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Targeting the CB1 Receptor for Enhanced Obesity Management: Efficacy Comparison of Rimonabant and GLP-1 Receptor Agonist in Diet-Induced Obesity

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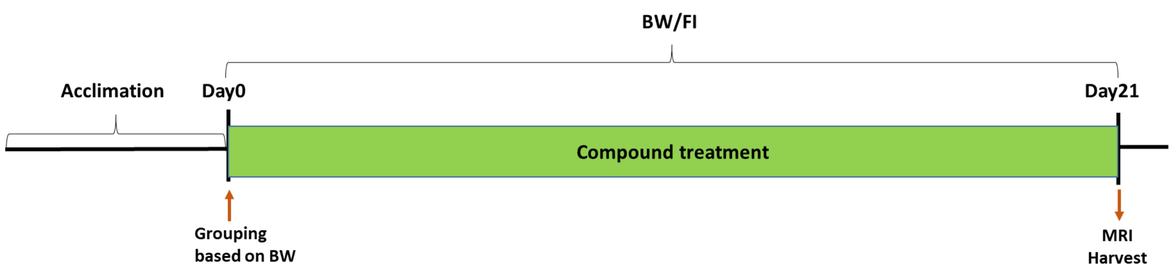
Introduction

Obesity is a significant global health crisis that increases the risk of type 2 diabetes, cardiovascular disorders, and certain cancers, while also negatively impacting bone health, reproductive function, and overall quality of life. Since 1990, adult obesity has more than doubled, and adolescent obesity has quadrupled. By 2022, 16% of adults and 160 million children and adolescents were living with obesity, with 1 in 8 people worldwide affected[1]. Despite promising advancements like GLP-1 receptor agonists and dual/triple target therapies, concerns about long-term safety, tolerability, accessibility, variable efficacy, and the potential weight regain after medication discontinuation remain[2].

The cannabinoid-1 (CB1) receptor is emerging as a promising target for obesity treatment due to its critical role in regulating energy balance, appetite, and metabolism. Although rimonabant, a CB1 receptor antagonist, was withdrawn from the market due to psychiatric side effects[3], the strategy of targeting the CB1 receptor remains promising. This study aims to compare the efficacy of rimonabant with GLP-1 receptor agonists on body weight reduction, body composition changes, and other metabolic parameters using a diet-induced obesity (DIO) mouse model.

Method

Five-week-old male C57BL/6J mice were fed a high-fat diet (60% kcal, D12492) for 25 weeks to induce diet-induced obesity (DIO). Mice were randomized into three treatment groups: vehicle control, Rimonabant (10 mg/kg, orally, once daily for 21 days), or Semaglutide (0.04 mg/kg, subcutaneously, every three days for 21 days). Body weight and food intake were monitored daily, while adipose tissue mass and metabolic biomarkers (e.g., leptin, insulin) were assessed at the endpoint.



