Semaglutide and lanifibranor differentially alter MASH and liver fibrosis in diet-induced obese hamsters with or without free access to alcohol

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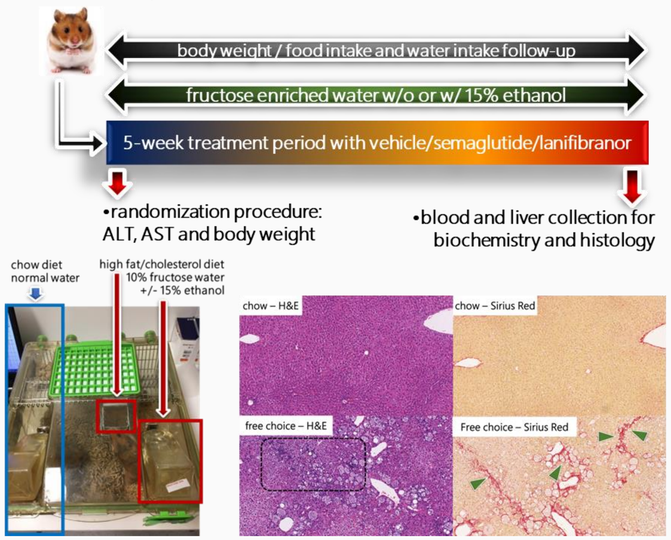
BACKGROUND:

GLP-1 receptor agonist semaglutide and pan-PPAR agonist lanifibranor are currently evaluated in humans for MASH treatment. While chronic alcohol intake may aggravate liver lesions in patients, rodent studies suggested that both GLP-1 and PPAR agonists reduce alcohol intake in mouse and rat, but these species are not truly alcohol dependent. The golden Syrian hamster spontaneously shows a high preference for alcohol and may represent a better animal model. Here we tested the effects of semaglutide and lanifibranor in diet-induced obese hamsters, a preclinical model with human-like MASH, with or without free access to alcohol.

METHODS:

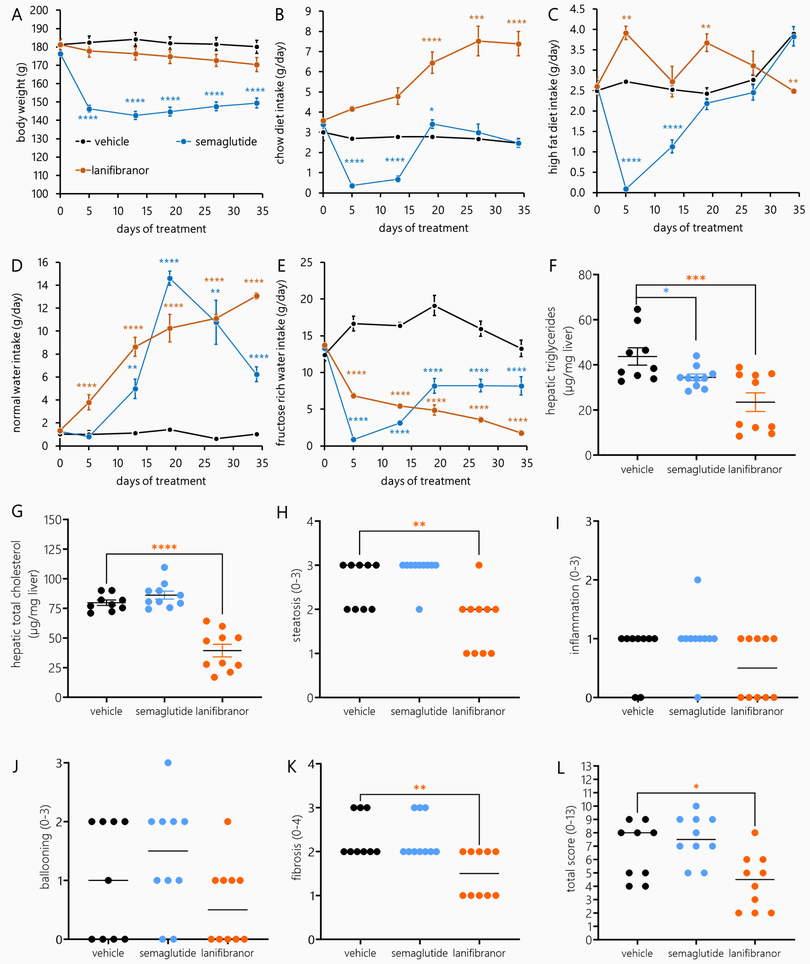
Obesity and MASH were induced with a free choice diet, which presents hamsters with a choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose water. After a 20-week diet induction, hamsters were maintained on the same diet with the 10% fructose water supplemented without or with 15% alcohol, and animals were simultaneously treated with vehicle, semaglutide 0.06mg/kg s.c. QD or lanifibranor 30mg/kg p.o. QD (n=6-10/group) for 5 weeks.



