ABSTRACT

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Title of Doctoral Thesis **Anthelmintic and other xenobiotic biotransformation in helminths and its contribution to resistance development**

Parasitic helminths such as tapeworms, flukes or nematodes pose a threat for domestic, farm and wild living animals. Helminths cause significant health problems in animals. Moreover, they cause economical losses to farmers due to production decrease and treatment costs. The treatment with veterinary anthelmintics is still a basic method to fight off helminth infections. However, the long-term use of anthelmintics caused an emergence of resistance to anthelmintics. The increasing incidence of multiresistant strains of many helminth species is the greatest problem. Therefore, research of drug resistance mechanisms became an actual field of study. Increased biotransformation of anthelmintics, transport out of parasite bodies and contact of lower developmental stages with anthelmintics in the environment are some of possible mechanisms that lead to decrease of anthelmintic therapy effectivity and resistance development.

The presented thesis focuses on the study of these mechanisms in three helminth species. High performance liquid chromatography coupled with mass spectrometry was used in drug and their metabolite analysis. In a barber's pole worm (Haemonchus contortus) study, we focused on differences in metabolism and transport of a drug flubendazole in resistant and susceptible strains. We studied metabolism of benzimidazole anthelmintics and activities of xenobiotic-metabolising enzymes in a sheep tapeworm (Moniezia expansa) and a giant liver fluke (Fascioloides magna) as well. Another part of the thesis was focused on measurement of albendazol and its metabolites levels in sheep faeces and relationship to helminth resistance development. Summarising the knowledge about novel aminoacetonitrile anthelmintic monepantel to a review article was another partial task.

The results of H. contortus studies show that flubendazole gets to H. contortus bodies via passive diffusion. Flubendazole appears not to be a substrate of any transport protein. H. contortus is able to biotransform flubendazole and many other model xenobiotics. Multiresistant strain creates more metabolites and has higher enzyme activities compared to susceptible one. These differences might participate in resistance development to other drugs. Studies with a sheep tapeworm and a giant liver fluke determine both helminth species are able to reduce carbonyl group of mebendazole or flubendazole and both are able to oxidise albendazole to sulphoxide. However, no conjugates of studied drugs were found. M. expansa is able to oxidise albendazole sulphoxide to sulphone. This reaction is not present in the fluke and neither oxidation of triclabendazole documented in liver fluke Fasciola hepatica is present. The pharmacokinetic study of albendazole in sheep shows the concentrations of albendazole and its active metabolite in faeces are ovicidal and larvicidal for H. contortus. Preincubation of eggs and larvae of H. contortus with sublethal doses of albendazole did not increase resistance of adults to albendazole.

Obtained results contribute to better understanding of mechanisms that helminths use to protect themselves against anthelmintics and other xenobiotics. This knowledge could be used to prevent further spread and emergence of resistance.