Effect of mirtazapine on the CYP2D activity in the primary culture of rat hepatocytes

Anna Haduch1, Ewa Bromek1, Marta Kot1, Katalin Jemnitz2, Zsuzsa Veres2, László Vereczkey2, Władysława A. Daniel1

1Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland
2Chemical Research Center, Hungarian Academy of Sciences, P.O. Box 17, H-1525 Budapest, Hungary

Correspondence: Władysława A. Daniel, e-mail: nfdaniel@cyf-kr.edu.pl

Abstract
Our previous studies carried out on rats showed that mirtazapine given intraperitoneally at a dose of 3 mg/kg, twice a day for two weeks, increased the activity of CYP2D measured as ethylmorphine O-deethylation in liver microsomes. The aim of the present work was to find out whether the mirtazapine-induced increase in the CYP2D activity observed in vivo is connected with the central action of mirtazapine or the drug acts directly on hepatocytes. For this purpose, we studied the influence of pharmacological concentrations of mirtazapine (0.1, 1.0, 10 µM for 96 h) on the activity of CYP2D measured as the rates of ethylmorphine O-deethylation and dextromethorphan O-demethylation in the primary culture of rat hepatocytes. Additionally, we tested the ability of CYP isoforms to catalyze ethylmorphine O-deethylation, using cDNA-expressed CYPs and CYP inhibitors applied to liver microsomes. The obtained results indicate that mirtazapine applied at pharmacological concentrations can moderately increase the activity of rat CYP2D in hepatocytes, and CYP2D2 isoform contributes mostly to this effect. Similar result was previously obtained after in vivo administered mirtazapine in liver microsomes, but not in brain microsomes, the latter containing mainly CYP2D4 isoform. Mirtazapine appears to act directly on hepatocytes and its effect does not seem to depend on the central pharmacological action of the antidepressant. CYP2D2 is the main isoform catalyzing ethylmorphine O-deethylation while CYP2A2, CYP2C6 and CYP2C11 are of minor importance.

Key words: mirtazapine, rat, CYP2D, ethylmorphine O-deethylation, dextromethorphan O-demethylation, hepatocytes, cDNA-expressed CYPs, liver microsomes, CYP inhibitors