Incretin-based therapies reduce alcohol intake in lean and obese hamster models of chronic alcohol consumption

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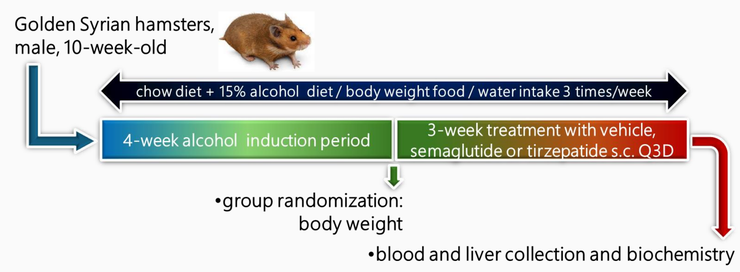
BACKGROUND:

Rodent studies suggested that GLP-1 receptor agonists reduce alcohol intake in mouse and rat, but these species are not truly alcohol dependent. Golden Syrian hamsters spontaneously show a high preference for alcohol and may represent a better animal model. Here we setup two hamster models of chronic alcohol consumption to evaluate incretin-based therapies.

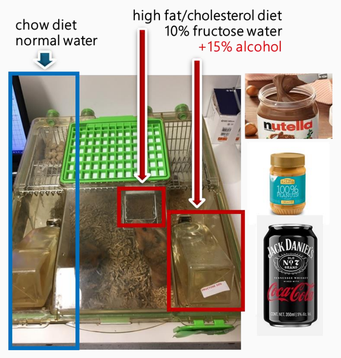
METHODS:

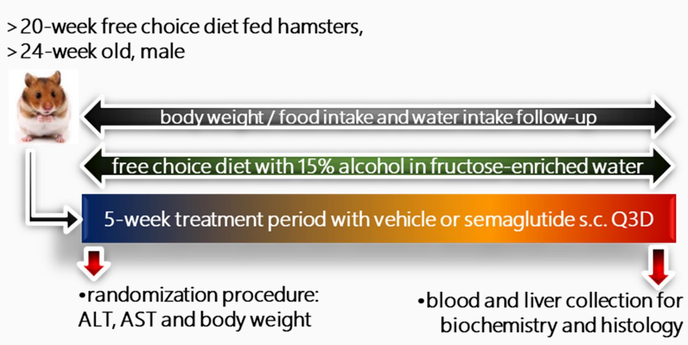
In the first model, normal hamsters were fed a 4-week chow diet with free access to normal water or 15% alcohol-enriched water. Hamsters were then kept on the same diet and treated for 3 weeks with vehicle, semaglutide 0.04 mg/kg or tirzepatide 0.05 mg/kg subcutaneously every 3 days.
The second model used hamsters with obesity and metabolic dysfunction-associated steatohepatitis (MASH), induced with a 20-week free choice diet which presents hamsters with a choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose-enriched water. Hamsters were then maintained on the same diet with the 10% fructose water supplemented with 15% alcohol and treated with vehicle or semaglutide 0.06 mg/kg subcutaneously QD for 5 weeks.

