Metabolic effects of survodutide in DIO mice at thermoneutrality

Authors
Michele Cavalera[1], Line Fisker Zachariassen[1] Grzegorz Maciag[1], Louise Humle Kruse[1], Henrik Björk Hansen[1] and Marco Tozzi[1].

[1]Gubra, Hørsholm Kongevej 11B, Hørsholm, Denmark

Corresponding author
mto@gubra.dk

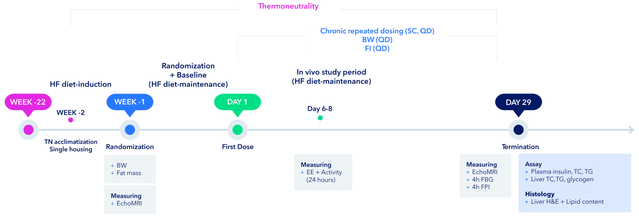
Background & Aim

Survodutide is a dual agonist of the glucagon receptor (GCGR) and glucagon-like peptide-1 receptor (GLP-1R), currently in clinical development for obesity and related metabolic disorders. By concurrently enhancing GCGR and GLP1R signaling, survodutide offers a synergistic approach to improving metabolic function. The present study aimed to evaluate the effects of survodutide on metabolic markers and energy expenditure (EE) in diet-induced obese (DIO) mice.

Methods

Male C57BL/6J mice were fed a high-fat diet (60 kcal-% fat) for 22 weeks. DIO mice were single-housed and acclimatized to thermoneutrality (28° C) two weeks prior to study start. Mice were randomized and stratified into treatment groups based on body weight and whole-body fat mass. Mice were administered (SC, QD) with vehicle or survodotide (30 nmol/kg) for 29 days. Endpoints included body weight, food intake, whole-body fat/lean tissue mass (echoMRI), plasma/liver metabolic markers and real-time EE assessment using indirect calorimetry.

1 Study outline



Group	Animal model	Sex	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing Concentration
1	DIO mice	Male	12	**Vehicle**	SC	QD	**NA**
2	DIO mice	Male	8	**Survodutide**	SC	QD	**30 nmol/kg**

Figure 1: Study outline.

2 Body weight and composition

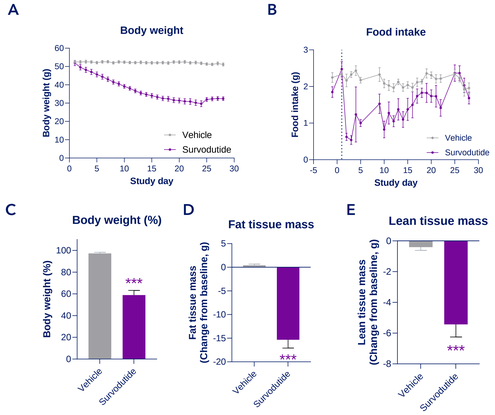


Figure 2: Survodutide promotes robust weight loss in DIO mice. (A) Body weight profile. **(B)** Discrete food intake profile. **(C)** Body weight (% of baseline, day 29). **(D)** Whole-body fat mass (g, change from baseline), **(E)** Whole-body lean mass (g, change from baseline). ***p<0.001 compared to Vehicle (Dunnett's test one-factor linear model).