Results

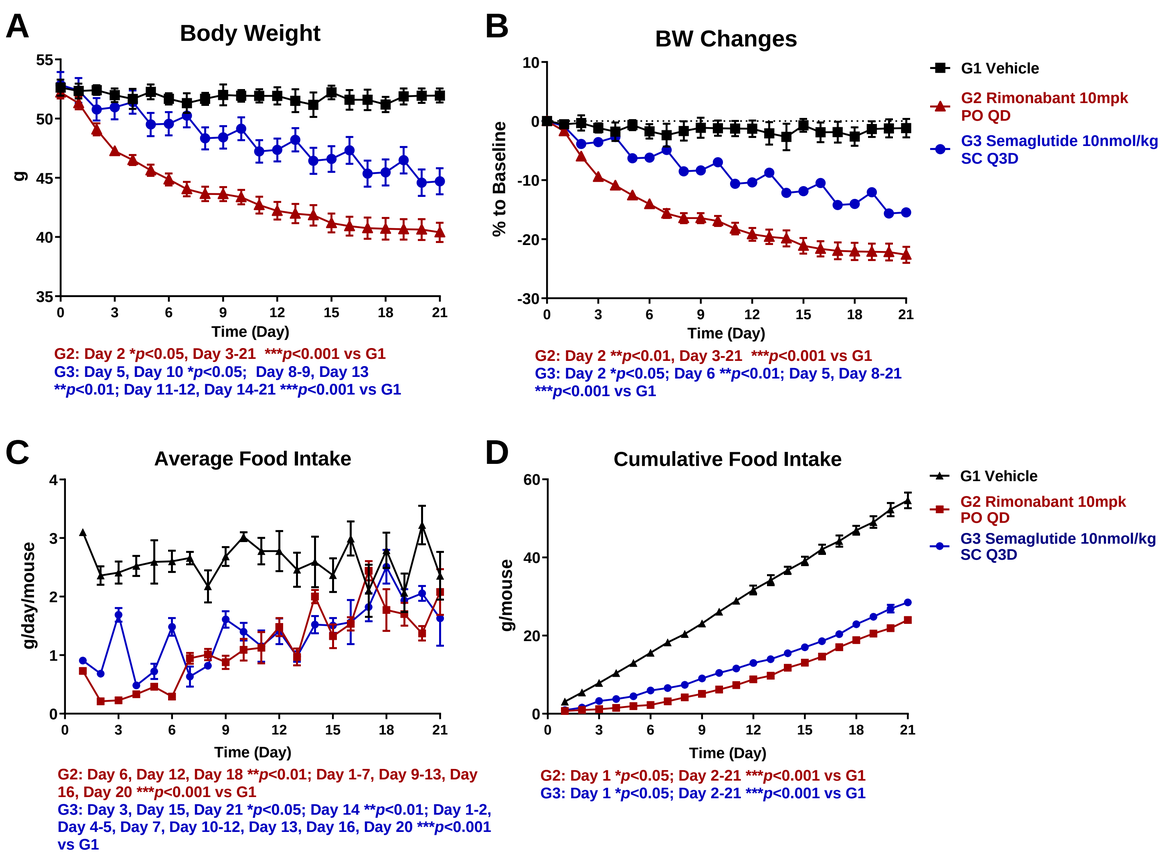


Figure 1. Body Weight and Food Intake in Diet-Induced Obese (DIO) Mice After Treatment. DIO mice were administered Rimonabant at a dose of 10 mg/kg once daily (QD) via oral gavage or Semaglutide at a dose of 0.04 mg/kg every 3 days via subcutaneous injection. (A, B) Body weight and body weight changes. (C, D) Average and cumulative food intake.

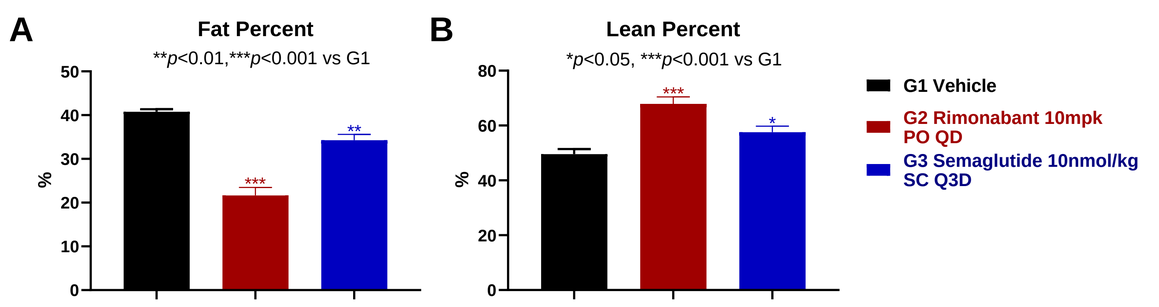


Figure 2. Analysis of Body Composition (A) Fat mass percentages and (B) lean mass percentages after 21 days of compound administration.

