ABSTRACT

Aristolochic acids (AA) are human carcinogens which have also very strong nephrotoxic properties. A mixture of AA is present in *Aristolochiacae* plant species. These plants were and still are used in traditional medicine in some countries, particularly in Asia. Aristolochic acids participate in development of two types of nephropathies. The first disease is designated as Aristolochic Acid Nephropathy (AAN), the second one is Balkan Endemic Nephropathy (BEN). Both nephropathies are associated with urothelial malignancies, which are caused by AA. One of the common features of ANN and BEN is that not all individuals exposed to AA suffer from nephropathy and tumour development. One cause for these different responses may be individual differences in the activities and expression levels of the enzymes catalyzing the biotransformation of AAI, the major toxic component of AA contained in *Aristolochia* species. Detailed knowledge of enzymes which participate in metabolism of AAI may contribute to elucidation of inter-individual susceptibility to AAN, BEN and later urothelial malignancies. Aristolochic acid I is either oxidative detoxicated or reductive activated by biotransformation enzymes. Reductive bioactiovation of AAI leads to formation of covalent AA-DNA adducts in organism which result in producing of unique AT→TA transversion in tumour suppressor gene *p53*. Oxidative detoxification of AAI leads to formation of a demethylated product, 8-hydroxyaristolochic acid I (AAIa). In this thesis, we investigated cytochromes P450 (CYP)-mediated reductive activation and oxidative detoxication of AAI in a rat and mouse model. Inducers and inhibitors of CYP enzymes, rat recombinant cytochromes P450 and special transgenic mouse models we used to identify which CYP enzymes are involved in metabolism of AAI. The effect of cytochrome b_5 on detoxication and activation of AAI was also studied. This protein is facultative component of a mixed function oxidase system and may influence activity of some CYP enzymes. Results found in this work demonstrate a major role CYP1A1 and 1A2 in detoxification of AAI *in vitro* and *in vivo*. CYP1A1/2 also contribute to reductive bioactivation of AAI which leads to formation of very reactive *N*-acylnitrenium ion and AT→TA transversion in *p53* gene.

(In Czech)