LXR inverse agonists demonstrate liver lipid lowering effects through multiple mechanisms in rodent models of NASH and in human hepatocytes

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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/γ or FXR. Activation of Liver X Receptor (LXR) in the liver by potent, synthetic agonists is known to result in severe steatosis and hyperglyceridemia in various animal models 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 a rat steatosis model. These final results confirm the findings by another group1,2, 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

Cellular reporter assay that differentiates between agonists, antagonists and inverse agonists of LXRα or LXRβ

Assay setup

[Diagram of assay setup]

GaL-LXR-2-hybrid assay using a GaL driven luciferase. Compressors or coactivators were transfected as fusions to GaL DNA-binding domain, LXR-LBD as fusion to transactivation domain.

Anti steatotic effects in primary human hepatocytes

Lipid droplet accumulation

[Graph showing lipid droplet accumulation in normal medium, 120 mM palmitate, 25 mM glucose, and 2 mM palmitate and 2 mM glucose conditions]

LXR inverse agonists show liver lipid lowering in high fat diet fed mice

Study design

C57BL/6 mice were maintained on a Sunlight-type high-fat diet with 1% cholesterol for two weeks. PX-L633 (10 mg/kg, po) LXR inverse agonist or vehicle was administered for the following 4 weeks on the same diet. Hepatic triglyceride content was significantly reduced from 52.1 (±14.4) mg/g to 29.1 (±4.4) mg/g. Total cholesterol in the liver of animals treated with PX-L633 was 5.0 (±3.4) mg/g compared to 12.2 (±3.1) mg/g of vehicle treated animals.

Reduced intestinal fatty acid uptake upon LXR inverse agonism

Intestinal gene regulation

[Graph showing reduced intestinal fatty acid uptake and gene expression analysis]

Mouse liver gene expression analysis

[Graph showing gene expression analysis]

CONCLUSION

Inhibition of LXR’s transcriptional activity by synthetic inverse agonists results in:

- Inhibition of de novo lipogenesis (DNL)
- Reduction of free fatty acid (FFA) release from chylomicrons and reduced FFA uptake
- Reduced triglyceride synthesis through downregulation of Mogat and Dgat
- Downregulation of Pppla3 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.

REFERENCES