Safe and Selective small molecule RXRα agonist modulates glucose and lipid metabolism in ob/ob mice

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Introduction

Treatment of 16 weeks old ob/ob mice for 4 weeks with CNX-013-B2 resulted in a 22% reduction in fed glucose 16% in fasting serum triglycerides, 20% free fatty acids, 14% fasting glycerol, 14% cholesterol and 26% LDL cholesterol. There was no change in food intake and body weight displayed a decreasing trend. In oral glucose tolerance test a 19% decrease in glucose AUC was observed indicating improvement in insulin sensitivity. No significant change in weight of different fat depots, kidney, pancreas and a non-significant increase in liver weight was observed. Treatment of 16 week old C57BL6/j mice on HFD (for 11 weeks) with CNX-013-B2 for 10 weeks resulted in 20% reduction in body weight gain, 14% reduction in fasting glucose, 7 % in fed glucose, 13% in fasting triglycerides, 13% free fatty acids, 11% fasting glycerol and 20% cholesterol. A significant 20% reduction in body weight gain and an increase in thermogenesis were observed.

Gene expression analysis indicates enhanced glucose and fat oxidation in muscle, increased de novo lipogenesis in liver, increased insulin sensitivity/browning of inguinal fat mass and modulation of cholesterol and bile acid metabolism. Treatment of C57BL6/j DIO mice on HFD with 100mg/kg for 5 weeks with CNX_013_B2 did not reduce serum levels of T3, T4 and TSH which indicates minimal impact on the HPT axis.

Material and Methods

CNX-013-B2, a RXR selective Rexinoid, is a lead molecule designed, synthesized and developed at Connexios Life Sciences, Bangalore, India.

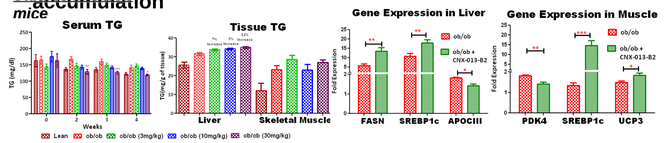
16 weeks old female ob/ob mice with postprandial hyperglycemia and 16 week old C57BL6/j DIO mice on high fat diet (for 11 weeks) were treated, BID, with 3, 10 & 30mpk of CNX-013-B2 for 4 weeks in ob/ob mice and 10mpk of CNX-013-B2 for 10 weeks in DIO mice respectively. The animals were provided feed and water ad libitum and several parameters such as thermogenesis, IP stimulated lipolysis, serum biochemistry and cholesterol in stools were measured at selected intervals. Thermogenesis was evaluated by exposing animals to 4°C temperature for 75min and to room temperature (23°C) for further 30 min. Rectal temperature was measured at regular intervals. Oral Glucose Tolerance Test (OGTT) was performed with oral glucose load of 2g/kg b.wt. Serum bile acids were measured using Crystal Chem Kit by colorimetric method. After termination expression of various genes and proteins in various organs was measured through RT_PCR and western blot respectively.

1 CNX-013-B2 – a potent, selective and safe Rexinoid

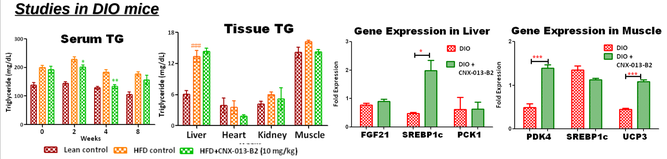
- CNX-013-B2 has an EC50 48nM towards human isoform of RXRa and almost similar activity against human isoforms of RXRβ and RXRγ
- CNX-013-B2 activates PPARα, PPARδ and PPARγ
- CNX-013-B2 does not activate of RARα, LXRα, PXR, CAR and AhR upto 10μM.
- No change in serum levels of T3, T4 and TSH up to 100mg/kg b. wt
- No signs of edema and cardiac hypertrophy
- No hepatomegaly

2 No hypertriglyceridemia caused *in vivo*; CNX-013-B2 reduces triglycerides in serum without increasing ectopic triglycerides accumulation

