EFFECTS OF PHENOTHIAZINE NEUROLEPTICS ON THE RATE OF CAFFEINE DEMETHYLATION AND HYDROXYLATION IN THE RAT LIVER

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The primary metabolic pathways of caffeine are 3-N-demethylation to paraxanthine (CYP1A2), 1-N-demethylation to theobromine and 7-N-demethylation to theophylline (CYP1A2 and other enzymes), and 8-hydroxylation to 1,3,7-trimethyluric acid (CYP3A). The aim of the present study was to investigate the influence of phenothiazine neuroleptics (chlorpromazine, levomepromazine, thioridazine, perazine) on cytochrome P-450 activity measured by caffeine oxidation in rat liver microsomes. The obtained results showed that all the investigated neuroleptics competitively inhibited caffeine oxidation in the rat liver, though their potency to inhibit particular metabolic pathways was not equal. Levomepromazine exerted the most potent inhibitory effect on caffeine oxidation pathways, the effect on 8-hydroxylation being the most pronounced. This indicates inhibition of CYP1A2 (inhibition of 3-N- and 1-N-demethylation; $K_i = 36$ and $32\,\mu M$, respectively), CYP3A2 (inhibition of 8-hydroxylations; $K_i = 20\,\mu M$), and possibly other CYP isoenzymes (inhibition of 7-N-demethylation; $K_i = 58\,\mu M$) by the neuroleptics. The potency of inhibition of caffeine oxidation by perazine was similar to levomepromazine. Thioridazine was a weaker inhibitor of caffeine 3-N- and 7-N-demethylation, while chlorpromazine was weaker in inhibiting caffeine 1-N- and 7-N-demethylation, compared to levomepromazine. In summary, the obtained results showed that all the investigated neuroleptics had a broad spectra of CYP inhibition in the rat liver. The isoenzymes CYP1A2 and CYP3A2 were distinctly inhibited by all the investigated neuroleptics, while other CYP isoenzymes (CYP2B and/or 2E1) by perazine and levomepromazine. The CYP3A2 inhibition was most pronounced. ($K_i = 20–40\,\mu M$).

Key words: caffeine oxidation, rat, cytochrome P-450 activity, chlorpromazine, levomepromazine, thioridazine, perazine