3 Plasma and liver biochemical parameters

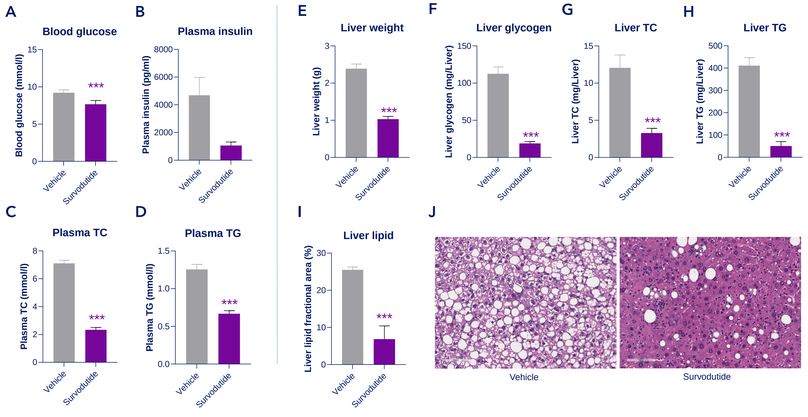


Figure 3: Survodutide improves systemic and hepatic metabolic parameters in DIO mice. (A-D) Plasma markers: **(A)** Fasting blood glucose. **(B)** Fasting plasma insulin. **(C)** Plasma total cholesterol (TC). **(D)** Plasma triglycerides (TG). **(E-J)** Liver markers: **(E)** Liver weight **(F)** Liver glycogen **(G)** Liver cholesterol **(H)** Total liver triglycerides. **(I)** Liver lipid fractional area (%). **(J)** Representative images of liver H&E staining. ***p<0.001 compared to Vehicle. (Dunnett's test one-factor linear model).

4 Energy Expenditure

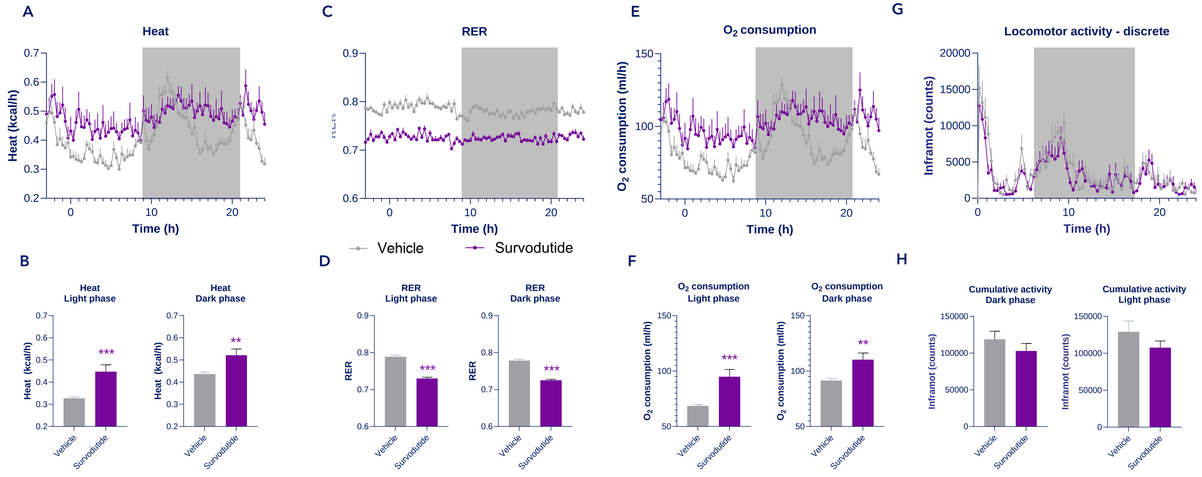


Figure 4: Survodutide increases energy expenditure in DIO mice. EE was performed at 6 days after treatment start. (A) Heat production profile. **(B)** Average heat production during light and dark phase. **(C)** Respiratory exchange ratio (RER) profile. **(D)** Average respiratory exchange ratio during light and dark phase. **(E)** Oxygen consumption profile. **(F)** Average oxygen consumption during light and dark phase. **(G)** Discrete locomotor activity profile. **(H)** Cumulative locomotor activity during light and dark phase. **p<0.01, ***p<0.001 compared to Vehicle (Dunnett's test one-factor linear model).

Conclusion

Survodutide improves metabolic outcomes in DIO mice by:

+ Promoting robust weight loss
+ Reduced adiposity, albeit accompanied by lean mass loss
+ Suppressing food intake
+ Improving glycemic control
+ Improving plasma and liver lipid profile
+ Reducing liver glycogen levels
+ Enhancing energy expenditure

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