Synergistic induction of CYP1A1 by polycyclic aromatic hydrocarbons and dihydropyridine calcium channel blockers

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CYP1A1 plays an important role in metabolic activation of polycyclic aromatic hydrocarbons (PAHs) such as 3-methylcholanthrene (MC). It is known that the induction of CYP1A1 by PAHs occurs through the activation of aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor. Recently, we have reported that a dihydropyridine calcium channel blocker, nicardipine (Nic), has the ability to enhance the MC-mediated induction of CYP1A1 and the formation of MC-DNA adduct in a human hepatoma cell line, HepG2. In the present study, the mechanism for synergistic induction of CYP1A1 in HepG2 cells by simultaneous treatment with MC and Nic was investigated.

Using [^{3}H]MC, We found that the intracellular accumulation of MC is markedly increased by Nic in HepG2 cells. This increase seems to be dependent on the inhibition of the function of drug efflux transporters by Nic. The luciferase-reporter gene assay using the HepG2-A10 cell line, which has been previously established for the screening of AhR activators, indicated the enhancement of MC-mediated activation of AhR by Nic. A protein synthesis inhibitor, cycloheximide is reported to superinduce CYP1A1 mRNA probably via inhibition of ligand-mediated degradation of the AhR. Therefore, we next examined whether or not Nic inhibits MC-mediated degradation of the AhR. However, Western blot analysis for the AhR indicated that Nic has no such effect. Moreover, because induction of CYP1A1 mRNA in HepG2 cells co-treated with MC and Nic was maintained longer than that in the cells treated with MC alone, stabilization of CYP1A1 mRNA by Nic was examined using a transcription inhibitor, actinomycin D. The result of the experiment indicated that CYP1A1 mRNA is slightly stabilized in the presence of Nic.

In conclusion, the present findings suggest that dihydropyridine calcium channel blockers can enhance the PAH-mediated induction of CYP1A1 mainly through an increase in intracellular accumulation of PAH in HepG2 cells.