The pan-PPAR agonist lanifibranor improves liver inflammation, ballooning, and fibrosis in a diet-induced obese MASH hamster model of binge drinking

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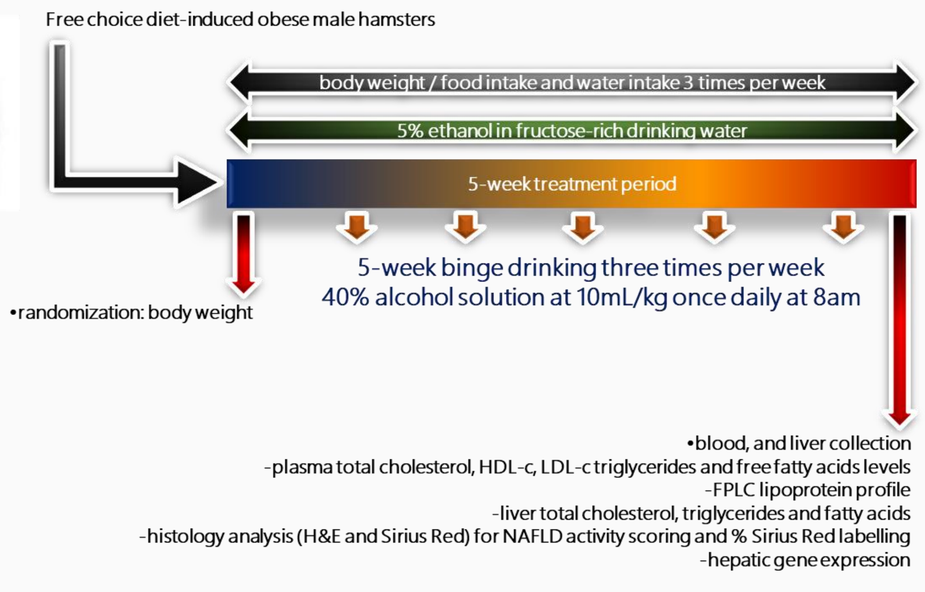
BACKGROUND:

We aimed to validate an animal model to evaluate the efficacy of drugs targeting MASH in a context of moderate to heavy alcohol use, which may aggravate liver lesions in patients with MASH. Because mouse and rat are not convenient models to study the effects of alcohol, we previously characterized a diet-induced obese MASH hamster model that spontaneously shows a high preference for alcohol. Here we further optimized our model to evaluate the effects of the pan-PPAR agonist lanifibranor (LANI) on liver lesions induced by binge drinking.

METHODS:

