.

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