AHR LIGAND ACTIVITY OF ENVIRONMENTAL CONTAMINANTS AND THE EFFECT OF METABOLIC MODIFICATION
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Aryl hydrocarbon receptor (AhR) has the ability to bind with polycyclic aromatic hydrocarbons, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin, leading to induction of mRNA expression of the drug-metabolizing enzyme CYP1A1/2. AhR is thought to mediate a broad spectrum of biological responses, including teratogenesis, tumor promotion, and thymic atrophy. With the aim of discovering novel AhR agonists and antagonists, we screened various environmental contaminants for AhR ligand activity using yeast AhR reporter assay and HepG2 luciferase reporter assay. In yeast AhR reporter assay, benzophenone derivatives, diphenyl derivatives, fluorene derivatives, pyrene derivatives, stilbene derivatives, chalcone derivatives and parabens exhibited AhR ligand activity. Among fluorene derivatives, 2-nitrofluorene exhibited the highest activity, while 2-aminofluorene and 7-hydroxy-2-nitrofluorene showed relatively low activity. Benzyl paraben exhibited the highest activity of all parabens examined. Diphenyl did not exhibit the activity, but its hydroxylated metabolites did. Pyrene, benzophenone-3, trans-stilbene and chalcone exhibited AhR ligand activity, but their activities were dramatically altered after metabolic transformation with liver microsomes. These results suggest that metabolism of environmental contaminants alters their AhR ligand activity. In HepG2 luciferase reporter assay, fluorene derivatives exhibited AhR agonist activity, while stilbene derivatives, pyrene derivatives, diphenyl derivatives and parabens exhibited AhR antagonist activity.

CHARACTERIZATION OF THE RAT CARBOXYLESTERASE 2(CES2) ISOZYME INDUCED BY DRUGS AND THEIR MOLECULAR MECHANISMS
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Carboxylesterases (CESs) play an important role in the hydrolytic metabolism of many ester-drugs. Recently, it has been revealed that CES isozymes induced by several drugs. However, little is known about the mechanism of induction. In the present study, we characterized the rat CES2 isozyme was induced by dexamethasone (Dex), peroxisome proliferators (PP) and Phenobarbital (PB). Since the results of ESI/MS/MS analysis revealed that both induced CES 2 isozyme and CES RL4 possessed identical peptide fragments, we hypothesized that these were the same enzyme. When the rats were treated with Dex and PB, expression of CES RL4 mRNA were 365- and 31-fold induced in rat liver, respectively. In the treatment of PP, the induced protein was detected by Western blotting using CES RL4 specific antibodies. In addition, the hydrolytic activity for irinotecan and MPHS was induced by the treatment of rat with those inducers and inhibited by CES RL4 specific antibodies in both control and inducer treated rat liver microsomes. These results suggested that the induced CES2 isozyme by those inducers was CES RL4 and CES RL4 significantly contributed to irinotecan and MPHS hydrolase activity induced. Then, we cloned genomic DNA to clarify about the mechanism of the regulation of CES RL4 gene transcription. CES RL4 gene promotor site was included in many transcription factor binding sites. The result from this study, we suggested that glucocorticoid receptor play a crucial role in induced by Dex. However, the mechanism of induction by Dex have been less clear. We have tried further investigation to make clear the mechanism of induction by Dex, PB and PP in detail.