Effect of cytochrome P450 (CYP) inducers on caffeine metabolism in the rat

Marta Kot, Wladyslawa A. Daniel

Department of Pharmacokinetics and Drug Metabolism, Institute of Pharmacology, Polish Academy of Sciences, Smejna 12, PL 31-343 Kraków, Poland

Correspondence: Wladyslawa A. Daniel, e-mail: mtdania@cyf-007.edu.pl

Abstract:
Our previous studies, carried out using rat cDNA-expressed cytochrome P450 (CYP) isoforms, liver microsomes and specific CYP inhibitors, showed that the 1-N- and 3-N-demethylation of caffeine at a therapeutic concentration was predominantly catalyzed by CYP1A2 and CYP2C, its 7-N-demethylation was governed by P450s of the CYP2C subfamily, while its 8-hydroxylation was specifically mediated by CYP1A2. The present study was aimed at corroborating the above-described results using another experimental model, i.e. a study of caffeine metabolism in the liver microsomes and specific CYP inducers. Animals received one of the following inducers: β-naphthoflavone (100 mg/kg ip for 4 days), phenobarbital (10 mg/kg for 6 days or 100 mg/kg ip for 4 days), pregnenolone 16α-carbonitrile (100 mg/kg ip for 4 days) or 15% ethanol (∼11 g/kg in drinking water for 6 days). Sixteen hours after the last dose of an inducer liver microsomes were prepared and the caffeine metabolism and CYP isoform activities (testosterone 2α-, 2β-, 6β-, 7α-, 16β-hydroxylation and warfarin 7-hydroxylation) were investigated. β-Naphthoflavone (mainly a CYP1A inducer and CYP2C11 inhibitor) potently accelerated the metabolism of caffeine, the effect on 7-N-demethylation being the weakest. Moreover, the influence of β-naphthoflavone on caffeine metabolism was more potent at the substrate concentration of 100 μM than 800 μM, in particular in the case of 7-N-demethylation and 8-hydroxylation. Pregnenolone 16α-carbonitrile (mainly a CYP3A inducer and CYP2C11 inhibitor) moderately induced 8-hydroxylation only. Phenobarbital (an inducer of CYP2B and other CYPs and a CYP2C11 inhibitor) modertely stimulated the metabolism of caffeine, but practically did not affect 7-N-demethylation. Ethanol (mainly a CYP2E1 inducer) modestly increased the rates of the N-demethylation reactions. The presently obtained data confirm the pivotal role of CYP1A2 in the metabolism of caffeine, as well as the involvement of CYP3A in the 8-hydroxylation of caffeine and that of CYP2C11 in its 7-N-demethylation.

Key words: rat, liver microsomes, cytochrome P450 induction, β-naphthoflavone, phenobarbital, pregnenolone 16α-carbonitrile, ethanol, testosterone hydroxylation, warfarin 7-hydroxylation, caffeine metabolism