•First model - experimental design 1



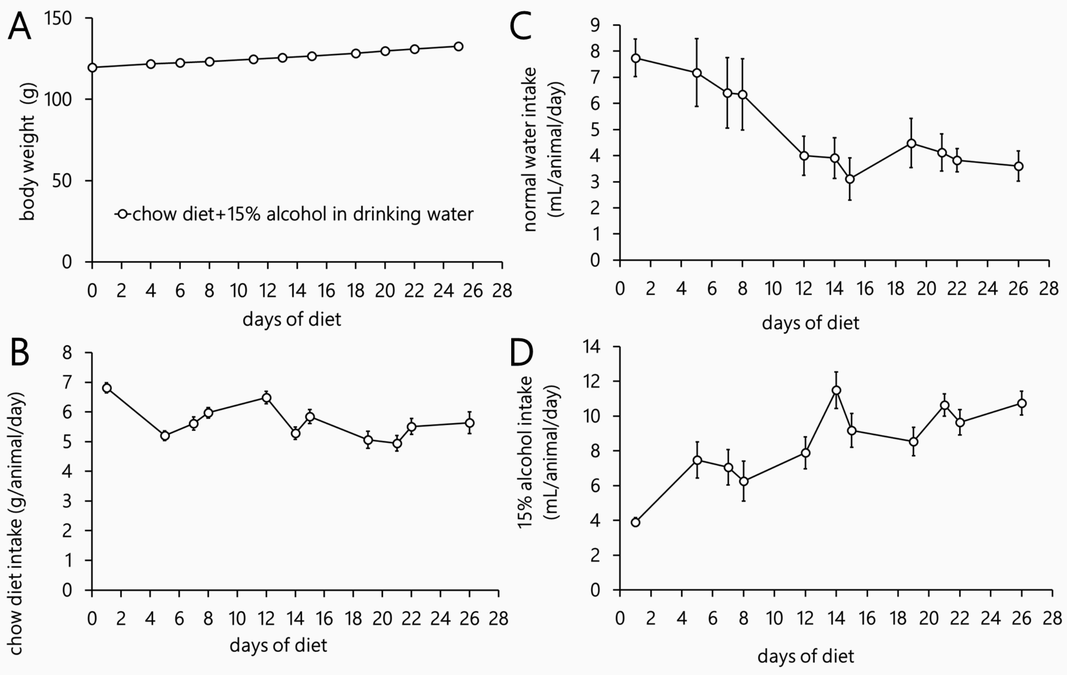
•Second model – experimental design 2





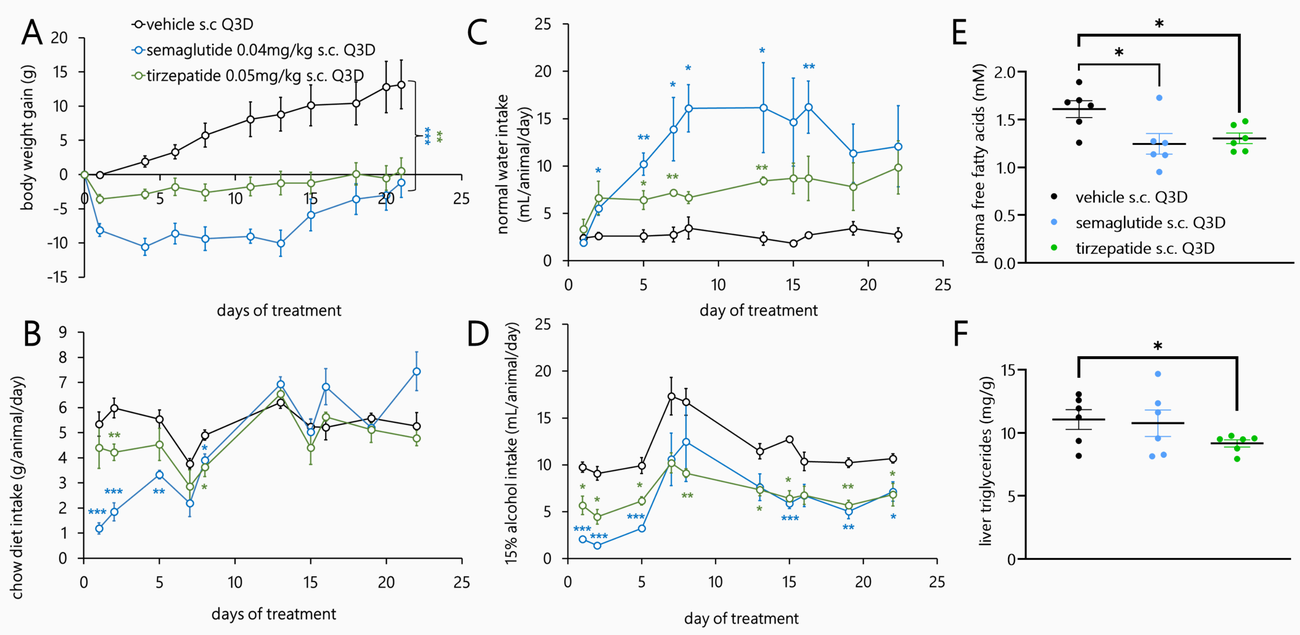
RESULTS:

