Pharmacological Reports
2008, 60, 957–965
ISSN 1734-1140

Effect of selected antidepressant drugs on cytochrome P450 2B (CYP2B) in rat liver. An *in vitro* and *in vivo* study

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Abstract:
The aim of the present study was to investigate the influence of antidepressants with different chemical structures and mechanisms of action affecting serotonergic and/or noradrenergic systems – tricyclic antidepressant drugs (TAD), selective serotonin reuptake inhibitors (SSRIs) and novel antidepressants (mirtazapine, nefazodone) – on the activity of rat CYP2B measured as the rate of 16β-hydroxylation of testosterone. The reaction was studied in control liver microsomes in the presence of antidepressants, as well as in microsomes of rats treated intraperitoneally for one day or two weeks (twice a day) with pharmacological doses (mg/kg) of the drugs (imipramine, amitriptyline, clomipramine, nefazodone 10; desipramine, fluoxetine, sertraline 5; mirtazapine 3). The obtained K_i values indicated that nefazodone and the SSRIs sertraline and fluoxetine were the most potent inhibitors of the studied reaction (K_i = 10–20 μM). The inhibitory effects of TADs were modest (K_i = 62–85 μM), while mirtazapine was a very weak inhibitor of CYP2B activity (K_i = 286 μM). After a one-day exposure of rats to the investigated antidepressants, a significant increase in CYP2B activity was only observed after sertraline exposure (300% of the control). Chronic treatment with the antidepressants led to a significant enhancement of CYP2B activity after sertraline, fluoxetine and desipramine (580, 200 and 150% of the control, respectively) treatment, which positively correlated with the observed elevation in CYP2B protein levels. In summary, two different mechanisms of the antidepressant-CYP2B interaction are postulated: 1) a direct inhibition of CYP2B shown *in vitro* by nefazodone, SSRIs and TADs; 2) *in vivo* induction of CYP2B produced by prolonged administration of SSRIs and desipramine, which suggests their influence on enzyme regulation. The marked CYP2B-induction produced by SSRIs corresponds with their selective serotonin reuptake inhibition, while the effect of desipramine corresponds with its selective inhibition of noradrenaline reuptake.

Key words:
antidepressants, CYP2B, rat liver microsomes, *in vitro* study, one-day treatment, chronic treatment, enzyme inhibition, enzyme induction