Synergistic activity of GLP-1 peptide analog XW003 and the long-lasting GIP receptor agonist XW017 in a diet induced obese mouse model

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP, also known as gastric inhibitory polypeptide) are small peptide hormones termed incretins. Incretins are produced by the gut following food intake and act to stimulate insulin secretion and lower blood sugar. Incretins have additional effects on the digestive tract, liver, pancreas, and central nervous system to maintain metabolic health.

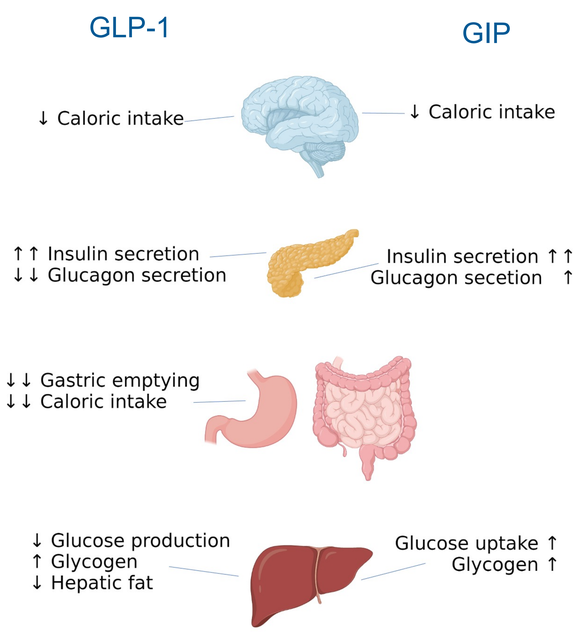
GLP-1 receptor agonists have shown promise for treating obesity, type 2 diabetes, and nonalcoholic steatohepatitis (NASH). GIP receptor agonists have the potential to work synergistically with GLP-1 agonists to enhance efficacy.

XW003 is a GLP-1 peptide analog that is currently in Phase 2 clinical studies in patients with type 2 diabetes and obesity. XW017 is a long-lasting GIP peptide analog that is in preclinical development as a potential combination partner for XW003.

AIM

To investigate GLP-1 peptide analog, XW003, alone or in combination with GIP peptide analog XW017 in a diet induced obesity (DIO) mouse model.

Effects of incretins on physiology



GLP-1 and GIP are peptide hormones that act on the physiology of the brain, pancreas, digestive tract, and liver. Figure adapted from Nauck 2021[2], created with Biorender.

METHOD

We investigated GLP-1 peptide analog, XW003 (3 nmol/kg), alone or in combination with a long-lasting GIP peptide analog, XW017 (3, 10, 30, 100 nmol/kg), in the diet induced obesity (DIO) mouse model.

DIO mice can be used to model metabolic conditions including obesity and diabetes.

GLP-1 and GIP peptide analogs were dosed subcutaneously (SC) QD for 21 days [n=5 mice per experimental group, and n=4 in the vehicle only group]. We evaluated the activity of a dual GLP-1/GIP receptor agonist, tirzepatide (10 nmol/kg) in parallel in this mouse model.

Animals and Diet

- C57BL/6 mice were placed on a high fat diet for 17 weeks
- High fat diet was sourced from Research Diets, Inc. (#D12492)
- An average body weight of 50 g was achieved after 17 weeks on the diet

Dosing

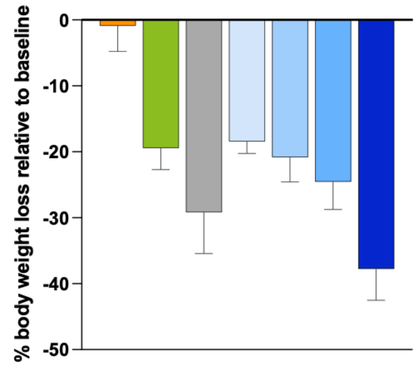
- Daily subcutaneous (SC) dosing for 21 days
- Body weights were measured daily for each animal

Treatments

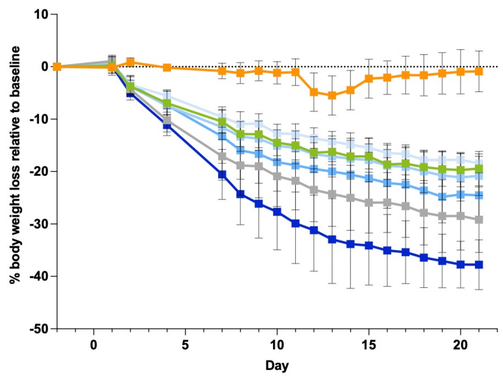
- XW003: a GLP-1 peptide analog
- XW017: a GIP peptide analog
- Tirzepatide: a dual GLP-1 & GIP analog peptide

RESULTS

Total body weight loss on Day 21 (%)



Body weight loss over time (%)



Total percent body weight loss compared to baseline was measured on Day 21 (top panel). Percent body weight loss compared to baseline on each study day (bottom panel). Mean and standard deviation are plotted.

- The treatments were all well tolerated, and all mice survived until the end of the study
- Treatment of mice with the GIP peptide analog XW017 alone did not result in significant weight loss (data not presented)
- Combination of XW003 (GLP-1) with XW017 (GIP) showed an enhanced effect in inducing body weight loss compared to XW003 peptide alone
- Increasing XW017 (GIP) doses while maintaining the XW003 dose at 3 nmol/kg increased body weight loss in a dose dependent manner
- Daily SC doses of 10 nmol/kg tirzepatide achieved 29.2% body weight loss by Day 21
- Daily SC doses of 10 nmol/kg of XW003 + 100 nmol/kg of XW017 achieved 37.8% body weight loss by Day 21

CONCLUSIONS

- Combinatory treatment of GLP-1 and GIP receptor agonists showed a synergistic effect on promoting weight loss in a mouse model of obesity
- The GLP-1:GIP receptor agonist ratio impacted the total body weight loss achieved in the obesity mouse model
- Separating GLP-1 (XW003) and GIP (XW017) receptor agonist activity into two separate peptides enables the selection of an optimized GLP-1:GIP ratio for improved efficacy and tolerability in future clinical trials

REFERENCES

1. **Nauck MA** The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. *Diabetes, Obesity and Metabolism* 2021; 23(s3): 5-29.
2. **Chao-Yung Wang et al.** A mouse model of diet-induced obesity and insulin resistance. *Methods Mol Biol.* 2012; 821: 421–433.

CONTACT INFORMATION

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