1 Alcohol intake substantially increases over 4 weeks in lean hamsters with free access to alcohol



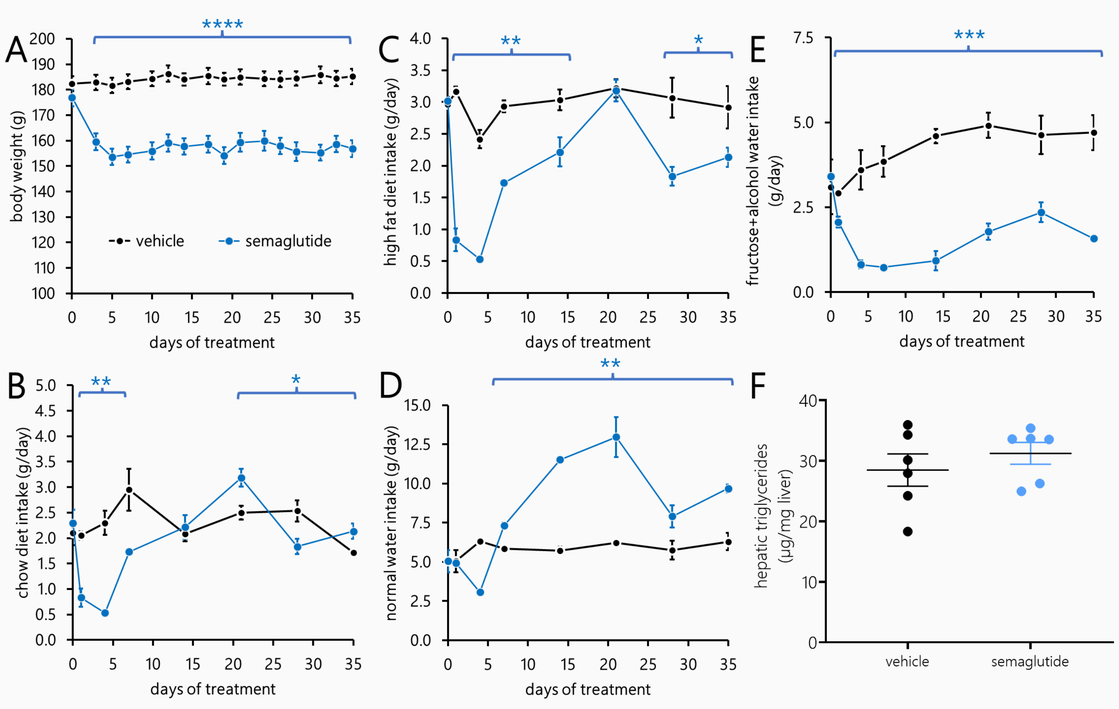
Body weight (A), food intake (B), normal water intake (C), and 15% alcohol-enriched water intake in lean golden Syrian hamsters with free access to normal water or 15% alcohol enriched water for 4 weeks.

2 Semaglutide and tirzepatide lower alcohol intake in lean hamsters with free access to alcohol



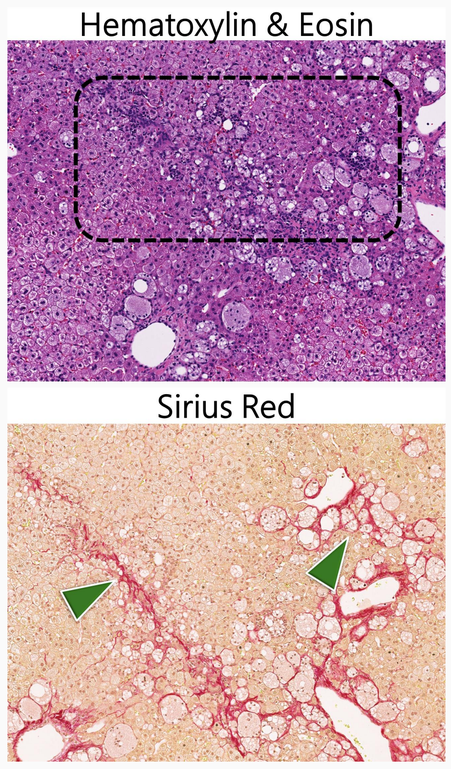
Body weight gain (A), food intake (B), normal water intake (C), 15% alcohol-enriched water intake (D), plasma free acids (E) and liver triglycerides (F) levels in lean golden Syrian hamsters with free access to normal water or 15% alcohol enriched water, and treated with vehicle, semaglutide or tirzepatide for 3 weeks.*p<0.05, **p<0.01 and ***p<0.001 vs. vehicle*

