Abstract

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Title of Dissertation Thesis:	New aspects of pregnane X receptor function and regulation

The pregnane X receptor belongs to the superfamily of nuclear receptors; it is a ligand dependent transcription factor regulating expression of its target genes. During last two decades, PXR was extensively studied as a xenosensor, i.e. the receptor, which is able to bind xenobiotics including many drugs and to regulate their metabolism by induction of the most important metabolizing enzymes of both phase I. and phase II. Induction, i.e. transcriptional stimulation of expression of the most important cytochrome P450 enzymes, by PXR ligands was described in details at many levels.

Within this dissertation thesis, I am dealing with aspects of regulation via PXR, which extend the common understanding of PXR as a receptor whose exclusive function is to up-regulate drug metabolizing enzymes mediated by its agonists.

Within the first, project I studied regulation of OCT1 transporter in hepatic cell models, I shown that PXR did not induce, but it rather suppressed the expression of this important transporter of drugs and endogenous substances. This work is the first detailed study presenting mechanism of down-regulation of drug transporter via PXR.

Within the second work, I studied resveratrol and structurally related stilbenoid substances to regulate expression of PXR target genes. Resveratrol was described as one of the PXR inhibitors, however studies published on this issue were contradictory in their findings.

Within the third research field, I participated on the study of interaction of endogenous bile acids and their hypothetical metabolites with PXR. The aim of the study was to elucidate if metabolites of bile acids can act as endogenous ligands of PXR.

Overall, my work extended our general understanding of PXR from the perspective of down-regulation of OCT1 or the potential inhibition of PXR by substances structurally related to resveratrol.