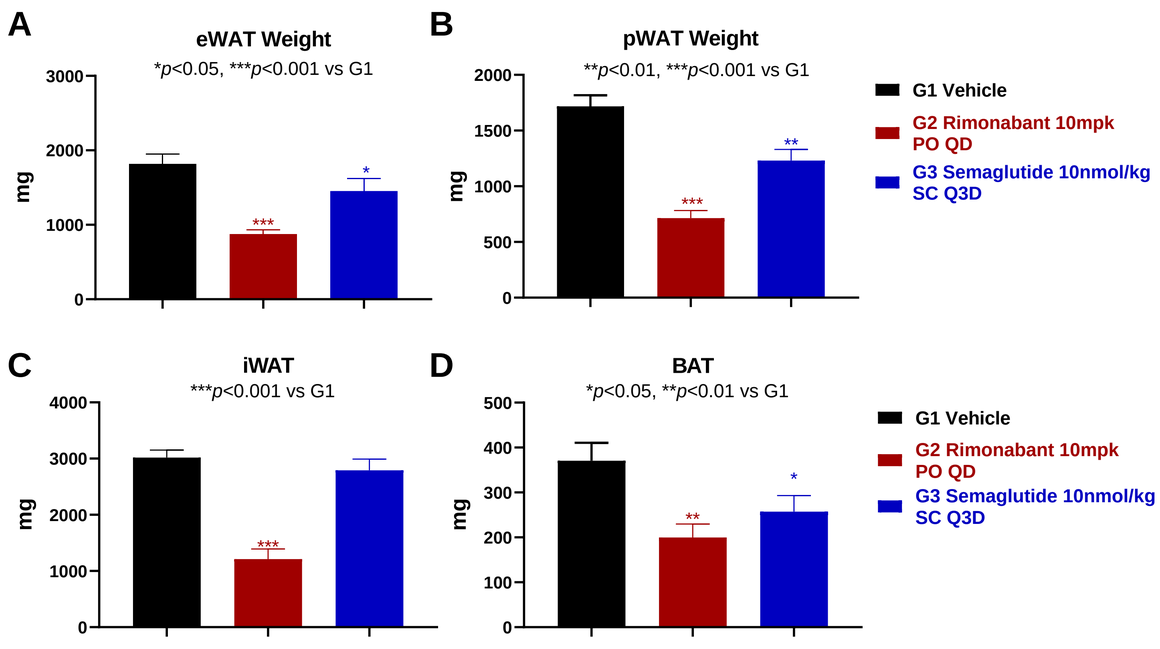


Figure 3. Quantification of Adipose Tissue. Weight of (A) epididymal white adipose tissue (eWAT), (B) perirenal white adipose tissue (pWAT), (C) inguinal white adipose tissue (iWAT), and (D) scapular brown adipose tissue (BAT) quantified after 21 days of compound treatment.

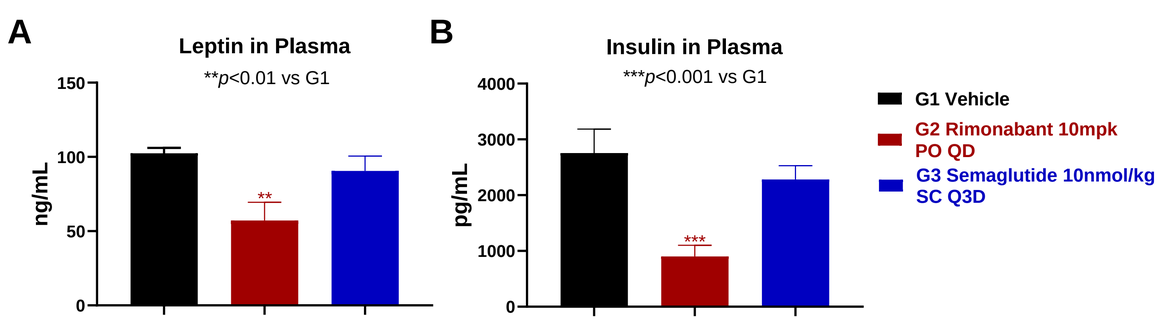


Figure 4. Quantification of Leptin and Insulin. (A) Fasting plasma leptin and (B) fasting plasma insulin concentrations measured after 21 days of compound treatment.

Summary

This study demonstrates that rimonabant, a selective CB1 receptor antagonist, outperformed semaglutide in reducing body weight and key metabolic parameters. Although historical safety concerns have restricted the clinical application of CB1 antagonists, these results suggest that the development of next-generation CB1 antagonists with enhanced safety profiles could offer a promising avenue for advancing obesity therapeutics.

References

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