EFFECTS OF ANTIDEPRESSANT DRUGS ON THE ACTIVITY OF CYTOCHROME P-450 MEASURED BY CAFFEINE OXIDATION IN RAT LIVER MICROSONES

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Caffeine is a marker drug for testing the activity of CYP1A2 (3-N-demethylation) in humans and rats. Moreover, it is also a relatively specific substrate of CYP3A (8-hydroxylation). In the case of 1-N- and in particular 7-N-demethylation of caffeine, apart from CYP1A2, other cytochrome P-450 isoenzymes play a considerable role. The aim of the present study was to investigate the influence of imipramine, amitriptyline and fluoxetine on cytochrome P-450 activity measured by caffeine oxidation in rat liver microsomes. The obtained results showed that imipramine exerted a most potent inhibitory effect on caffeine metabolism. Imipramine decreased the rate of 3-N-, 1-N- and 7-N-demethylation, and 8-hydroxylation of caffeine, the effect on 3-N-demethylation being most pronounced ($K_i = 33 \, \mu M$). Amitriptyline showed distinct inhibition of 3-N- and 1-N-demethylation of caffeine, though its effect was less potent than in the case of imipramine ($K_i = 57$ and $61 \, \mu M$, respectively). The influence of amitriptyline on 8-hydroxylation and especially on 7-N-demethylation of caffeine was weaker ($K_i = 108$ and $190 \, \mu M$, respectively) than on 3-N- or 1-N-demethylation, suggesting a narrower spectrum of cytochrome P-450 inhibition by amitriptyline than by imipramine, involving mainly the subfamily CYP1A2, and – to a lesser degree – CYP3A. In contrast to the tested tricyclic antidepressants, fluoxetine did not exert any considerable effect on the 3-N- or 1-N-demethylation of caffeine ($K_i = 152$ and $196 \, \mu M$, respectively), which indicates its low affinity for CYP1A2. However, fluoxetine displayed a clear inhibitory effect on caffeine 7-N-demethylation ($K_i = 72 \, \mu M$), the reaction which is catalyzed mainly by other than CYP1A2 isoenzymes. Fluoxetine diminished markedly the 8-hydroxylation of the marker drug; as reflected by $K_i$ values, the potency of inhibition of rat CYP3A by fluoxetine was similar to that of imipramine ($K_i = 40$ and $45 \, \mu M$, respectively). In summary, CYP1A2 was distinctly inhibited by imipramine and amitriptyline, CYP3A by imipramine and fluoxetine, while other CYP isoenzymes (CYP2B and/or 2E1) by imipramine and fluoxetine.

Key words: caffeine metabolism, rat, cytochrome P-450 activity, imipramine, amitriptyline, fluoxetine