Metabolic Effects of Tirzepatide and Semaglutide: Energy Expenditure and Adaptations During and After Treatment

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Background & Aim

Obesity pharmacotherapy has significantly improved weight management, with semaglutide (GLP-1 receptor agonist) and tirzepatide (dual GLP-1 and GIP receptor agonist) demonstrating substantial efficacy in reducing body weight. These drugs primarily act by suppressing appetite and improving glucose metabolism. However, their acute and long-term effects on energy expenditure and metabolic adaptations following treatment withdrawal' remain poorly understood. The present study aimed to characterize the effect of semaglutide and tirzepatide on chronic energy expenditure in diet-induced obese mice at thermoneutrality.

Methods

Male C57BL/6J mice were fed a high-fat diet (60 kcal-% fat) for 20 weeks. The diet-induced obese (DIO) mice were acclimatized to thermoneutrality (28◦ C) for two weeks prior to study start and randomized into treatment groups based on body weight. DIO mice were administered (QD) with vehicle, semaglutide (10 nmol/kg, SC) or tirzepatide (10 nmol/kg, SC) for 4 weeks, followed by a two-week washout period. EE was continuously monitored in real-time with indirect calorimetry alongside measurements of food and water intake and physical activity levels using a Phenomaster system (TSE Systems, Berlin, DE).

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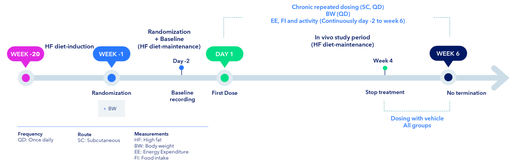
1 Study outline and group overview



Group	Treatment	Number of animals	Animal model	Route of administration	Dosing Frequency	Dosing Concentration
1	Vehicle	8	DIO mouse	SC	QD	NA
2	Semaglutide	8	DIO mouse	SC	QD	10 nmol/kg
3	Tirzepatide	8	DIO mouse	SC	QD	10 nmol/kg

Figure 1: Study outline.

2 Body weight

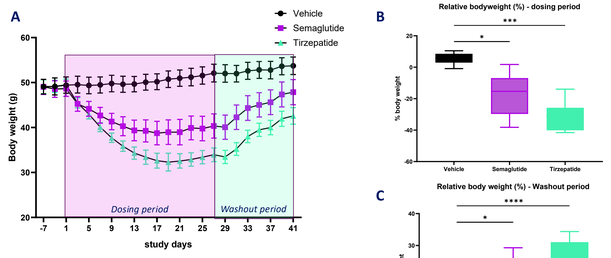


Figure 2: Body weight profile during treatment and treatment withdrawal. (A) Absolute body weight (g). **(B)** Body weight change at day 28 relative to baseline (day 1). **(C)** Body weight change at day 42 relative to day 28. *p<0.05, ***p<0.001, ****p<0.001 compared to DIO vehicle (Tukey's multiple comparisons test).

3 Food intake

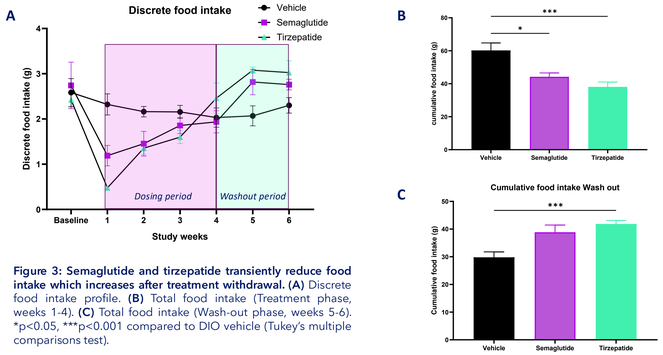


Figure 3: Semaglutide and tirzepatide transiently reduce food intake which increases after treatment withdrawal. (A) Discrete food intake profile. **(B)** Total food intake (Treatment phase, weeks 1-4). **(C)** Total food intake (Wash-out phase, weeks 5-6). *p<0.05, ***p<0.001 compared to DIO vehicle (Tukey's multiple comparisons test).

