ABSTRACT

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Title of Doctoral Thesis:

METABOLISM OF ANTHELMINTICS IN HELMINTHS

Anthelminthic drugs are presently the principal method for the control of helminth diseases. Knowledge of detoxification mechanisms that helminths possess is important for understanding the processes that affect the drug concentration within a helminth organism and may be crucial in the treatment efficacy. When the drug concentration in a target organism does not reach the therapeutic level, it results in a decreased efficacy of pharmacotherapy which may further lead to the induction of helminth biotransformation enzymes and eventually issue in resistance development to the administered drug.

Present knowledge of helminth biotransformation enzymes is insufficient. Often it is not known whether a given individual helminth species possesses such enzymes or whether it is capable of employing them in treatment evasion.

In the presented thesis, the objective was to investigate the biotransformation pathways of selected anthelminthics in model helminth species, identify the formed metabolites and characterize biotransformation enzymes of the studied parasites. Our research was focused on two species, the barber pole worm (*Haemonchus contortus*) and the lancet fluke (*Dicrocoelium dendriticum*) and their ability to metabolize selected benzimidazole anthelminthics albendazole, flubendazole and mebendazole.

The results showed unambiguously that both helminth species have enzymatic systems capable of engaging in the xenobiotic metabolism. By means of liquid chromatography in conjunction with mass spectrometry, the investigation of phase I and phase II biotransformation in selected helminths showed that the studied parasitic species possessed an ability to oxidize and reduce given anthelminthic substrates. Sulfoxidation of albendazole to albendazole sulfoxide and albendazole sulfone and reduction of flubendazole and

mebendazole carbonyl groups occurred. Formation of second phase biotransformation products indicated presence of conjugation enzymes in examined helminths. Glucose conjugates of albendazole, flubendazole and reduced flubendazole were found in experiments with *H. contortus*. Methylmodification of flubendazole, mebendazole and reduced flubendazole was observed in experiments with *D. dendriticum*. None of the identified conjugation reactions of xenobiotics in helminths has been published until now. Such metabolic modifications of drugs can substantially affect their anthelminthic action and can be considered a detoxication and defense mechanisms. Substantial interspecies differences in the second phase enzyme selectivities were observed. This finding confirmed the fact that data valid for one species cannot be easily extrapolated to another.

Deeper and more detailed knowledge of anthelminthic biotransformation in helminths, and also the knowledge of differences in host and parasite biotransformation enzymes, can contribute to render the anthelminthic treatment more effective, can help to cushion the impact of helminth resistance development and have implicatons for the design of new anthelminthic drugs.