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

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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) moderately 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