Abstract

17α-ethinylestradiol (EE2) is a synthetic hormone, derivative of the natural hormone estradiol. EE2 is one of the the most prescribed drugs in the world. It belongs to the estrogenic endocrine disrupter chemicals. These compounds are able to alter functions of the endocrine system and cause adverse effects in the organism, offspring and (sub)population.

In this thesis, there are observed effects of 17α-ethinylestradiol on enzyme activities of main enzymes involved in phase I of xenobiotic biotransformation, i.e. cytochromes P450 (CYP), *in vitro*. Isoforms of CYP subfamilies 1A, 2B, 2C, 2E and 3A were studied in rats and humans. Each CYP isoform was incubated with EE2 at two concentrations, 10μM EE2 and the concentration corresponding to the substrate concentration in the specific marker reactions of individual CYP isoforms.

The results indicate, that in rat liver microsomes the activity of all studied isoforms except CYP1A2 was decreased in the presence of EE2. When EE2 was added to the incubation mixture at the concentration of the reaction substrate, the greatest decrease in enzyme activity was observed for CYP2C6, with the remaining activity only 36%. In human liver microsomes, the activity of CYP2B6, CYP2C9, CYP2E1 and CYP3A4 was also effected by EE2. As in the case of rat model, CYP2C subfamily isoform was inhibited the most. The remaining activity of CYP2C9, after incubation with EE2 in the concentration of CYP marker reaction substrate, was only 54%. CYP1A2 was not affected by 17α-ethinylestradiol in human liver microsomes.

The concentrations of EE2 causing 50% inhibition (IC_{50}) of human rCYP1A1 (25,6 μM) and rCYP3A4 (4,5 μM) were determined.

In the case of rat CYP1A1, the type of inhibition was determined by kinetic study. Results revealed that CYP1A1 is autoactivated at low concentrations of 7-ethoxyresorufin (7-ER) and that EE2 inhibits CYP1A1 in competitive manner at high concetrations of 7-ER. The inhibition constant was estimated to be 6,4 μM.

[In Czech]

Key words: endocrine disruptors, 17α-ethinylestradiol, cytochrome P450, inhibition, IC_{50}