Effect of short- and long-term treatment with antidepressant drugs on the activity of rat CYP2A in the liver

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Abstract:
The aim of the present study was to investigate the influence of tricyclic antidepressants (TADs: imipramine, amitriptyline, clomipramine, desipramine), selective serotonin reuptake inhibitors (SSRIs: fluoxetine, sertraline) and novel antidepressant drugs (mirtazapine, nefazodone) on the activity of CYP2A measured as a rate of testosterone 7α-hydroxylation. The reaction was studied in control liver microsomes in the presence of the antidepressants, as well as in microsomes of rats treated intraperitoneally (ip) for one day or two weeks with pharmacological doses of the drugs (imipramine, amitriptyline, clomipramine, nefazodone 10 mg/kg ip; desipramine, fluoxetine, sertraline 5 mg/kg ip; mirtazapine 3 mg/kg ip), in the absence of the antidepressants in vitro. Most of the investigated drugs directly inhibited the CYP2A activity when added in vitro to control liver microsomes. Their inhibitory effects were strong (clomipramine, fluoxetine and desipramine: \(K_I = 15, 20\) and \(25 \text{ µM}\), respectively), moderate (sertraline and imipramine: \(K_I = 50\) and \(75 \text{ µM}\), respectively) or weak (amitriptyline, nefazodone and mirtazapine: \(K_I = 107, 127\) and \(250 \text{ µM}\), respectively). A one-day (i.e. 24-h) exposure to the investigated antidepressant drugs did not produce any significant changes in the rate of 7α-hydroxylation of testosterone in the rat liver microsomes, while chronic treatment with clomipramine or sertraline significantly increased the activity of CYP2A, which suggests enzyme induction. In summary, two different mechanisms of the antidepressant-CYP2A interaction have been found in rat liver: 1) the direct inhibition of CYP2A by most of the investigated TADs and SSRIs; 2) the in vivo weak induction of CYP2A by clomipramine and sertraline. This observation may be important to the interpretation of the results of pharmacological tests carried out on rats. It seems of primary importance to determine whether the influence of antidepressants on CYP2A6 in humans is analogous as on CYP2A1/2 in rats.

Key words:
CYP2A, testosterone 7α-hydroxylation, liver microsomes, rat, antidepressants, chronic treatment