Abstract

Endocrine disruptors are exogenous and endogenous compounds that interfere with the production, signaling and metabolism of natural hormones, thereby disturbing the balance of the endocrine system. Exogenous endocrine disruptors include 17α-ethinylestradiol and endogenous endocrine disruptors include 17β-estradiol.

This thesis examinates effects of these endocrine disruptors on the specific activities of rat cytochromes P450 1A1 and 3A1. The enzyme specific activity of CYP1A1 is determined by the marker reaction *O*-deethylation 7-ethoxyresorufin and the activity of CYP3A1 is determined by the marker reaction 6β-hydroxylation of testosterone.

It has been confirmed that both estrogens 17β-estradiol and 17α-ethinylestradiol inhibit activity of CYP1A1 and CYP3A1. The stronger inhibitor of CYP1A1 was 17β-estradiol and of CYP3A1 was 17α-ethinylestradiol.

The concentration of estrogens causing 50% inhibition (IC50) of enzymes has been determined, for 17β-estradiol it was 4,6 μM and for 17α-ethinylestradiol 7,9 μM. CYP1A1 is a important enzyme for the biotransformation of carcinogens, it can be said that estrogens can modulate the genotoxicity of CYP1A1 activated carcinogens.

The results show that CYP1A1 inhibition increased after pre-incubation of estrogens with NADPH (cofactor of cytochromes P450), that suggest inhibition can be caused by metabolites of 17β-estradiol and 17α-ethinylestradiol produced by their pre-incubation with NADPH. E2 metobolites produced by pre-incubation with NADPH increased inhibition twice compared to E2. EE2 metabolites produced by preincubation with NADPH increased inhibition four times compared to EE2.

In the case of CYP3A1 IC_{50} of 17β-estradiol was 27,6 μM and IC_{50} of 17α-ethinylestradiol was 8,3 μM. Both are effective inhibitors of CYP3A1.

(In Czech)

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