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Synergistic effect of nicardipine on 3-methylcholanthrene-mediated induction of cytochrome P450IA1 in HepG2 cells

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Dihydropyridine-type calcium channel antagonists including nicardipine (Nic) are commonly used as anti-hypertensive medications. These drugs are known to show inhibitory effects on cytochrome P450 (CYP) enzyme activities. Recently, we have found that treatments of rats with dihydropyridine-type calcium channel antagonists, especially Nic, resulted in induction of hepatic CYP enzymes, such as CYP1A, CYP2B, and CYP3A subfamily enzymes, and further demonstrated that Nic-repetitive treatment reduced its therapeutic effect on development of hypertension in spontaneously hypertensive rats (SHR). Therefore, it would be important to accurately evaluate whether these drugs produce inhibitory and/or enhancing effect(s) on CYPs in an effort to provide effective and safe treatment. However, studies regarding the induction of hepatic CYPs by dihydopyridine-type antagonists have little been performed.

In the present study, we examined a mechanism for Nic-mediated CYP1A1 induction. In general, xenobiotic-mediated CYP1A induction is considered to occur in an aryl hydrocarbon receptor (AhR)-dependent manner. Since Nic does not possess a chemical structure required for binding to AhR, Nic-mediated CYP1A1 induction might occur in an AhR-independent manner. Therefore, we first examined whether Nic can be an AhR ligand by use of a HepG2-A10 cell line, which we have previously established for a luciferase reporter gene assay of AhR ligands. The results indicated that Nic showed little capacity for activating (binding to) AhR, although it increased the level of CYP1A1 mRNA in HepG2 cells. These findings suggest that Nic can activate the *CYP1A1* gene expression without activation of AhR. Then, we selected 3-methylcholanthrene (MC) as an AhR ligand and further examined the effect of Nic on MC-mediated CYP1A1 induction in HepG2 cells. Interestingly, the results demonstrated a synergistic effect of Nic on AhR ligand-mediated CYP1A1 induction, although a mechanism for Nic-mediated CYP1A1 induction remains unclear.