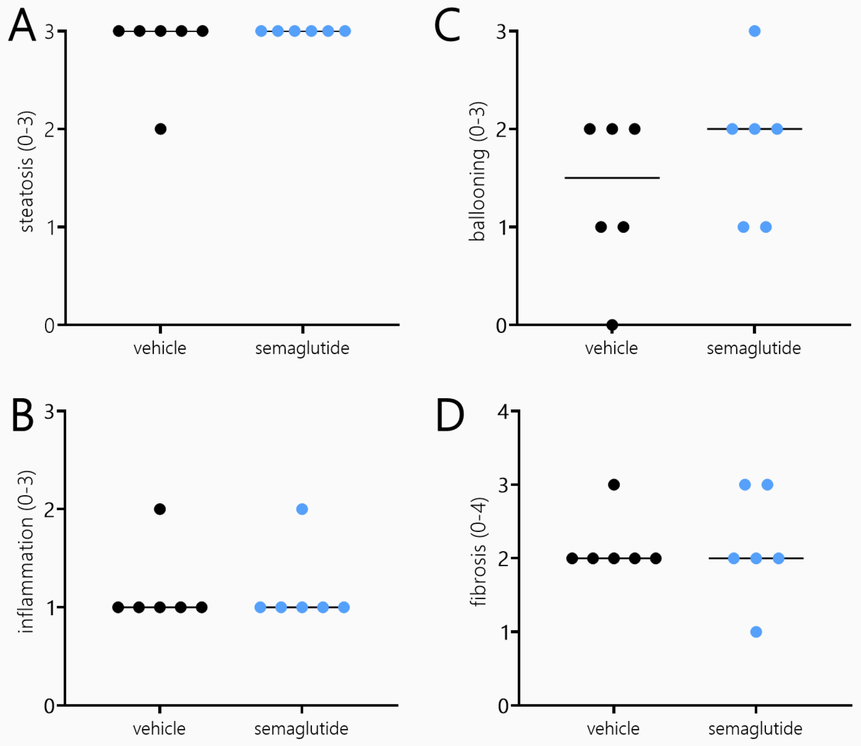
3 Semaglutide lowers body weight and reduces fructose+alcohol enriched water intake in obese MASH hamsters with free access to fructose+alcohol



Body weight (A), chow diet intake (B), high fat diet intake (C), normal water intake (D), fructose+alcohol-enriched water intake (E) and hepatic triglycerides levels (F) in obese MASH hamsters fed a free choice diet with a free access to a fructose+alcohol enriched water, and treated with vehicle or semaglutide for 5 weeks.
**p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001 vs. vehicle*

4 Semaglutide does not alter MASH and liver fibrosis in obese MASH hamsters with free access to fructose+alcohol





Representative liver H&E and Sirius Red staining in obese MASH hamsters. *Black dashed square indicates microvesicular steatosis, inflammatory foci and hepatocyte ballooning. Green arrows indicate portal and bridging fibrosis, and fibrosis around ballooned hepatocytes.* Hepatic steatosis (A), inflammation (B), ballooning (C) and fibrosis (D) scores in obese MASH hamsters fed a free choice diet with a free access to fructose+alcohol enriched water, and treated with vehicle or semaglutide for 5 weeks.

CONCLUSION

Incretin-based therapies reduce alcohol intake in lean and obese hamsters having free access to alcohol.
These preclinical models will be helpful to evaluate the benefits of novel therapies on chronic alcohol consumption.

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