Background & Aims

Several mechanisms are currently evaluated as potential pharmacotherapies for the spectrum of non-alcoholic fatty liver disease (NAFLD), including modulators of nuclear receptors such as PPARα/δ or FXR. Activation of Liver X Receptor (LXR) in the liver by potent, synthetic agonists is known to result in severe steatosis and hypertriglyceridemia in various animal models in mice and in humans. Thus, we have designed and synthesized LXR inverse agonists with the aim to inhibit LXR’s pro-steatotic transcriptional activity. The pharmacological effects of these LXR inverse agonists were evaluated in human hepatocytes and in a mouse and rat steatosis model. These first results confirm the findings by another group, that synthetic LXR inverse agonists can reduce liver fat content which may provide a new mechanism for the treatment of NAFLD / NASH.

In vitro activities

Compounds PX-L493 and PX-L603 were characterized in cellular reporter assays as inverse agonists of LXRα and LXRβ. Obtained AC50 for LXR(α/β) in NCoR recruitment Gal4 2-hybrid assay: PX-L493 (5.3/1.4 nM) ; PX-L603 (966/326 nM) (5.3/1.4 nM) for 72 h. To quantify the de novo lipid biosynthesis, incorporation of 13C was determined using MR-UCMS after fatty acid isolation.

In vivo activities

C57Bl/6 mice were maintained on a Survit-type high fat diet with 1% cholesterol for two weeks. PX-L603 (10 mg/kg, po) LXR inverse agonist T0901317 (50 mg/kg) was orally administered once daily for 42 days. The livers of animals treated with PX-L603 were 5.0 (±3.4) µg/mg compared to 12.2 (±3.1) µg/mg of vehicle-treated animals.

Conclusions

The results presented here suggest that inhibition of LXR’s transcriptional activity by synthetic inverse agonists results in:

- Inhibition of de novo lipogenesis (DNL)
- Reduced of free fatty acid (FFA) release from chylomicrons and reduced FFA uptake
- Reduced triglyceride synthesis through downregulation of Mogat and Dgat
- Downregulation of Pnpla3 expression, an enzyme with proven clinical significance in NASH patients

Ultimately resulting in reduced liver fat.

This suggests that inhibition of the LXR pathway in the liver is a useful novel approach for a pharmacotherapy of NAFLD.