Enhancement of Reduction Activity of 4NQO in Animals pretreated with 3-Methylcholanthrene-type PCB and PCDF

IKUO WADA,^a NOBUYUKI KOGA,^a KIYOSHI NAGATA,^a HIDETOSHI YOSHIMURA,^a HIROAKI KUROKI^b and YOSHITO MASUDA^b

Faculty of Pharmaceutical Sciences, Kyushu University,^a Fukuoka 812 and Daiichi College of Pharmaceutical Sciences,^b Fukuoka 815, Japan

(October 8—9, 1981)

Previously we reported that 3, 4, 5, 3', 4'-pentachlorobiphenyl (PenCB) and 2, 3, 4, 7, 8-pentachlorodibenzofuran (PenCDF), both of which are potent 3-methylcholanthrene (MC)-type inducers, showed strong acute toxicity in rats and that the toxic potency was well correlated with the inducing ability for the hepatic microsomal mixed function oxidase and cytosolic DT-diaphorase.^{1,2)} At present, the mechanism responsible for such a correlation has not been identified. It may be assumed, however, that the toxicity induced by PenCB and PenCDF is attributable, at least in part, to the disturbance of intermediary metabolism caused by the marked increases of the above enzymes. Apart from such a direct effect, these compounds may also affect the appearance of toxicity of certain xenobiotics through increased metabolic activation. As an example of this activation by DT-diaphorase, we now wish to report a remarkable enhancement of reduction of 4-nitroquinoline *N*-oxide (4NQO), a well-known precarcinogen, to a proximate carcinogen, 4-hydroxylaminoquinoline *N*-oxide (4HAQO), in various organs of Wistar rats pretreated with PenCB or PenCDF.

PenCB or PenCDF was dissolved in corn oil and injected into weanling male Wistar rats intraperitoneally at a single dose of 0.5 mg/kg. The animals were sacrificed 5 d after the injection, and the 9000×*g* supernatant was prepared from various organs such

as the liver, lung, small intestine, heart, kidney, spleen and skin of the abdomen.

Activities for the reduction of 4NQO and dichlorophenol-indophenol (DCPIP) increased about 6-fold in the liver, 4-fold in the lung and 3-fold in the skin as compared with the control after the pretreatment with PenCB or PenCDF. Interestingly, the ratios of reduction activities of 4NQO to those of DCPIP varied widely among these organs. This difference is thought to be due to the heterogeneity of DT-diaphorase. Besides, both activities were almost completely inhibited in the presence of 0.1 mM dicoumarol, a specific inhibitor of DT-diaphorase, indicating that the reduction of 4NQO in these organs was catalyzed solely by DT-diaphorase. Such an enhancement of the reduction activity for 4NQO by pretreatment with PenCB or PenCDF was also observed to various extents in the small intestine, the heart, the kidney and the spleen. The ratio of the reduction activity for 4NQO to that for DCPIP also varied considerably among these organs.

In view of these results, we suggest that such a marked increase of DT-diaphorase activity after pretreatment with MC-type PCB or PCDF may play an important role in the appearance of the toxicities of certain xenobiotics, due to the enhancement of their metabolic activation.

References

- 1) H. Yoshimura, S. Yoshihara, N. Ozawa and M. Miki: Possible correlation between induction modes of hepatic enzymes by PCBs and their toxicity in rats, *Ann. N.Y. Acad. Sci.*, **320**, 179—192 (1979).
- 2) S. Yoshihara, K. Nagata, H. Yoshimura, H. Kuroki and Y. Masuda: Inductive effect on hepatic enzymes and acute toxicity of individual polychlorinated dibenzofuran congeners in rats, *Toxicol. Appl. Pharmacol.*, **59**, 580—588 (1981).