Abstract

In recent years, the inhibiition of tyrosine kinases,which may incorrectly regulate some singaling pathway has been used to treat cancer as so-called biological therapy. An example of such inhibitors are vandetanib and lenvatinib. These two substances are used to treat thyroid gland tumors because they affect vascular growth factor receptor or endothelial growth factor receptor that can regulate tumor growth and metastasis. Ellipticine, which has anti-tumor effects on lots of tumor disease, has been investigated in this study together with vandetanib and lenvatinib.

In this diploma thesis, the effect of mentioned tyrosine kinase inhibitors, ellipticine and their combinations on gene and protein expression of CYP1A1, 1A2, 3A1 and 3A2 in rat liver *in vivo* was determined. Protein expression was studied using Western blot method with imunodetection. Gene expression was assessed by quantitative PCR. Moreover, the effect of tested substances and their combinations on CYP1A activity (measured as 7-ethoxyresorufin *O*-deethylation), CYP1A2 activity (measured as 7-methoxyresorufin *O*-demethylation), CYP1A1 activity (measured as Sudan I oxidation), CYP3A specific activity (measured as testosteron 6β-hydroxylation) and ellipticine, vandetanib, lenvatinib metabolism was determined.

It has been confirmed that ellipticine significantly induces the expression of CYP1A1 in liver. This induction potential of ellipticin was not significantly affected by its co-administration with vandetanib or lenvatinib. A significant increase in ellipticine-induced expression was observed in CYP1A2. The effect of the tyrosine kinase inhibitors on cytochrome P450 expression has not yet been known. Both vandetanib and lenvatinib increased the gene expression and protein expression of CYP1A1, however, with much less efficacy than ellipticin. No effect on expression was observed for CYP1A2. All studied, inhibitors of tyrosine kinases and ellipticine, caused a slight increase in CYP3A1 gene expression and enzyme activity. In the conversion of ellipticin from hepatic microsomes from premedicated rats, the formation of 9-hydroxyellipticine metabolite increased with the use of microsomal liver fractions of rats exposed to ellipticine, which showed increased CYP1A activity. This result confirms the significant role of CYP1A1/2 in this metabolic response.

(In Czech)

Key words: vandetanib, lenvatinib, ellipticine, cytochromes P450, tyrosine kinase inhibitors