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THE EFFECT OF POLYCYCLIC AROMATIC HYDROCARBONS ON CYP3A4 EXPRESSION THROUGH PREGNANE X RECEPTOR-MEDIATED TRANSCRIPTION

Takeshi Kumagai1, Chie Igarashi1, Hiroyuki Suzuki3, Yasushi Yamazoe2 and Kiyoshi Nagata1

1Department of Environmental Health Science, Tohoku Pharmaceutical University, Sendai, Japan
2Division of Drug Metabolism and Molecular Toxicology, Graduate School of Pharmaceutical Science, Tohoku University, Sendai, Japan

Polycyclic aromatic hydrocarbons (PAHs) are common air pollutants generated from automobile exhaust and cigarette smoke, and it is known that PAHs cause transactivation of CYP1A1 and 1A2 genes via aryl hydrocarbon receptor (AhR). CYP3A4 is induced by treatment of a wide variety of xenobiotics via pregnane X receptor (PXR). In this study, we investigated the effect of PAHs on transactivation of the CYP3A4 gene using HepG2-derived cells (3-1-20 cells) stably expressing luciferase reporter mediated through the CYP3A4 gene promoter/enhancer. Among PAHs used such as 3-methcholanthrene (3-MC) and benzo[a]pyrene (BaP), 9 PAHs were increased the CYP3A4 reporter activity. β-naphthoflavone that is reported to be an agonist of AhR was not increased the CYP3A4 reporter activity. Expression of the human PXR-short hairpin RNA (hPXR-shRNA) inhibited the CYP3A4 reporter activity induced by 3-MC or BaP, whereas α-naphthoflavone, an antagonist of AhR, had no effect on the induction. In addition, expression of CYP3A4 mRNA was also induced by 3-MC in HepG2 cells. In contrast, Reuber cells from rat hepatoma cell lines did not induce the CYP3A1 mRNA by 3-MC. Furthermore, by expression of hPXR, 3-MC induced CYP3A4-derived reporter activity in Reuber cells. These results strongly suggest that PAHs induce CYP3A4 via PXR pathways in human.

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INDUCTION OF CYTOPROTECTIVE ENZYMES BY EDIBLE JAPANESE PLANTS, CRYPTOTAENIA JAPONICA AND ARALIA CORDATA

Shinji Nakayama, Tomokazu Ohunuma, Takahito Nishiyama, Kenichiro Ogura and Akira Hiratsuka

Department of Drug Metabolism and Molecular Toxicology, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji-shi 192-0392, Japan

Drug metabolizing enzymes such as glutathione S-transferase (GST) and NAD(P)H:quinone oxidoreductase (NQO) play a major role in the cellular detoxification of oxidative stress and electrophilic toxicants. It is now widely recognized that the induction of these cytoprotective enzymes is a highly efficient strategy for protection against toxicity and chemical carcinogenesis. Previously, we screened the extracts of 79 herbal medicines for the induction activities of GST and NQO, and revealed that Notopterygium Rhizoma (Apiaceae) extract the most potently induced GST and NQO activities. However, Notopterygium incisum Ting ex H. T. Chang and Notopterygium forbesii Boissieu, which are origins of Notopterygium Rhizoma, have been mainly distributed in China, not in Japan. To find edible Japanese plants which possess the induction activity, we examined plants belong to Apiaceae or Araliaceae. As a result, the methanol soluble fractions of Cryptotaenia japonica (Apiaceae) and Aralia cordata (Araliaceae) induced GST and NQO activities in rat liver Clone 9 cells. Moreover, when the extracts of both plants were orally administered to male C57BL/6J mice for 4 days, the induction of GST and NQO activities was observed in cytosols from liver, small intestine, kidney and lung. These results suggest that the daily consumption of Cryptotaenia japonica and Aralia cordata may reduce the risks of cancer and several other chronic diseases caused by oxidative and electrophilic stress through the induction of cytoprotective enzymes.