Abstract

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmacology and Toxicology

Student: Karolína Ondraszková

Supervisor: PharmDr. Tomáš Smutný, Ph.D.

Title of diploma thesis: **An identification of selective antagonists of constitutive androstane receptor**

The constitutive androstane receptor (CAR) is an important ligand-regulated xenosensor that regulates the transcription of important drug biotransforming enzymes (e.g. CYP2B6). The pregnane X receptor (PXR) belongs to the same family of nuclear receptors as the CAR. The structure and function of both receptors share many common features. However, PXR has a larger and more flexible ligand-binding domain. At present, a selective, highly potent and non-toxic inhibitor of CAR is not practically available.

This work aims to determine the affinity of previously identified compounds in our group with antagonistic activity towards CAR. This is a replication study. For this purpose, we tested the compounds using gene reporter and two-hybrid assay.

Of all the tested substances, we obtained desired results with substance 1A. Using the gene reporter assay method, we found that substance 1A can reduce basal CAR expression but also suppresses CAR activity induced by the model agonist CITCO. The high affinity of the substance for the receptor was confirmed by a two-hybrid assay. Moreover, the substance does not affect PXR function. The IC_{50} value (= 18,88 μM) of 1A was determined by cytotoxicity assays.

The conclusion of this thesis is that substance 1A has high affinity and exhibits an antagonistic effect on CAR, while not activating PXR. The results of this thesis may help to identify new substances that will allow to study unique CAR functions without affecting PXR activity.