4 Energy expenditure (heat production)

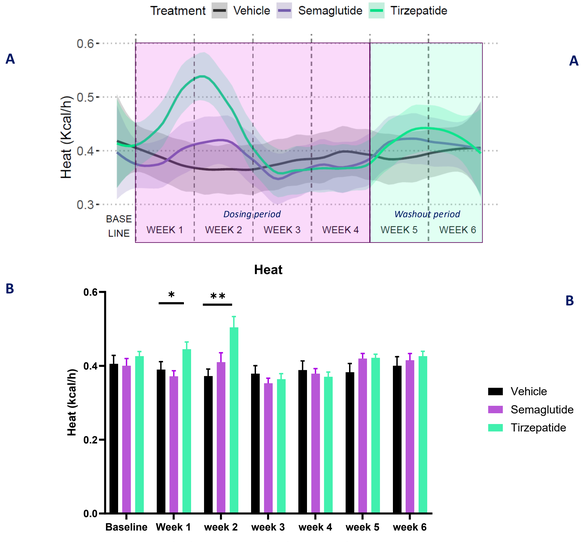


Figure 4: Tirzepatide, but not semaglutide, transiently increases energy expenditure. (A) Energy expenditure profile (heat production). **(B)** Weekly average heat production. *p<0.05, **p<0.001 compared to DIO vehicle. (Tukey's multiple comparisons test).

5 Respiratory exchange ratio (RER)

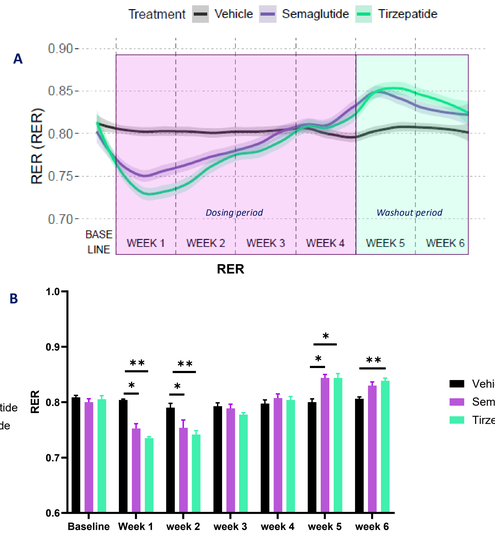


Figure 5: Semaglutide and tirzepatide transiently decrease RER, which increases after treatment withdrawal. (A) Respiratory exchange ratio. **(B-D)** Weekly average respiratory exchange ratio. *p<0.05, **p<0.001 compared to DIO vehicle. (Tukey's multiple comparisons test).

6 Locomotor activity

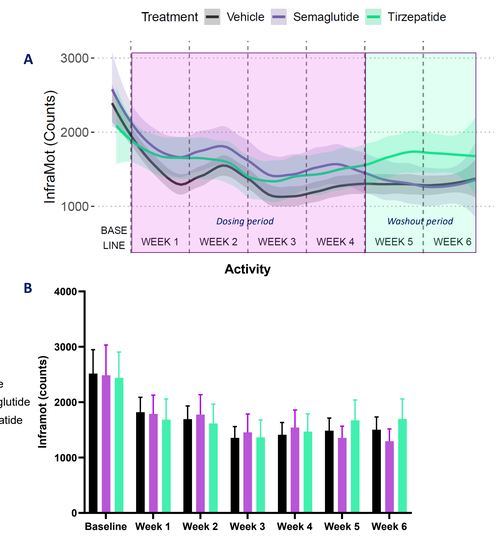


Figure 6: Semaglutide and tirzepatide have no effect on overall locomotor activity. (A) Activity profile. **(B)** Weekly average activity.

Conclusion

Semaglutide and tirzepatide equally reduce body weight and food intake, but elicit distinct metabolic adaptations, in DIO mice:

- Tirzepatide, but not semaglutide, transiently increases energy expenditure (EE) independently of physical activity, indicating a direct metabolic effect.
- During treatment, both agents lower respiratory exchange ratio (RER), indicating a shift in substrate utilization towards increased fat oxidation.
- Treatment withdrawal result in rapid body weight regain accompanied by a compensatory increase in food intake and RER, suggesting a shift to carbohydrate utilization.

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