ABSTRACT

Endocrine disruptors (ED) are compounds that interfere with the endocrine system by mimicking or antagonising the effects of endogenous hormones. The synthetic estrogen 17α-ethinylestradiol (EE2), a major component of oral contraceptives and a human strong carcinogen benzo[a]pyrene (BaP) are assigned as an exogenous ED whereas the natural estrogenic hormone 17β-estradiol (E2) figures as an endogenic endocrine disruptor.

In this thesis the rats were treated with these ED individually and in combination, and their effect was studied on the gene and protein expression of cytochrome P450 1A1, 2C11 and 2C6 in rat liver, lung and kidney. In addition, the effect of the mentioned ED and their combinations on CYP1A and CYP2C specific enzyme activity and on metabolism of 17α-ethinylestradiol in rat liver microsomal samples was studied. Changes in CYP gene and protein expression were analyzed by real-time PCR and Western blotting, CYP specific activity and metabolism of EE2 were investigated by HPLC method.

It has been confirmed that BaP acts as a strong inducer of CYP1A1 in rat liver, lung and kidney, whereas EE2 or E2 alone revealed no significant effect on the expression of this CYP. However, when EE2 or E2 were administered to rats together with BaP, they considerably decreased the BaP-mediated CYP1A1 induction in rat hepatic microsomes and on the contrary increased the induction potential of BaP in rat lung. Furthermore, treatment of BaP in combination with estrogens significantly increased CYP1A1 specific enzyme activity in rat liver microsomal samples.

In the case of CYP2C11, BaP and all other ED and their combinations lead to the decrease CYP2C11 gene and protein expression in rat liver and kidney, while BaP alone increased expression of this CYP in lung. These results correspond to a decrease in CYP2C11 specific activity after rat premedication by all of the ED and their combinations in liver microsomal samples. On the contrary, in the case of another studied CYP, CYP2C6, after premedication of rats by all endocrine disruptors and their combinations, except of BaP itself, they increase of expression and specific enzyme activity in the liver. Furthermore, it was determined that 17α-ethinylestradiol induces its own metabolism.

The changes in CYP1A and 2C expression caused by the studied ED and their combinations modulate their metabolic pathways and genotoxic potential in organism, as well as their environment effects.

(In Czech)

Keywords: endocrine disruptors, benzo[a]pyrene, 17α-ethinylestradiol, 17β-estradiol, cytochrome P450, expression, specific activity