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Caffeine metabolism during prolonged treatment of rats with antidepressant drugs

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Abstract:
Our previous studies showed that some of the tested antidepressants (tricyclics, SSRIs, mirtazapine, nefazodone) directly inhibited the metabolism of caffeine when added *in vitro* to liver microsomes. The aim of the present study was to investigate a possible indirect effect of prolonged *in vivo* administration of these antidepressants on the rate of caffeine oxidative metabolism: 1-N-, 3-N- and 7-N-demethylation and 8-hydroxylation in rat liver. The reactions were studied in liver microsomes of rats treated intraperitoneally *(ip)* for one day or two weeks with pharmacological doses of the drugs (imipramine, amitriptyline, clomipramine, nefazodone at 10 mg/kg; desipramine, fluoxetine, sertraline at 5 mg/kg; mirtazapine at 3 mg/kg), in the absence of the antidepressants *in vitro*.
One-day treatment with imipramine and amitriptyline decreased, while fluoxetine accelerated the metabolism of caffeine. Nefazodone stimulated 1-N-demethylation only. Fluoxetine given chronically increased exclusively 7-N-demethylation, while imipramine showed only such tendency. Sertraline and mirtazapine enhanced the rates of all caffeine oxidation pathways.
We conclude that the tested antidepressant drugs may affect the metabolism of caffeine not only in a direct way (binding to the enzyme), but also indirectly *via* inducing CYP1A2 (sertraline and mirtazapine) and CYP2C isoforms (fluoxetine, sertraline, mirtazapine) after prolonged administration. In addition, the presented data provide further experimental evidence for the importance of the subfamily CYP2C for the 7-N-demethylation of caffeine in the rat.

Key words:
caffeine metabolism, rat, cytochrome P450, antidepressants