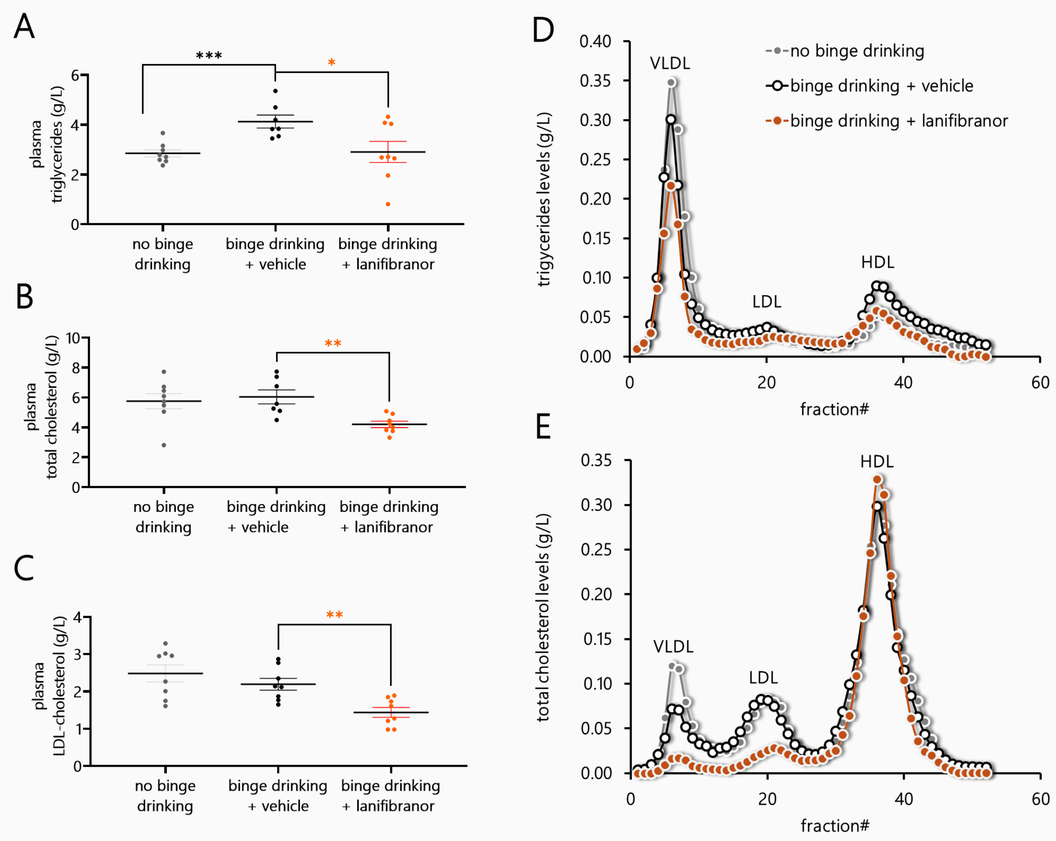
Obesity and MASH were first induced with a free choice diet, which presents golden Syrian hamsters with a choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose water. After a 20-week diet induction, animals were maintained on the same diet with the 10% fructose water supplemented with 5% alcohol, without (control) or with alcohol binge drinking (40% alcohol at 10mL/kg p.o., 3 times per week), and hamsters were simultaneously treated with vehicle or LANI 30mg/kg p.o. QD for 5 weeks.



Treatment groups (n=8 per group):
- Group #1: no binge drinking
- Group #2: binge drinking + vehicle p.o. QD in the afternoon
- Group #3: binge drinking + lanifibranor 30mg/kg p.o. QD in the afternoon

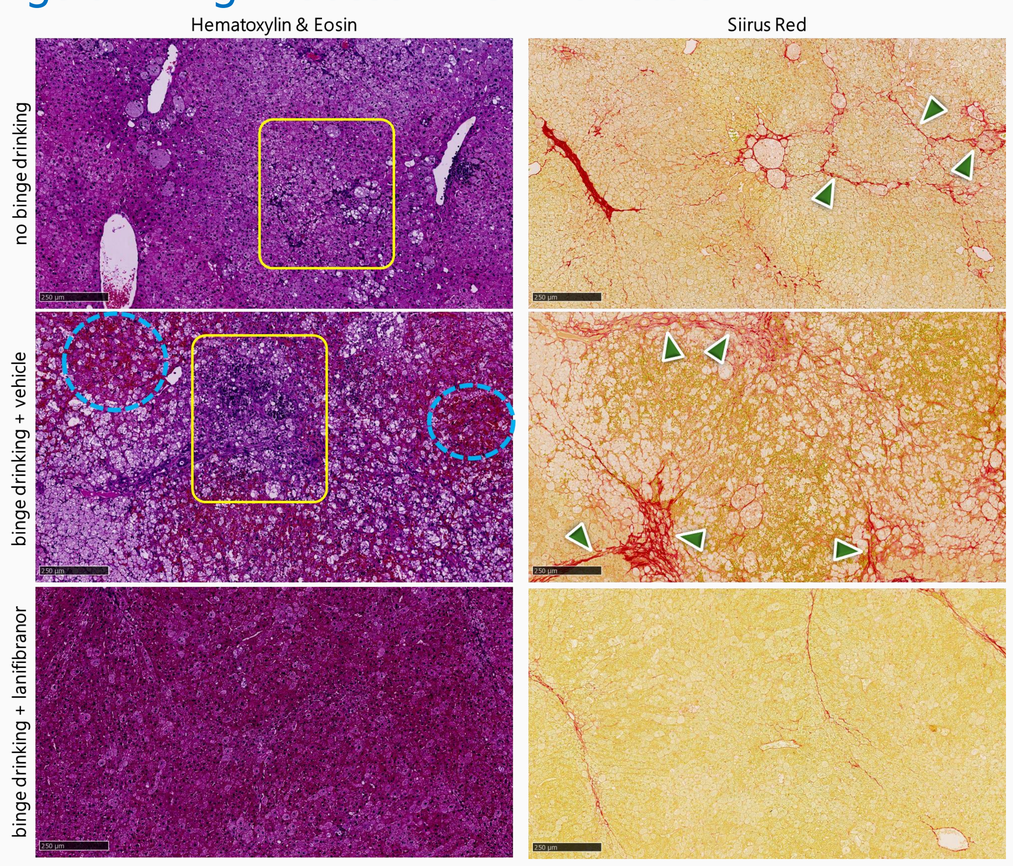
RESULTS:

