CORRELATIONS BETWEEN MATERNAL-FETAL TRANSFER RATES AND PHYSICO-CHEMICAL PROPERTIES OF PCBS, OCPS, PBDES, AND DIOXIN-LIKE COMPOUNDS

Akifumi Eguchi[1], Masamichi Hanazato[2], Norimichi Suzuki[2], Yoshiharu Matsuno[2], Chisato Mori[2, 3]

[1]Chiba University, Clinical Cell Biology and Medicine: Graduate School of Medicine, Chuo-ku Inohana 1-8-1, Chiba-city, Japan; [2]Chiba University, Center for Preventive Medical Sciences, Inage-ku Yayoi-cho 1-33, Chiba-city, Japan; [3]Chiba University, Department of Bioenvironmental Medicine, Graduate School of Medicine

Introduction

Polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), and dioxin-like compounds are restricted or banned in Japan. Nevertheless, these chemicals have been detected in human fetuses and human milk (Fukata et al., 2005[1]; Mori, 2003[2]; Mimura et al., 1999[3]; Kawashiro et al., 2008[4]). Because of their highly lipophilic and stable nature, these compounds have a long half-life in human tissue. Moreover, because human adipose tissue accumulates these compounds, fetuses may be exposed to PCBs, OCPs, PBDEs, and dioxin-like compounds through the blood stream. Thus, the measurement of PCBs, OCPs, and dioxin-like compounds in maternal blood (MB) and umbilical cord blood (CB) provides an important means of assessing fetal exposure to these chemicals. Recent studies have reported that the transfer rates of PCBs and dioxin-like compounds in cases of fetal exposure to higher chlorinated congeners of PCBs or dioxins with large molecular weights might be lower than in cases of exposure to lower molecular weight molecules in humans (Needham et al., 2010[5], Mori et al., 2014[6], Hanazato et al., 2014[7]). However, correlations between other physico-chemical properties and the maternal-fetal transfer rate of these compounds were unclear.

The aim of this study was to quantify the levels of PCBs, OCPs, dioxin-like compounds, and their congeners/isomers in human CB and MB. We compared the concentrations of PCBs, OCPs, and dioxin-like compounds in sample sets normalized to wet and lipid weights. These data were then used to determine the placental transfer rates of PCBs, OCPs, dioxin-like compounds, and their congeners/isomers, to investigate the use of generalized linear regression models, and to determine whether these transfer rates correlated with the physico-chemical properties (logBCF, logKoa, logKow, molecular weights, and water solubility) of these compounds.

Materials and methods

MB and CB sample sets (n = 79) were collected at deliveries at Chiba University Hospital and various other obstetrics units in Japan. The samples were stored at -20°C until use. The "Congress of Medical Bioethics" of Chiba University approved the study, and all samples were obtained only after the receipt of written, informed consent. The concentrations of PCBs (TriCB, TetraCB, PentaCB, HexaCB, HeptaCB, OctaCB, NonaCB, and DecaCB) and OCPs (*p, p'*-DDE, trans-nonachlor, hexachlorocyclohexane (HCH), hexachlorobenzene (HCB), and heptachlor epoxide) were analyzed in 29 sample sets using an Agilent 6890 Plus gas chromatograph Agilent Technologies, Palo Alto, CA, USA) and an AutoSpec Ultima NT mass spectrometer (Micromass Ltd., Manchester, UK) equipped with a programmed temperature vaporization (PTV) injection system (Agilent Technologies) (Jotaki et al., 2011)[8]. We used an analytical method described by Sakurai et al. (2004)[9] in 41 sample sets for dioxin-like compounds (polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofuran (PCDF), and dioxin-like polychlorinated biphenyl (DL-PCB)). These compounds were analyzed by high resolution gas chromatography/high resolution mass spectrometry (HRGC-HRMS). An analytical method for the measurement of PBDEs (BDE47, 100, 153) in nine samples was described by Kawashiro et al., (2008)[4], and these compounds were also analyzed using high resolution gas chromatography/high resolution mass spectrometry (HRGC-HRMS). The lipid weights in MB and CB were measured using a technique previously described by Patterson et al., (1989)[10].

