Abstract

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Title of diploma thesis: The role of drug transporters in activation of pregnane X receptor

The nuclear pregnane X receptor (PXR) is involved in maintaining the homeostasis of endogenous substances as well as in regulation of excretion of exogenous substances. PXR activation regulates the expression of transport and biotransformation enzymes I. and II. phase. Due to the high flexibility of PXR ligand binding domain, it can be activated by a wide range of xenobiotics. Including e.g., rifampicin, well-known PXR agonist causes clinically significant drug-drug interactions. However, rifampicin is not stable under physiological conditions and degradation occurs (into rifampicin quinone, 25-desacetylrifampicin, 3-formylrifamycin SV and rifampicin N-oxide).

The aim of our experiments was to compare the interspecies activation of PXR (human, monkey, mouse and rat) by rifampicin and its derivatives. Hence, gene reporter experiments were performed using the HepG2 cell line. Statistically significant results in PXR activation were observed for human hPXR and monkey oPXR for all rifampicin derivatives except 25-desacetylrifampicin. Similarity in the activation of hPXR and oPXR was shown by all rifampicin derivatives, but in the case of oPXR there was several times lower activation of the reporter construct. The potential of rifampicin and its derivatives to be transported by MDR1 was determined indirectly using the gene reporter assay method performed on the HepG2 cell line transfected with MDR1 or an empty vector. The affinity to the MDR1 transporter was observed in the case of rifampicin, rifampicin quinone, rifampicin N-oxide, 3-formylrifamycin SV and 25-desacetylrifampicin.

The studied interactions of rifampicin and its derivatives with PXR and MDR1 transporter play an important role in the drug-drug interactions but have not been investigated in more details so far.