1 Lanifibranor corrects dyslipidemia in obese MASH hamsters under alcohol binge drinking



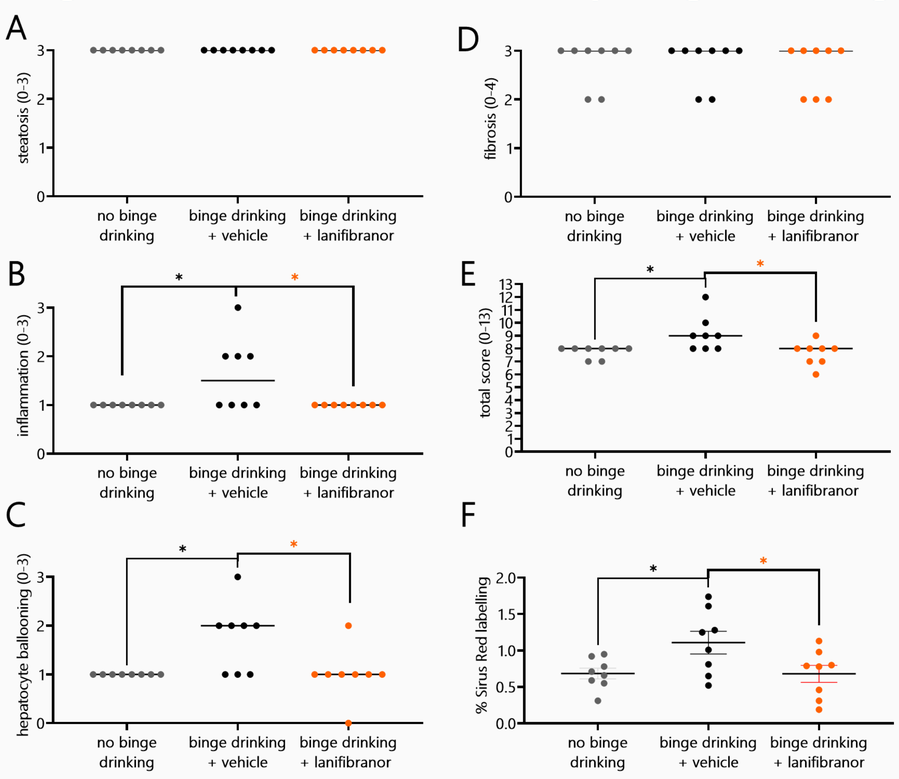
Plasma triglycerides (A), total cholesterol (B) and LDL-cholesterol levels (C), Fast Protein Liquid Chromatography (FPLC) lipoprotein profiles for triglycerides (D) and total cholesterol (E) in obese MASH hamsters without or with binge drinking and treated with vehicle or lanifibranor. *n=8/group*p<0.05, **p<0.01 and ***p<0.001*

