ABSTRACT

In recent years, tyrosine kinase inhibitors have been widely used for the treatment of certain tumors as so-called targeted therapy. Many studies are concerned with their metabolism and the role of enzymes in the biotransformation process, but very little is known about the impact of tyrosine kinase inhibitors on the expression and activity of biotransformation enzymes. Nevertheless modification of the expression and activity of enzymes may cause adverse interactions of co-administered drugs and their negative impact on the human body.

This diploma thesis studies the effect of tyrosine kinase inhibitors vandetanib and lenvatinib and cytotoxic alkaloid ellipticine on biotransformation enzymes in a rat model organism *in vivo*. The aim was to characterize the effect of the investigated compounds on gene expression, protein expression and activity of cytochromes P450 (CYP) 1A1, 1A2 and 1B1 and flavin-containing monooxygenases FMO1 and FMO3 in renal and hepatic microsomes.

Microsomes and RNA were isolated from kidneys of control rats and the pretreated rats. Western blot and immunodetection was used to compare the protein expression levels of studied enzymes in kidney and liver. By reverse transcription, cDNA was prepared from isolated RNA and used as a template for quantitative PCR to compare the relative gene expression in kidney. The effect of investigated substances on CYP1A activity in the microsomal fractions was measured as 7-ethoxyresorufin *O*-deethylation. FMO activity was measured as methyl p-tolyl sulfide oxidation.

It has been confirmed that ellipticine is potent inducer of CYP1A1/1A2 in kidney as well as CYP1B1 in both liver and kidney. The results indicate that vandetanib and lenvatinib induce CYP1A1 at the level of protein expression, gene expression and activity. Furthermore, they potencially increase the inducing impact of ellipticine on CYP1A1/1A2. FMOs were not significantly affected by the investigated substances at the protein or gene expression level.

The inducing effect of vandetanib and lenvatinib on the expression of CYP1A1 could result in a modulation of metabolism and changes in the efficacy of the co-administred drugs, which undergo biotransformation by this enzyme, and cause adverse effects on the organism.

(In Czech)

Keywords: biotransformation, cytochromes P450, ellipticine, flavin-containing monooxygenases, lenvatinib, vandetanib, tyrosinkinase inhibitors