Abstract

Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole), an alkaloid isolated from Apocynaceae plants, exhibits significant antitumor and HIV activity. This antitumor agent binds to DNA and forms covalent DNA adducts. Enzymes, which are involved in its enzymatic activation, are cytochromes P450 (CYP) and peroxidases.

To elucidate the effect of ellipticine on the expression and enzymatic activity of the individual components of the microsomal mixed function oxidase system in different tissues, we used rat model. Simultaneously, the effect of ellipticine and its cytotoxicity on different tumor cell lines was also investigated. Another part of the presented work was targeted on preparation of anti-peptide antibody against orphan cytochrome P450 2S1, which is highly expressed in many human tumours of the epithelial origin, for its detection in these tissues. For better understanding how CYP2S1 can contribute to the metabolism of xenobiotics, the protein was prepared by heterologous expression in *E. coli*. Furher, its role in metabolism of an antitumor drug ellipticine, a carcinogenic environmental pollutant benzo[a]pyrene (BaP) and its derivate BaP-7,8-dihydrodiol was examined. Utilizing a mouse model, the impact of pulmonary inflammation on the metabolism of an environmental carcinogen was investigated, too.

The results found in this thesis fully demonstrate the role of ellipticine in induction of rat cytochrome CYP1A1/2, CYP3A and cytochrome b_5, resulting in an increase in CYP enzyme activities and oxidation of ellipticine to both its detoxification and activation metabolites forming DNA adducts. Moreover, an increased level of cytochrome b_5 may modulate the CYP-mediated bioactivation and detoxification of ellipticine as well as two carcinogens, BaP and Sudan I. It was also shown that CYP2S1 participates in the oxidation of ellipticine and BaP-7,8-dihydrodiol *via* the NADPH/POR-independent reaction using organic peroxide. The highly affinity anti-peptide antibody against CYP2S1 protein was successfully prepared and may be used as diagnostic tool for various cancers, in particular, as a prognostic marker for pancreatic cancer.

In the last part of the thesis, the effect of pulmonary inflammation on metabolism of an environmental carcinogen BaP was elucidated. Pulmonary inflammation may inhibit enzymatic activity of CYP1A1, which results in a decrease in pulmonary BaP detoxification, thereby enhancing BaP genotoxicity (DNA adduct formation) in the lung.