ABSTRACT

Plant alkaloid aristolochic acid (AA) is a proven human carcinogen which causes two serious diseases: Aristolochic Acid Nephropathy (AAN) and Balkan Endemic Nephropathy (BEN). One of the characteristic features of both AAN and BEN is their close association with the development of upper urothelial carcinoma (UUC) in the renal tissue of patients. Although both nephropathies are mediated by the same compound (i.e. AA), their development differs slightly. The differences might be explained by a different exposure schedule of patients or interindividual differences in expression levels and activities of the enzymes metabolising AA in organisms. Detailed knowledge of these enzymes can contribute to the elucidation of the interindividual susceptibility to AA. In this thesis, enzymes participating in both oxidative detoxification of AAI, a major component of natural mixture of AA, and its reductive activation leading to the formation of AA-DNA adducts were studied. In a rat experimental model (*Rattus norvegicus*), NAD(P)H:quinone oxidoreductase 1 (NQO1) and its role in reductive bio-activation of AAI *in vivo* were examined utilising a specific inhibitor of this enzyme, dicoumarol. Oxidative detoxification of AAI resulting in formation of a demethylated derivative AAIa (8-hydroxyaristolochic acid) was studied using induction of cytochromes P450 (CYP) 1A1 and 1A2, the enzymes catalysing the formation of AAIa most efficiently. Nevertheless, CYP1A1/2 can also reductively activate AAI forming AAI-DNA adducts *in vivo* and *ex vivo*. Therefore, one of the aims of the thesis was to evaluate which AAI biotransformation pathway prevails *in vivo*. In this study, we aimed to clarify the aetiology of BEN/UUC, particularly the effect of other suspect environmental factors on development of this life-threatening renal disease. In the rat experimental model, we investigated the influence of ochratoxin A (OTA) on AA metabolism to elucidate whether this nephrotoxic mycotoxin is capable of affecting the AA-mediated BEN/UUC development. We also studied the effect of other factors which are hypothesised to participate in BEN/UUC development (i.e. ions of heavy metals and metalloids, and organic compounds being present in lignite deposits located in BEN regions), namely on oxidative detoxification of AAI to AAIa. The results found in the thesis demonstrate the crucial role of NQO1 in AAI bio-activation not only *in vitro* but also *in vivo*, and the major role of CYP1A1/2 in oxidative detoxification of AAI *in vivo*. In the study investigating the aetiology of BEN/UUC, the results show for the first time that OTA can be capable of influencing AA metabolism thereby potentiating the development of BEN/UUC.

(*In Czech*)