Effects of food additives on 3-methylcholanthrene-mediated activation of aryl hydrocarbon receptor in human hepatoma HepG2-A10 cells

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Aryl hydrocarbon receptor (AhR) plays an important role in induction of CYP1A subfamily enzymes, which mediate metabolic activation of carcinogenic polycyclic aromatic hydrocarbons and aromatic amines. In this study, we examined the effects of food additives, such as curcumin (CUR), thiabendazole (TBZ), propyl gallate (PG), and butylated hydroxytoluene (BHT), on the activation of AhR by a representative AhR ligand, 3-methylcholanthrene (MC), and on MC-mediated CYP1A induction in a human hepatoma cell line, HepG2-A10, which has been established for screening of AhR activators. Treatment with MC (0.1 mM) alone activated AhR up to 6~12 h. The MC-mediated AhR activation was augmented by co-treatment with TBZ or BHT (each 10 mM). Co-treatment with CUR (10 mM) resulted in significant suppression of the MC-mediated AhR activation at 3 and 6 h, whereas BHT showed little effect on the MC-mediated AhR activation. Since the strongest augmentation of MC-mediated AhR activation by co-treatment with TBZ occurred at 24 h, the effects of these additives on MC-mediated induction of CYP1A subfamily enzymes were examined at 24 h after each chemical treatment. TBZ, but not other food additives tested, enhanced the MC-mediated induction of CYP1A family enzymes at levels of mRNA, protein, and enzyme activity. Furthermore, we examined the combination effects of TBZ and other AhR ligands, such as b-naphtoflavone, benzo[*a*]pyrene, and dimethylbenz[*a*]anthracene, on the AhR activation. All the AhR ligands used were confirmed to act as AhR activators in HepG2-A10 cells, and these chemical-mediated AhR activation were augmented by co-treatment with TBZ. The present findings suggested that a non-ligand type AhR activator TBZ, but not other food additives, enhance the AhR ligand-mediated toxicities.

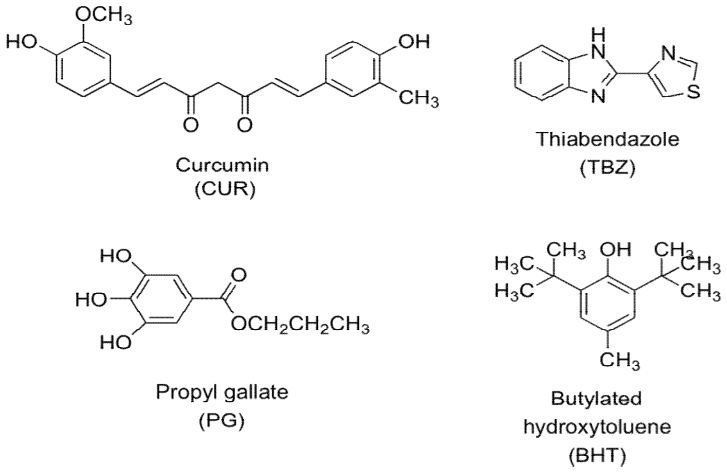

Fig.1. Food additives used in this study