INFLUENCE OF CLASSIC AND ATYPICAL NEUROLEPTICS ON CAFFEINE OXIDATION IN RAT LIVER MICROSOMES

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Caffeine is a marker drug for testing the activity of CYP1A2 (3-N-de- methylation) in humans and rats. Moreover, CYP3A seems to be essential for its metabolism (8-hydroxylation). In the case of 1-N- and, in particular, 7-N-demethylation of caffeine, apart from CYP1A2, other CYP isoenzymes play a considerable role, probably CYP2B and/or CYP2E1. The aim of the present study was to investigate the influence of two classic neuroleptics (promazine and haloperidol) and two atypical ones (risperidone and sertindole) on cytochrome P-450 activity measured by caffeine oxidation in rat liver microsomes.

The obtained results showed that promazine, a phenothiazine neuroleptic with the simplest chemical structure, significantly inhibited 1-N- and 3-N-demethylation and 8-hydroxylation of caffeine via competitive or mixed mechanism (Ki = 21.8, 25.4 and 58.2 μM, respectively). This indicates inhibition by promazine of CYP1A2 (inhibition of 3-N- and 1-N-demethylation), and possibly CYP3A2 (inhibition of 8-hydroxylation), but not of other CYP isoenzymes involved in 7-N-demethylation of caffeine (e.g. CYP2B2 and/or CYP2E1). In contrast to promazine, haloperidol had no effect on the oxidation reactions of caffeine in the applied in vitro metabolic model. The potency of inhibition of caffeine oxidation by risperidone and sertindole resembled rather haloperidol than promazine. Risperidone appeared to be a very weak inhibitor of 3-N-demethylation and 8-hydroxylation (Ki = 202.5 μM) and had no effect on 1-N- and 7-N-demethylation of caffeine. Sertindole was a very poor inhibitor of 1-N- and 7-N-demethylations and 8-hydroxylation pathways of the marker substance (Ki = 132.1, 434.1 and 173.3 μM, respectively); even the observed in vitro inhibition of 3-N-demethylation of caffeine by sertindole (Ki = 68.9 μM) cannot be of practical significance in vivo, considering extremely low pharmacological and therapeutic doses of the neuroleptic. In summary, among the investigated neuroleptics, only promazine showed significant inhibitory activity towards caffeine metabolism in vitro (inhibition of CYP1A2 and possibly CYP3A), which may be of pharmacological and clinical importance in vivo. In contrast to promazine, haloperidol and the investigated atypical neuroleptics had no or very weak effect on caffeine oxidation in vitro, of no in vivo significance. Considering the results of the present and previous studies, it seems highly likely that promazine may cause pharmacokinetic interactions, while atypical neuroleptics seem to be safe in this respect. Moreover, the observed reaction-dependent effects of promazine and sertindole provide indirect evidence that CYP1A2 is not the only isoenzyme important for the metabolism of caffeine, which requires further pharmacological and clinical consideration.

Key words: caffeine oxidation, rat, cytochrome P-450 activity, promazine, haloperidol, risperidone, sertindole

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