The physico-chemical properties (biodegradation half-life, logBAF, logBCF, logKow, molecular weights, and water solubility) of PCBs, OCPs, PBDEs, and dioxin-like compounds were obtained from the Estimation Program Interface (EPI) Suite (United States Environmental Protection Agency, Washington, DC, USA). The physico-chemical properties of TetraCB, PentaCB, HexaCB, HeptaCB, and OctaCB isomers were referred to as CB74, CB118, CB153, CB180, and CB194, respectively.

Statistical analysis was performed using R Ver. 3.1.0 (The R Foundation for Statistical Computing). We used generalized linear regression models (GLMs) to assess how the relationship between concentrations of contaminants in MB and CB determined the placental transfer rates of PCBs, OCPs, PBDEs, and dioxin-like compounds (Hanazato et al., 2014[6]). CB was the response variable. We used a stepwise GLM to assess the association between transfer rates of PCBs, OCPs, PBDEs, and dioxin-like compounds and logBAF, logBCF, logKow, molecular weights, and the water solubility of contaminants.

The concentrations of OCPs, PBDEs and dioxin-like compounds were not normally distributed; thus the data were analyzed by GLMs with a gamma distribution of the response variable and an identity-link function. For any model, the parameters that optimize the approximation of the likelihood can be identified numerically. The optimized likelihoods from different models can then be compared by means of the AIC:

$$AIC = 2k - 2\ln L \quad (1)$$

In this particular model, k represents the number of parameters, and L represents the maximized value of the likelihood. The model with the smallest AIC is selected, which provides a trade-off between model complexity (preferring models with fewer parameters) and the model's maximized likelihood. We assessed the multicollinearity of independent variables by calculating the variance inflation factor (VIF). This analysis included only those contaminants that were detected in at least 80% of the samples. We considered a *p*-value of < 0.05 to be statistically significant. Results below the LOQ were assigned a value of 0.5 LOQ.

Results and discussion

Table 1 shows the slopes (maternal-fetal transfer rates), standard error of the slopes, and *p*-values of the GLMs for PCBs, OCPs, PBDEs, and dioxin-like compounds from MB and CB. Table 2 displays the correlation between maternal-fetal transfer rates and the physico-chemical properties of PCBs, OCPs, PBDEs, and dioxin-like compounds. The results of the multivariable model revealed that dioxin-like compounds (Yes = 1, No = 0) (Estimate: -0.329, *p*-value: = 0.00214) and molecular weight (Estimate: -0.00167, *p*-value: = 0.0104) were strongly negatively associated with maternal-fetal transfer rates. The VIF values of the explanatory variables were < 10, which indicates a rejection of multicollinearity in the GLM.

These results clearly indicate that fetuses were not only exposed to PCBs, OCPs, PBDEs, and dioxin-like compounds in the maternal body, but that the transfer rates of these compounds decreased as molecular weight increased (Tables 1 and 2).

The transfer rates of dioxin-like compounds were significantly lower than other compounds (Yes = 1, No = 0) (Estimate: -0.329, *p*-value: = 0.00214). The aryl hydrocarbon receptor (AhR) protein was expressed in the human placenta (Jiang et al., 2010[11]), which indicates that dioxin-like compounds may be binding AhR proteins (Manchester et al., 1987[12]), thus having difficulty transferring across the human placenta.

This model suggests that even non-dioxin-like organohalogen compounds, with molecular weights greater than 1000, may have difficulty transferring across the human placenta (Table 2). However, the above analyses have limitations, including the sample size and the limited range of organohalogen compounds investigated. Additional comprehensive surveys that have larger sample sets and a wider variety of organohalogen compounds are therefore required to more clearly assess maternal-fetal transfer rates.