Studies in ob/ob mice

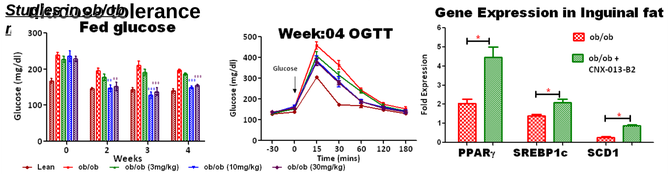


Studies in DIO mice

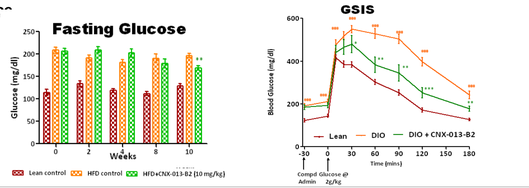


3 CNX-013-B2 reduces fasting & fed glucose and improves glucose tolerance

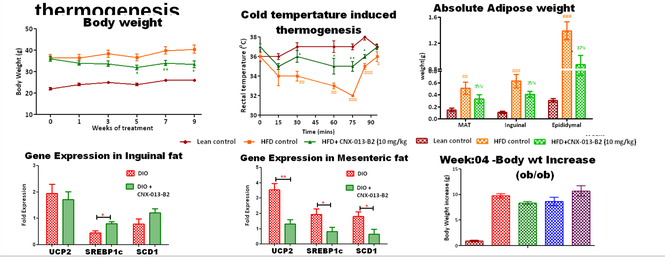
Studies in ob/ob mice



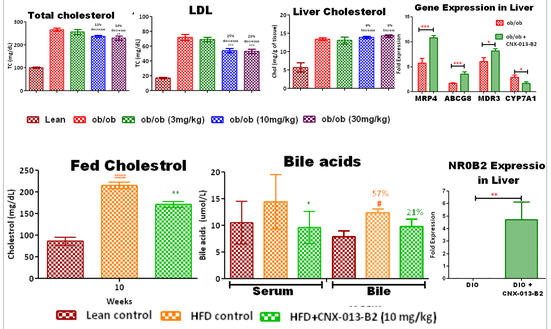
Studies in DIO mice



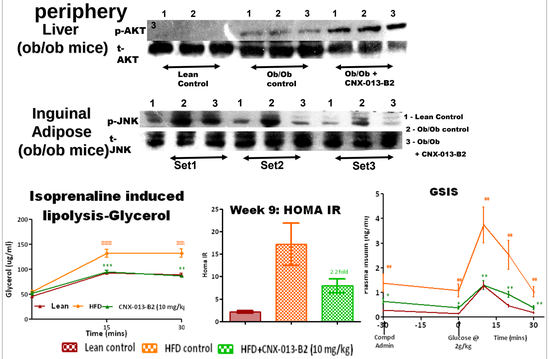
4 CNX-013-B2 reduces body weight : also increases thermogenesis



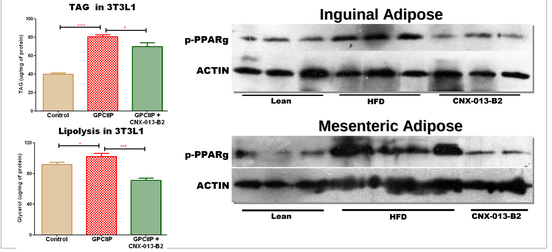
5 CNX-013-B2 reduces serum total and LDL cholesterol levels and modulates bile acid



6 CNX-013-B2 improves insulin sensitivity in the periphery



7 Effect of CNX-013-B2 on adipocytes function

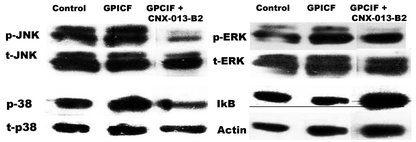


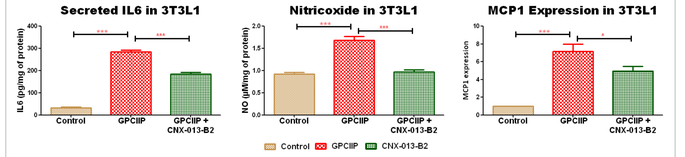
8 CNX-013-B2 does not increase organs' weight

Group	B.wt (g)	Liver wt (g)	Kidney (g)	Heart(g)	Pancreas (g)	Brain (g)
Lean Control	23.81 ± 0.80	0.96 ± 0.06	0.28 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	0.48 ± 0.01
HFD Control	38.64 ± 1.77	1.31 ± 0.07	0.33 ± 0.01	0.19 ± 0.02	0.15 ± 0.01	0.46 ± 0.01
CNX-013-B2 (10mpk)	31.51 ± 1.45	1.23 ± 0.05	0.34 ± 0.02	0.17 ± 0.01	0.15 ± 0.01	0.47 ± 0.01

9 CNX-013-B2 reduces cellular stress

Studies in Hepatocytes





Summary

- CNX-013-B2 is orally bioavailable, safe with good pharmacokinetic and pharmacodynamic profile
- CNX-013-B2 is non-genotoxic with minimal/no risk of drug-drug interaction and has no cardiac safety liabilities
- CNX-013-B2 does not cause hypertriglyceridemia, hepatomegaly, edema, HPT suppression or left ventricular hypertrophy
- CNX-013-B2 will be progressed into IND enabling studies

Connexios is open to early stage collaboration for RXR program

(For further details, please contact: m.r.jagannath@connexios.com)