2 Lanifibranor prevents the aggravated liver lesions due to binge drinking in obese MASH hamsters



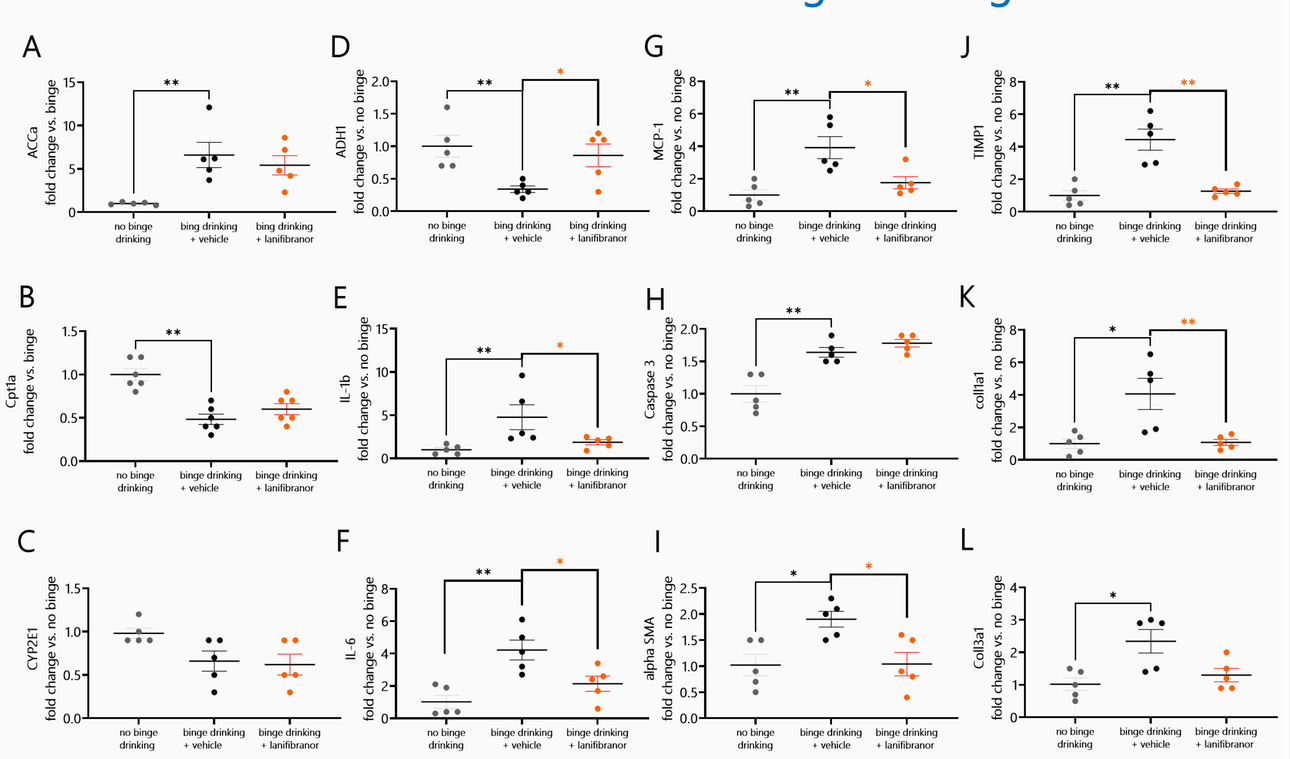
Representative H&E (left panel) and Sirius Red (right panel) pictures in obese MASH hamsters without or with binge drinking and treated with vehicle or lanifibranor. Yellow squares indicate microvesicular steatosis, inflammation and hepatocyte ballooning. Blue dashed circles indicate liver hemorrhage, and green arrows indicate bridging fibrosis.

3 Lanifibranor improves the aggravated histopathological scoring and liver fibrosis induced by binge drinking



Histopathological score for steatosis (A), inflammation (B), hepatocyte ballooning (C), fibrosis (D), total score (E) and % Sirius Red labelling in obese MASH hamsters without or with binge drinking and treated with vehicle or lanifibranor. **n=8/group. *p<0.05*

4 Lanifibranor reduces the greater expression of genes involved in inflammation and fibrosis under binge drinking



Hepatic gene expression of genes involved in lipogenesis (A), fat oxidation (B), alcohol metabolism (C, D), inflammation (E-G), cell death (H) and fibrosis (I-L) in obese MASH hamsters without or with binge drinking and treated with vehicle or lanifibranor.
**n=5/group. *p<0.05 and **p<0.01.*

CONCLUSION

Lanifibranor significantly improved dyslipidemia and liver lesions in a diet-induced obese MASH hamster model of alcohol binge drinking. This preclinical model will help to evaluate drugs targeting MASH in a context of moderate to heavy alcohol use and their potential benefits in humans.

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