Experimental design (upper panel), housing cage setting for free choice diet fed hamsters, and representative liver H&E and Sirius Red pictures in control chow diet fed or free choice diet fed obese MASH hamsters (lower panel) at treatment start. *Black dashed square indicates microvesicular steatosis, inflammatory foci and hepatocyte ballooning. Green arrows indicate portal and bridging fibrosis, and fibrosis around ballooned hepatocytes.*

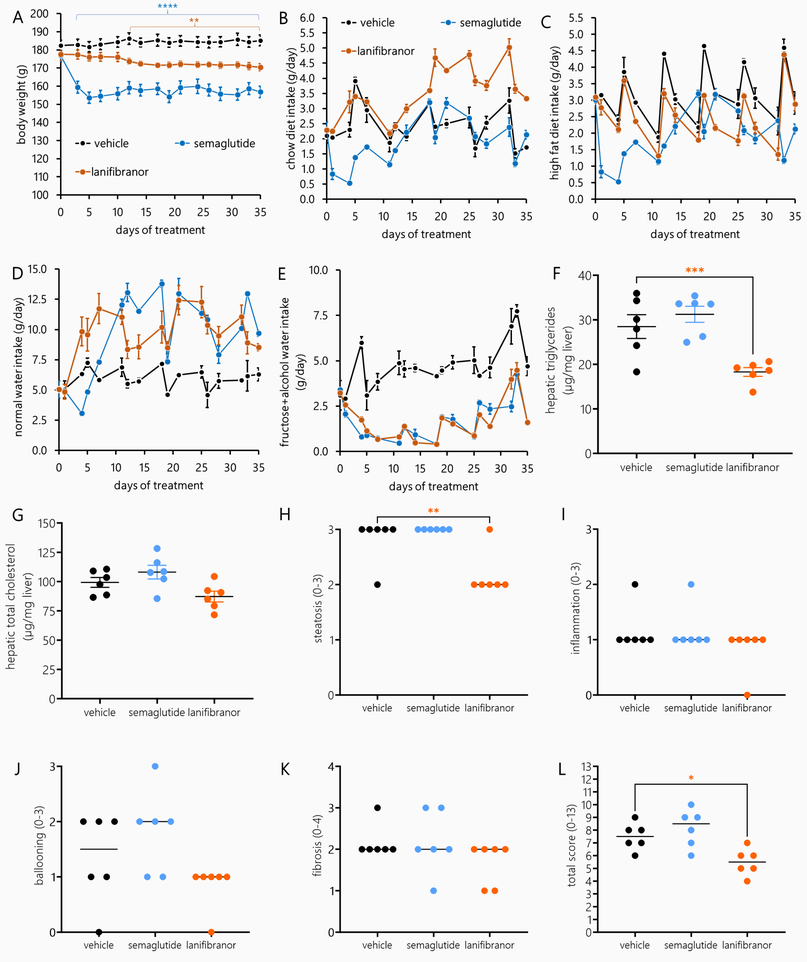
RESULTS:

1 In obese MASH hamsters without access to alcohol, semaglutide induces weight loss but only reduced liver triglycerides, while lanifibranor improves NAScore and fibrosis score



Body weight (A), chow diet (B), high fat diet (C), normal water (D) and fructose-rich water (E) intake, hepatic triglycerides (F) and total cholesterol (G) levels, steatosis (H), inflammation (I), ballooning (J), fibrosis (K) and total NAFLD activity (L) scores in free choice diet fed hamsters without access to alcohol and treated with vehicle, semaglutide or lanifibranor for 5 weeks.
**p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001 vs. vehicle*

2 In obese MASH hamsters with access to alcohol, both semaglutide and lanifibranor lower alcohol intake, but only lanifibranor reduces liver triglycerides and NAScore



Body weight (A), chow diet (B), high fat diet (C), normal water (D) and fructose+alcohol water (E) intake, hepatic triglycerides (F) and total cholesterol (G) levels, steatosis (H), inflammation (I), ballooning (J), fibrosis (K) and total NAFLD activity (L) scores in free choice diet fed hamsters with access to alcohol and treated with vehicle, semaglutide or lanifibranor for 5 weeks.
**p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001 vs. vehicle*

CONCLUSION

Semaglutide and lanifibranor both reduced fructose and alcohol intake but had different effects on MASH and liver fibrosis in obese MASH hamsters. This preclinical model will help to evaluate drugs targeting MASH on alcohol intake and their potential benefits in humans.

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Disclosures: François Briand and Thierry Sulpice are employees of Physiogenex and have shares in the company. Natalia Breyner and Estelle Grasset are employees of Physiogenex.