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Spotlight on the Effects of Incretin-Based Therapies on Metabolic and Muscular Homeostasis: A Comparative Study of GLP-1, GIPR, and GCGR Multi-Target Agonists

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Background

The global rise in metabolic diseases like type 2 diabetes and obesity burdens healthcare systems. Advances in metabolic regulation have led to incretin-based therapies improving glycemic control and weight loss. Recognized as the Breakthrough of the Year by *Science*, GLP-1 agonists have paved the way for dual and triple target agonists, which enhance outcomes by combining GLP-1 with GIP or GCGR agonism, improving metabolism, insulin sensitivity, and reducing side effects. This study evaluates the effects of GLP-1 agonist semaglutide, dual-target agonist tirzepatide, and triple-target agonist retatrutide on glycemic control, weight loss, body composition, and muscle function in a humanized mouse model.

Method

Male h-GLP1-r-C57BL6/J mice (28 weeks old, ~55g) were divided into four groups and treated subcutaneously with vehicle, semaglutide, tirzepatide, or retatrutide daily for 38 days. Daily recordings were made of body weight and food intake. Assessments were conducted for body composition, energy expenditure, muscle contractility, muscular function (grip strength tests, suspension experiments, and treadmill assessments), and bone density. On day 39, the mice were euthanized for tissue and blood sample collection.

Results

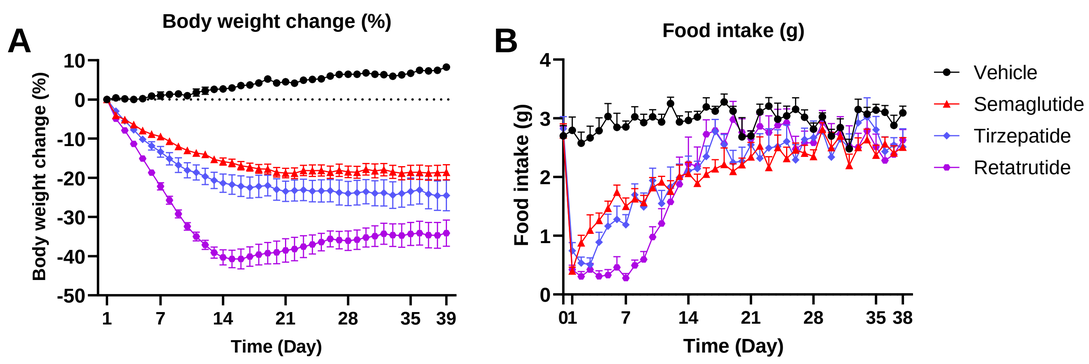

Figure 1. Body weight change (A) and daily food intake (B) in hGLP-1r C57BL/6J mice following administration of semaglutide, tirzepatide, and retatrutide.

As of day 38, the vehicle group showed a 7.40% weight increase, while the semaglutide, tirzepatide, and retatrutide treatment groups exhibited weight reductions of 18.7%, 24.54%, and 34.67%, respectively. Remarkably, retatrutide achieved a peak body weight reduction of 40.69% by day 16. Food intake dropped significantly in all treatment groups shortly post-dose, indicating a strong anorectic effect. Rebounding occurred in all groups, with retatrutide exhibiting a slower rebound than the other treatments.

