Study on the effect of calcium channel blockers on induced expression of CYP1A subfamily enzymes by their food-derived inducers

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The dihydropyridine calcium channel blockers (DHP-CCBs) including nicardipine (Nic) are commonly used as anti-hypertensive medications. Recently, we have found that treatments of rats with DHP-CCBs, especially Nic, resulted in induction of hepatic CYP enzymes, such as CYP1A, CYP2B, and CYP3A subfamily enzymes. Furthermore, we have demonstrated that DHP-CCBs induce CYP1A subfamily enzymes (CYP1A1/1A2) in human hepatoma cell line HepG2, and simultaneous treatment with DHP-CCBs and 3-methylcholanthrene (MC), a typical CYP1A inducer, synergistically induces them.

In the present study, we examined the effect of combination treatment with Nic and various CYP1A inducers (benzo[a]pyrene, beta-naphthoflavone, and Trp-P-1) on the induction of CYP1A subfamily enzymes in HepG2 cells. Western blot analysis demonstrated that increases in levels of the protein and enzyme activity of CYP1A1 by benzo[a]pyrene, but not other CYP1A inducers used, were synergistically augmented by Nic. CYP1A inducers used in this study have a capacity for activating arylhydrocarbon receptor (AhR), and its activation is crucial for induction of CYP1A subfamily enzymes by them. Therefore, we next examined whether or not Nic enhances CYP1A inducer-mediated AhR activation using a HepG2-A10 cell line, which has previously established for a luciferase reporter gene assay of AhR activators in our laboratory. The results indicated that Nic has little capacity for enhancing CYP1A inducer-mediated AhR activation.

The present findings demonstrate that co-treatment with Nic and benzo[a]pyrene, but not other CYP1A inducers used, synergistically induces CYP1A1 enzyme, and this synergistic induction occurs without enhancement of benzo[a]pyrene-induced AhR activation in HepG2 cells.