EFFECTS OF CLASSIC AND NEWER ANTIDEPRESSANTS ON THE OXIDATION PATHWAYS OF CAFFEINE IN RAT LIVER. IN VITRO STUDY

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Caffeine undergoes 3-N-demethylation via CYP1A2, as well as 1-N-demethylation, 7-N-demethylation and 8-hydroxylation, which may involve other CYP isoenzymes. The aim of the present study was to investigate the influence of clomipramine, desipramine, sertraline, nefazodone and mirtazapine on cytochrome P-450 activity measured by caffeine oxidation in rat liver microsomes. The obtained results showed that all the investigated antidepressants, with an exception of mirtazapine, added in vitro to liver microsomes had an inhibitory effect on caffeine metabolism (via competitive or mixed mechanism), though their potency towards particular metabolic pathways was different. Dixon analysis of caffeine metabolism carried out in the control liver microsomes, in the absence and presence of the antidepressant drugs showed that desipramine and clomipramine exerted the most potent inhibitory effect on caffeine metabolism. Desipramine decreased the rates of 1-N-, 3-N- and 7-N-demethylations, and 8-hydroxylation of caffeine ($K_i = 23.3, 36.6, 23.3$ and $63.3 \mu M$, respectively), the effect on 1-N- and 7-N-demethylation being the most pronounced. Clomipramine showed distinct inhibition of 1-N- and 3-N-demethylation and 8-hydroxylation of caffeine, the effects on N-demethylations being the most pronounced ($K_i = 38.6, 34.8, 45.6 \mu M$, respectively). Its effect on 7-N-demethylation was rather weak ($K_i = 97.8 \mu M$). Sertraline decreased significantly the rate of 1-N- and 3-N-demethylation and 8-hydroxylation ($K_i = 37.3, 69.3$ and $64 \mu M$, respectively), while its effect on 7-N-demethylation of caffeine was less pronounced ($K_i = 92.1 \mu M$). Nefazodone displayed clear effect on 3-N- and 7-N-demethylation ($K_i = 68.8$ and $66.4 \mu M$, respectively), but was weak in inhibiting 1-N-demethylation and 8-hydroxylation of caffeine ($K_i = 110$ and $186 \mu M$, respectively). In contrast to the above-tested antidepressants, mirtazapine did not decrease significantly the oxidation rates of 3-N-demethylation or 8-hydroxylation ($K_i = 264$ and $455 \mu M$, respectively) and had no effect on other oxidation pathways of caffeine. In summary, we have observed intra- and inter-drug differences in the inhibitory effects of the antidepressants on the four oxidation pathways of caffeine in rat liver microsomes. The tested antidepressants (with an exception of mirtazapine) may lead to drug-drug metabolic interactions at a level of a few CYP isoforms. The obtained results provide further indirect evidence that apart from CYP1A2, other CYP isoforms are also important for the metabolism of caffeine.

Key words: caffeine metabolism, rat, cytochrome P-450 activity, clomipramine, desipramine, sertraline, nefazodone, mirtazapine

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