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Table. 1 Maternal-fetal transfer rates and and physico-chemical property of PCBs, OCPs, PBDEs and dioxin-like compounds

Compound	Transfer rate*	*p*-value	Molecular weight	Dioxin	LogKow	LogKoA	Water Solubility	LogBCF
TetraCB	0.75315	5.97E-13	291.99	NO	6.34	9.058	0.02751	4.133
PentaCB	0.75458	5.55E-15	326.44	NO	6.98	9.049	0.007126	3.811
HexaCB	0.66764	2.01E-14	360.88	NO	7.62	10.777	0.001281	3.525
HeptaCB	0.58136	7.35E-14	395.33	NO	8.27	11.658	0.0002842	3.277
OctaCB	0.48856	3.85E-13	429.77	NO	8.91	12.068	7.72E-05	2.994
HCB	0.718	3.23E-03	284.78	NO	5.86	6.888	0.1922	4.201
HCH	0.69153	7.43E-14	290.83	NO	4.26	7.817	4.044	3.121
Trans Nonachlor	0.818326	1.97E-08	444.22	NO	6.44	9.344	0.00612	4.182
Heptachlor epoxide	0.5005	2.75E-07	389.32	NO	4.56	8.046	0.1991	3.835
p, p' -DDE	1.91	2.15E-11	318.03	NO	6	9.279	0.02653	3.88
BDE47	0.39409	0.00714	485.71	NO	6.77	10.686	0.001461	3.699
BDE100	0.340528	0.000603	563.62	NO	7.66	11.977	7.86E-05	3.2
BDE153	0.44992	0.000112	643.53	NO	8.55	13.265	4.15E-06	2.624
1,2,3,7,8-PeCDD	0.48396	3.13E-11	356.42	YES	7.56	10.57	0.000939	3.736
1,2,3,6,7,8-HxCDD	0.47368	4.08E-16	390.86	YES	8.21	12.311	2.65E-05	2.26
1,2,3,4,6,7,8-HpCDD	0.42117	1.58E-11	425.31	YES	8.85	10.145	2.44E-05	2.455
OCDD	0.66764	2.01E-14	495.75	YES	9.5	11.76	9.97E-06	2.222
2,3,4,7,8-PeCDF	0.4693	3.10E-14	340.42	YES	7.27	10.696	0.0003386	2.827
1,2,3,6,7,8-HxCDF	0.6288	2.73E-11	374.87	YES	7.92	11.476	0.00034944	2.337
1,2,3,4,6,7,8-HpCDF	0.61085	8.93E-08	409.31	YES	8.56	12.246	1.02E-05	2.076
CB77	0.68925	7.29E-10	291.99	YES	6.34	10.045	0.02976	3.59
CB126	0.3971	5.16E-15	326.44	YES	6.98	9.403	0.009394	3.957
CB169	0.31196	9.28E-09	360.88	YES	7.62	9.963	0.0025	3.755
CB105	0.44004	3.06E-16	326.44	YES	6.98	9.234	0.01337	4.06
CB114	0.43039	1.07E-14	326.44	YES	6.98	9.403	0.009394	3.947
CB118	0.45035	2.00E-16	326.44	YES	6.98	9.049	0.007126	3.811
CB123	0.49764	6.09E-14	326.44	YES	6.98	9.049	0.007126	3.811
CB156	0.3393	3.55E-16	360.88	YES	7.6	9.833	0.00533	3.663
CB157	0.41038	5.58E-16	360.88	YES	7.6	10.153	0.001721	3.651
CB167	0.39733	2.57E-15	360.88	YES	7.5	10.053	0.00223	3.653
CB189	0.28797	1.43E-15	395.33	YES	8.27	10.953	0.000753	3.063

*Maternal-fetal transfer rates were calculated by GLM from contaminants in MB and CB (lipid wt) (Hanazato, 2014)

Table 2. Association coefficients between maternal-fetal transfer rates and physico-chemical properties of PCBs, OCPs, PBDEs, and dioxin-like compounds by GLM

	Estimate	Standard Error	*p*-value
Intercept	1.90	0.466	0.000383
Dioxin*	-0.333	0.0887	0.000882
LogBCF	-0.142	0.0724	0.0605
Molecular weight	-0.00167	0.000607	0.0104

*Dioxin-like compound (Yes = 1, No = 0)