Toward better understanding of liver steatosis MoA: molecular modelling study of PPARγ receptor

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Introduction and Aims

Within the mode of action/adverse outcome pathway (MoA/AOP) framework the description and characterisation of the toxicological MoAs leading to liver toxicity are of specific interest. Liver plays a central role in free fatty acids and triglyceride metabolism (Fig. 1). Moreover, because of its unique function in the organism, the liver, and the hepatocyte in particular, is a major target for toxicity. Non-alcoholic fatty liver disease is one potential repeated dose toxicity adverse effect, known to encompass both steatohepatitis - the more aggressive form of the disease, and non-alcoholic fatty liver - grouping isolated steatosis and steatosis with mild lobular inflammation alone. There are growing evidences for the steatogenic role of hepatic peroxisome proliferator-activated receptor gamma (PPARγ), a ligand-inducible transcription factor from the nuclear receptor superfamily (Fig. 2).

In this study AOs from PPARγ activation to liver steatosis are identified based on a systematic literature analysis. Further, molecular modelling study is performed for the molecular initiating event (MIE) interaction between full agonists and the PPARγ receptor. It includes: (i) analysis of the 3D structural complexes of human PPARγ published in Protein Data Bank (PDB, http://www.rcsb.org); (ii) characterisation of the binding pocket of full agonists; (iii) identification of the ligand-receptor interactions; (iv) development of pharmacophore models of full agonists to be used inestablising filtering rules for effective virtual screening of compounds with potential agonistic activity towards PPARγ.

Methods

1. Literature search – main steps to identify key studies (Fig. 3) – all studies analysed and ranked according to an array of carefully defined criteria; the selected studies paved the way to describe PPARγ-dependent prosteatotic MoAs.

2. Extraction of all available PPARγ complexes (118) from the PDB (http://www.rcsb.org)

3. MOE software (MOE 2012.10, http://www.chemcomp.com) used to: (i) characterise binding pockets of the ligands; (ii) identify key ligand-interactions; (iii) perform pharmacophore modelling.

Results (1) – AOs

Four AOs were generalised that have been shown to cause fatty liver triggered by PPARγ activation – transport of fatty acids, de novo synthesis of fatty acids; triglyceride synthesis and lipid storage (Fig. 4).

The potential of the most studied target proteins to be starting points in a MoA leading to steatosis was evaluated and CD36, FSP27 and aP2 were selected as prosteatotic factors downstream PPARγ signalization.

A model for the toxicological MoA of PPARγ ligand-dependent activation in hepatocytes mediated by CD36, one of the cornerstones in the metabolic disruption leading to fatty liver, was proposed (Fig. 5).