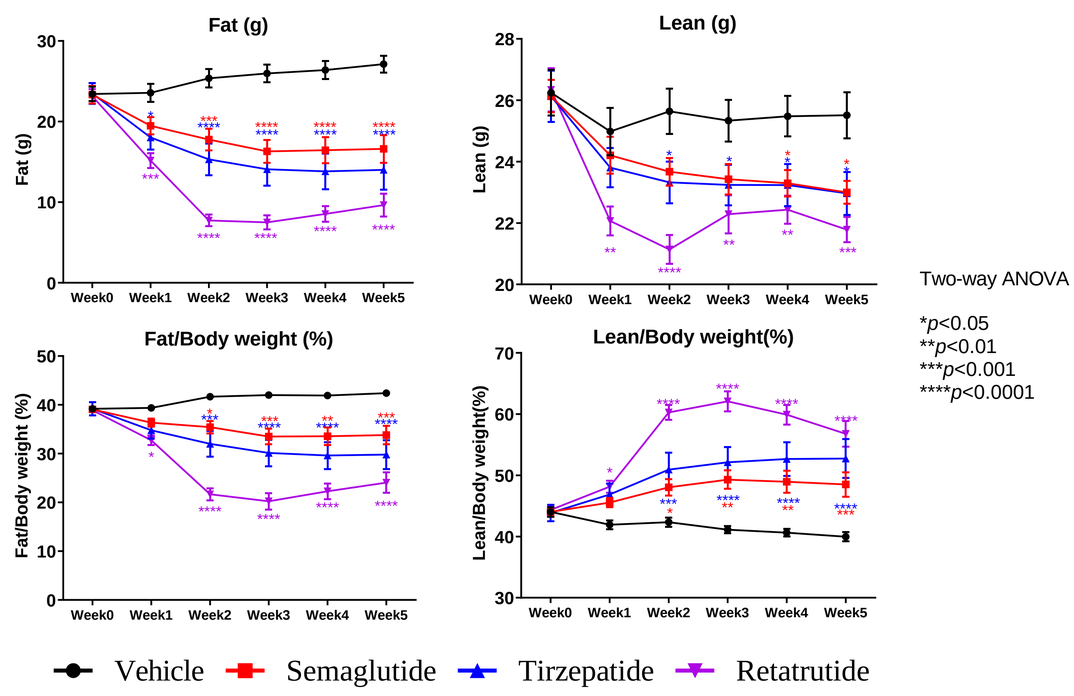

Figure 2. Body composition in hGLP-1r C57BL/6J mice following administration of semaglutide, tirzepatide, and retatrutide.

All three treatments reduced the fat-to-body weight ratio: retatrutide to 22.27%, tirzepatide to 29.6%, and semaglutide to 33.56%, compared to 41.92% in the vehicle group. Meanwhile, the muscle-to-body weight ratio was: retatrutide at 59.9%, tirzepatide at 52.68%, and semaglutide at 48.95%, compared to 40.62% in the vehicle group.

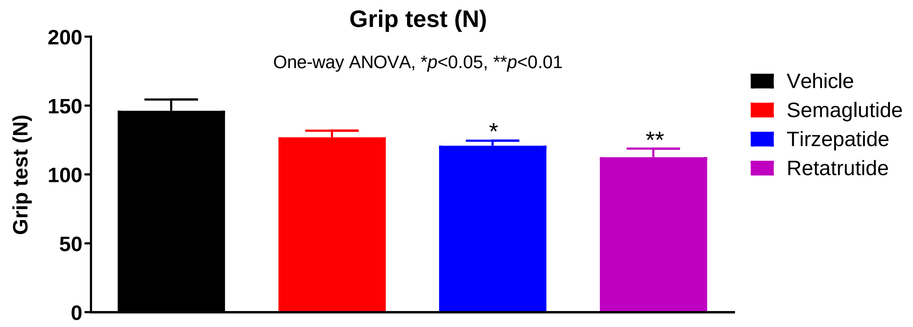

Figure 3. Grip strength in hGLP-1r C57BL/6J mice following administration of semaglutide, tirzepatide, and retatrutide.

Grip strength was significantly lower in the retatrutide and tirzepatide groups than in the vehicle control.

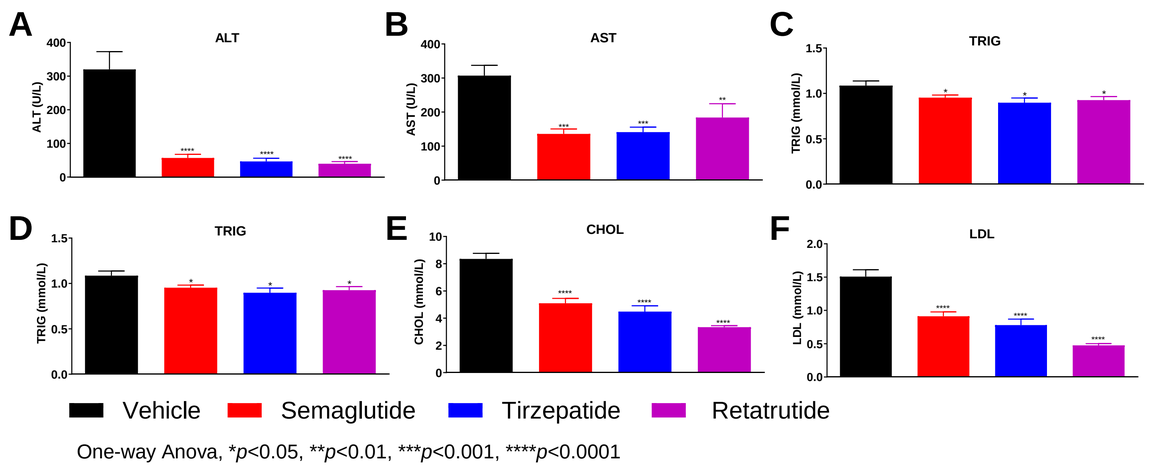

Figure 4. ALT (A), AST (B), TRIG (C), CHOL (D), HDL (E), and LDL (F) levels in plasma of hGLP-1r C57BL/6J following administration of semaglutide, tirzepatide, and retatrutide.

Following administration, levels of TG, TC, HDL-C, LDL-C, AST, and ALT were significantly decreased compared to the vehicle group, indicating improvements in lipid metabolism and a shift toward restored liver function.

Summary

Our study shows that the GLP-1 agonist semaglutide, dual-target agonist tirzepatide, and triple-target agonist retatrutide significantly reduce body weight and fat mass in a humanized diet-induced obesity (DIO) mouse model. Retatrutide showed the most pronounced effects on fat loss, though it slightly compromised muscular function. Further analyses on energy expenditure, tissue/fat weight, liver/renal function, and histopathology will provide more insights.

References

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