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Modeling activation of pregnane X receptor and mRNA expression of cytochromes P450 in 3D primary human hepatocytes

Ellen Tanaka Kahiya[1], Tomáš Smutný[2], Jurjen Duintjer Tebbens[1], Petr Pávek[2], Veronika Bernhauerová[1]

[1]Department of Biophysics and Physical Chemistry,
[2]Department of Pharmacology and Toxicology,
Faculty of Pharmacy, Charles University, Czech Republic
kahiyae@faf.cuni.cz
smutt6aa@faf.cuni.cz
jurjend@faf.cuni.cz
pavek@faf.cuni.cz
bernhauve@faf.cuni.cz

Pregnane X receptor (PXR) regulates the expression of cytochrome P450 (CYP) enzymes in the liver [1] and thus plays a crucial role in the metabolism of various drugs. Rifampicin (RIF) is a model PXR ligand [1] and forms its primary metabolite 25-desacetyl rifampicin (25-DRIF) [2]. In our previous study, we showed that quantification of PXR activation and its downstream effects on CYP enzymes in response to treatment with RIF is possible using mathematical modeling and the long-term experimental measurements of PXR-controlled CYP mRNA expression obtained from 3D primary human hepatocytes (3D PHHs) [3]. However, these effects may vary depending on ligand concentration and type. Here, we combine mathematical modeling with experimental data to quantitatively distinguish the effects of RIF and 25-DRIF on PXR activation and PXR-dependent transcription of CYP3A4, CYP2C9, and CYP2B6 in 3D PHHs. Our model estimated that 20 µM of 25-DRIF was required to achieve 78% PXR activation, a level comparable to the activation induced by 1 µM of RIF in [3]. 200 µM of 25-DRIF resulted in nearly maximal (99%) PXR activation, a level comparable to the activation achieved by 10 µM of RIF in [3]. We evaluated that the PXR-dependent rate constant controlling transcription of CYP3A4 was higher than that of CYP2B6 in 3D PHHs treated with 25-DRIF whereas the opposite was observed in 3D PHHs treated with RIF. In addition, the PXR-dependent rate constant controlling transcription of CYP3A4 was estimated to be higher in 3D PHHs treated with 25-DRIF than in 3D PHHs treated with RIF. The rate constant controlling PXR-dependent transcription

of CYP2C9 was the same in RIF- and 25-DRIF-treated 3D PHHs. Our results provide quantifications of the ligand-specific nature of PXR activation and suggest that transcription of PXR-controlled CYP enzymes in 3D PHHs may also be CYP-specific.

References

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