LXR inverse agonists inhibit de novo lipogenesis and reduce intestinal lipid and cholesterol absorption in a NAFLD mouse model

INTRODUCTION

Nuclear receptors LXR alpha and beta are both involved in the control of de novo lipogenesis (DNL) and of lipid and fatty acid uptake in various tissues including small intestine and liver.

We have developed potent synthetic LXR inverse agonists, PX-L25953 (5593) and PX-L25788 (5788), representing two different structural classes, which block transcriptional activity of both LXRs. Both compounds display anti-steatotic effects in a mouse NAFLD model. Through stable and radioactive isotope labelling we could demonstrate that these effects are exerted through a combined inhibition of liver and intestinal de novo lipogenesis which also results in a reduced intestinal lipid and cholesterol uptake. This offers a new opportunity to address NAFLD clinically through LXR inverse agonists.

IN VITRO RESULTS I

Cellular reporter assay differentiating between agonist, antagonist and inverse agonist of LXRs or LXR.

Mammalian-2-hybrid assay using a Gal4 driven luciferase. Coresspressors or coactivators were transfected as fusions to Gal4 DNA-binding domain. LXR-LBD as fusion to transactivation domain.

PK properties were established in C57BL/6J mice for LXR inverse agonists 5593 and 5788.

IN VIVO RESULTS II

Short term mechanistic study in C57BL/6J mice with four days treatment on HFD + 1% cholesterol with LXR inverse agonist 5593 and Tropifexor as comparator. Animals were given [14C]-acetate in drinking water to assess hepatic DNL. [14C]-labelled fatty acids from liver tissue were identified by MIDA (mass isotope distribution analysis).

[14C]-acetate incorporation as a proxy for DNL.

To assess intestinal uptake of triglycerides and cholesterol, animals were given an oral bolus of [14C]-triolein and [14C]-cholesterol. For cholesterol excretion, animals were injected with [14C]-cholesterol. After application, plasma samples were taken over 8 h and radioactivity was counted.

LXR inverse agonists as well as Tropifexor reduced intestinal lipid and cholesterol uptake as well as inhibited liver-borne DNL.

CONCLUSIONS

LXR inverse agonists, similar to FXR agonists are capable of reducing liver fat in animal models. Like FXR agonists they reduced DNL in intestine and liver and markedly reduced intestinal lipid and cholesterol uptake. Thus, LXR inverse agonists might offer a new treatment option for NAFLD/NASH which potentially lacks the FXR-associated liabilities like HDL lowering.

REFERENCES


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