Activation of farnesoid-X-receptor (FXR) by bioactive lipids

Jerry Thompson[1], Jun Zhang[1] and Jack Vanden Heuvel[1,2]
[1]Center for Nutrigenomics, Penn State University, University Park, PA
[2]INDIGO Biosciences, Inc., State College, PA

Introduction

FXR is a nuclear receptor that has gained a great deal of interest in terms of its biological role and potential as therapeutic target. Activating FXR increases transcription of genes that are geared toward preventing synthesis and uptake and promoting excretion of bile acids. One effect of FXR activation is decreased expression of *Cyp7A1* and thus bile acid synthesis; this is accomplished through induction of SHP (short heterodimer partner) which then represses *Cyp7A1* transcription (see Figure 1). FXR has significant effects on lipoprotein metabolism as well, in particular it has the effect of reducing triglycerides. Chenodeoxycholic acid (CDCA) is a bile acid and natural FXR agonist. In animal models, when CDCA or the synthetic ligand GW4064 is administered, they significantly reduce triglycerides and very-low-density (VLDL) cholesterol due to a reduction in the rate of VLDL production and reduce blood glucose At least some of the mechanisms involved in the reduction of triglycerides include decreased SREBP-1c, up. Thus an FXR agonist might be expected to be an effective triglyceride-lowering agent, with potentially beneficial effects on glucose metabolism as well.. The purpose of the present studies was to examine dietary fatty acids and bioactive lipids for their ability to activate FXR, and thus have a beneficial effect on lipid metabolism.

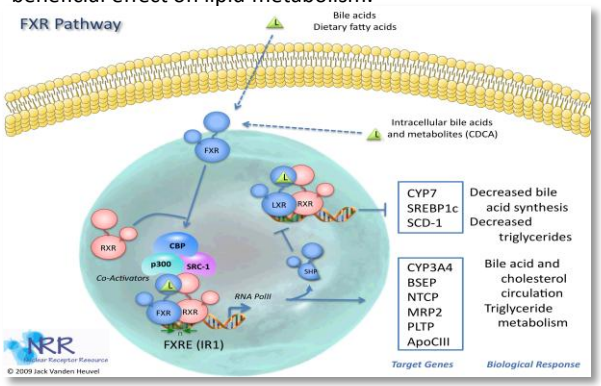


Figure 1 . Basic mechanism of action of FXR. http://nrresource.org

Methods

The FXR reporter assays were performed using the Human FXR Reporter Assay System from **INDIGO Biosciences, Inc.** (State College, PA), following the provider's instructions (384-well format, catalogue number IB00602). The Bioactive Lipid and Fatty Acid Libraries, as well as the reference compounds, were purchased from Biomol (Plymouth Meeting, PA). As shown in Figure 2, the FXR assay system was sensitive over a wide range of activities.

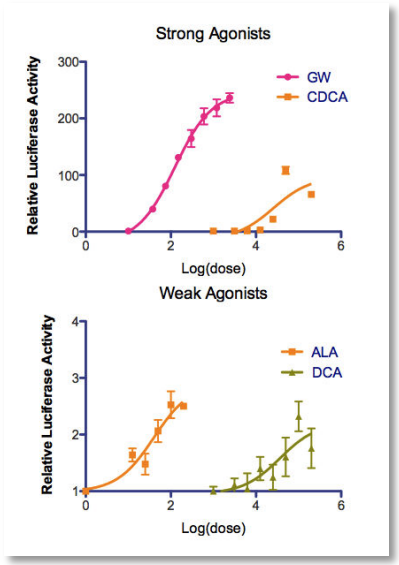
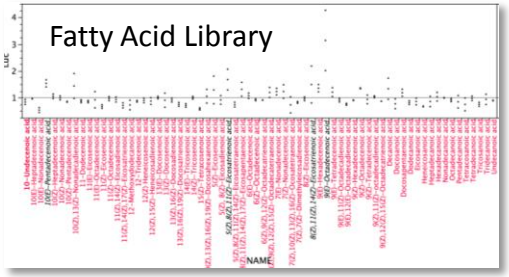


Figure 2 . Characterization of the human FXR reporter assay with potent and efficacious ligands top panel) and that are less active (right panel)

Results



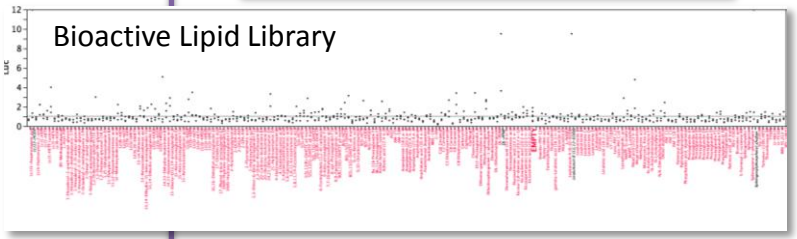


Figure 3 . Screening of chemical libraries with INDIGO Biosciences Inc Human FXR Assay System

Table 1. Compounds that signficantly activate human FXR

Compound	Dose (mM)
9(E)-Octadecanoic acid	10
5(Z), 8(Z), 11(Z)-Eicosatrienoic acid	10
10(E)-Pentadecenoic acid	10
10(Z), 13(Z)-Nonadecadienoic acid	10
9 (Z),12(Z) 15(Z) octadecatrienoic acid	**10**
DL-PPMP	1
13-HODE	1
Sphingosylphosphoryl choline	1
Leukotoxin B (12, 13-EODE)	1

Conclusions

Two libraries (~300 compounds) were examined at a single concentration in triplicate for their ability to regulate FXR (Figure 3). Nine compounds (Table 1) significantly affected FXR-driven luciferase activity including the known ligand ALA. Thus, human FXR receptor is activated by a variety of bioactive lipids, albeit with much lower activity than synthetic ligands.

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