Distinct metabolic effects of semaglutide and resmetirom at thermoneutrality in diet-induced obese mice

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Background & Aim

Semaglutide, a GLP-1 receptor agonist currently approved for the treatment of type 2 diabetes and obesity, is in late-stage clinical development for MASH. Resmetirom, a selective THR-β agonist, has recently been approved by FDA for MASH. The present study aimed to assess if thermogenesis is implicated in the beneficial metabolic effects of semaglutide and resmetirom in diet-induced obese (DIO) mice.

Methods

Male C57BL/6J mice were fed a high-fat diet (60 kcal-% fat) for 32 weeks. Animals were acclimatized to thermoneutrality (28◦ C) for two weeks prior to study start and randomized into treatment groups based on body weight and whole-body fat mass. DIO mice were administered (QD) vehicle, semaglutide (10 nmol/kg, SC) or resmetirom (10 mg/kg , PO) for 4 weeks. Chow-fed mice served as lean controls. Endpoints included body weight, food intake, whole-body fat/lean mass (echoMRI), 4h fasted plasma biochemistry and real-time energy expenditure (EE) assessed by indirect calorimetry.

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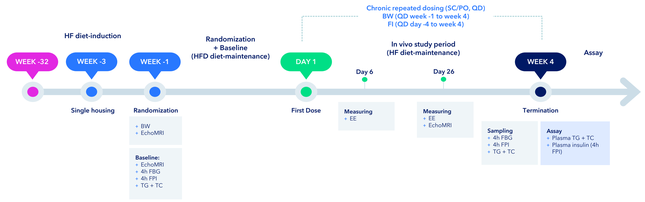
1 Study outline



Group	Animal model	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing Volume (ml/kg)	Dosing Concentration
1	Lean mice	male	10	**Vehicle**	SC	QD	5	**NA**
2	DIO mice	male	12	**Vehicle**	SC	QD	5	**NA**
3	DIO mice	male	12	**Semaglutide**	SC	QD	5	**10 nmol/kg**
4	DIO mice	male	12	**Resmetirom**	PO	QD	5	**10 mg/kg**

2 Body weight and composition

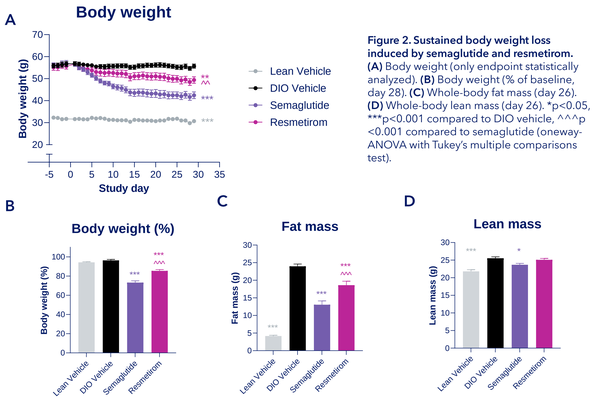


Figure 2. Sustained body weight loss induced by semaglutide and resmetirom. **(A)** Body weight (only endpoint statistically analyzed). **(B)** Body weight (% of baseline, day 28). **(C)** Whole-body fat mass (day 26). **(D)** Whole-body lean mass (day 26). *p<0.05, ***p<0.001 compared to DIO vehicle, ^^^p <0.001 compared to semaglutide (oneway-ANOVA with Tukey's multiple comparisons test).

3 Food intake and biochemical parameters

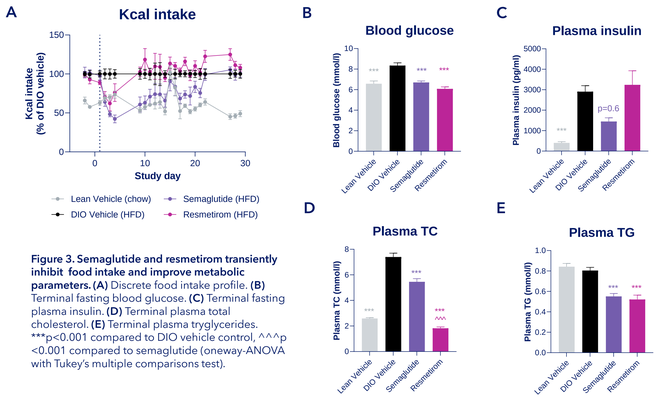


Figure 3. Semaglutide and resmetirom transiently inhibit food intake and improve metabolic parameters. **(A)** Discrete food intake profile. **(B)** Terminal fasting blood glucose. **(C)** Terminal fasting plasma insulin. **(D)** Terminal plasma total cholesterol. **(E)** Terminal plasma tryglycerides. ***p<0.001 compared to DIO vehicle control, ^^^p <0.001 compared to semaglutide (oneway-ANOVA with Tukey's multiple comparisons test).

4 Energy Expenditure

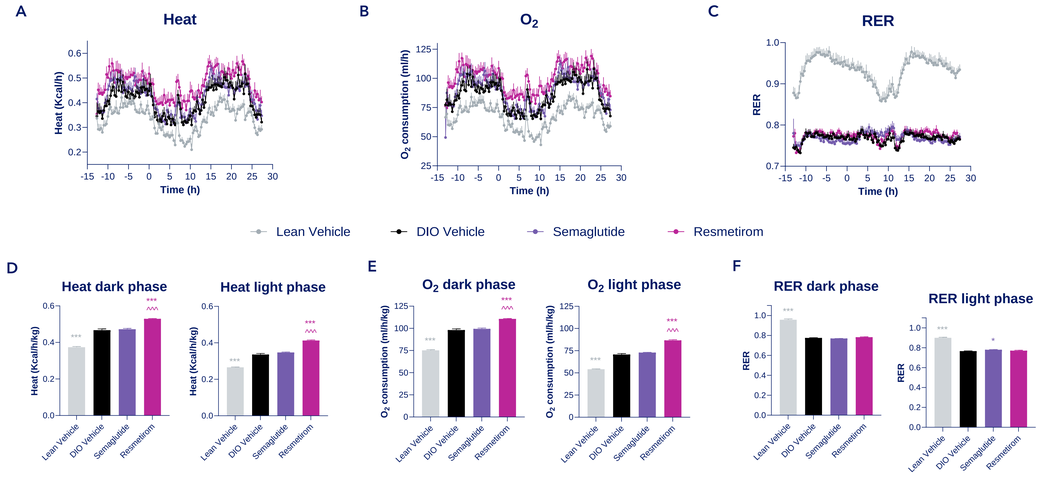


Figure 3. Resmetirom and semaglutide have differential effect on energy expenditure after 4 weeks of treatment. **(A)** Heat production profile. **(B)** Oxygen consumption profile. **(C)** Respiratory exchange ratio profile. **(D)** Heat production adjusted by body weight during dark and light phase. **(E)** Oxygen consumption adjusted by body weight during dark and light phase. **(F)** Respiratory exchange ratio during dark and light phase. *p<0.05, ***p<0.001 compared to DIO vehicle control, ^^^p <0.001 compared to semaglutide (oneway-ANOVA with Tukey's multiple comparisons test).

Conclusion

Semaglutide and resmetirom improve metabolic outcomes by different modes of action:

+ **Whereas semaglutide induces robust weight loss in DIO mice, resmetirom shows marginal effects on body weight**
+ **Semaglutide, but not resmetirom, suppresses food intake**
+ **The compounds equally reduce blood glucose and plasma triglyceride levels**
+ **Only semaglutide improves hyperinsulinemia while resmetirom shows greater cholesterol-lowering efficacy**
+ **Only resmetirom stimulates energy expenditure**

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