Induction of Glutathione S-Transferase-P by Chlorinated Biphenyls and Dibenzofurans, and Inhibitory Effect of Dexamethasone on the Induction

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Introduction

Coplanar polychlorinated biphenyl (PCB) congeners, e.g. 3,4,5,3',4'-pentachlorobiphenyl (PenCB) are considered to be promoters of liver tumor. Coplanar PCBs induce a tumor marker enzyme, glutathione S-transferase-P (GST-P) in primary cultured rat liver parenchymal cells, and protein kinase is suggested to play a role in the induction of GST-P. The configurations of chlorinated dibenzofurans (CDFs) are similar to those of PCBs, but the toxicological effect of CDFs was unclear. 2- and 3-Chlorodibenzofurans (2- and 3-CDF, respectively) were revealed to show mutagenicity to Salmonella typhimurium. We report here that CDFs also induce GST-P in cultured cells. Dexamethasone (Dex) inhibited the induction of GST-P by CDFs as well as by coplanar PCBs.

Methods

Isolated rat liver parenchymal cells were cultured in Williams’ medium E with 10% fetal calf serum for 4 h and then in medium without serum for 20 h. The cells were further incubated with PenCB, 2-CDF, 3-CDF, or 2,8-dichlorodibenzofuran (2,8-DCDF) for 12 h or 24 h. To study the effect of Dex on the GST-P and cytochrome P450IA2 induction, the cells were incubated with these compounds in the presence of Dex ($10^{-9} \text{ to } 10^{-5} \text{ M}$). Amounts of GST-P and cytochrome P450IA2 mRNA were determined by Northern blot hybridization.

Results and Discussion

2-CDF, 3-CDF, and 2,8-DCDF (0.1–100 μM) induced GST-P as well as PenCB in the primary cultured rat liver parenchymal cells. The induction of GST-P mRNA by 3-CDF was dose-dependent. 2,8-DCDF induced GST-P more intensively than 2-CDF or 3-CDF.

Dex inhibited the induction of GST-P by PenCB at the concentration of $10^{-9}$ M. However, Dex did not affect the expression of cytochrome P450IA2 mRNA, which is the typical gene induced by PCBs. These results suggest that GST-P is induced by a different process from cytochrome P450IA2 by PenCB. This is supported by the fact that H-7, protein kinase inhibitor, inhibited GST-P induction by PenCB, but did not inhibit P450 induction. Dex also inhibited the induction of GST-P by 3-CDF and 2,8-DCDF.

The upstream region of GST-P gene contains a TPA responsive element (TRE). AP-1, a transcriptional factor regulated by phosphorylation, is known to bind to TRE. Dex-glucocorticoid hormone receptor complex, however, has been demonstrated to attack AP-1 and to abolish the binding ability of AP-1 to TRE. Our results suggest that AP-1 is involved in the process of GST-P induction by chlorinated polyaromatic compounds.

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References