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DA-1726, a Balanced GLP1R/GCGR Dual Agonist, Effectively Controls both Body Weight and Blood Glucose

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Monday Jun 6, 2022 12:00 PM - 1:00 PM

American Diabetes Association's 82nd Scientific Sessions, June 3-7, 2022 in New Orleans, Louisiana

DONG-A ST

BACKGROUND

- **Oxyntomodulin is a gut hormone released from intestinal L-cells after meal ingestion and represents dual agonism of the GLP-1 receptor and glucagon receptor.**

- **Oxyntomodulin increases energy expenditure through glucagon receptors and increases appetite suppression and insulin secretion through GLP-1 receptor activation, ultimately inducing weight loss and glycemic control.**

- **Unimolecular poly-agonists are peptides that can activate more than two receptors, it is very important to balance the activity of each receptor. DA-1726 is a novel long-acting oxyntomodulin analogue that represents balanced activity against GLP-1 and glucagon receptors, and it is expected to effectively control body weight and blood glucose at the same time.**

- **Herein, we evaluated the weight loss effect and mechanism of DA-1726 in obese mice and compared the anti-obesity and anti-diabetic efficacy of DA-1726 with GLP-1 agonist in obese mice with hyperglycemia.**

Diabetes 2009;58(10):2258-2266.

METHODS

Receptor Reporter Assay

- The activity was confirmed to increase the transactivation of receptors by DA-1726 in CHO-K1 cells in which human GLP-1 receptor and glucagon receptor were transiently transfected, respectively.

Mode of Action of Body Weight Loss

- DIO mice were subcutaneously injected with DA-1726 or vehicle by every three days for 3 weeks, respectively. The pair-fed group was provided the same food amount as the average daily intake of the DA-1726 group. After final administration, the energy expenditure was measured using indirect calorimetry system for 72-hour.

Body Weight Loss in HF-DIO Mice

- DIO mice were subcutaneously injected vehicle, DA-1726, or Semaglutide twice a week for 4 weeks. Food consumption and body weight were recorded five times a week. After treatment, the gene expression of thermogenic related markers was analyzed using quantitative RT-PCR in white adipose tissue.

White Adipose Tissue Browning Analysis and Adipogenesis Assay

- Adipose tissue fixed in 10% neutral buffered formalin for more than 24 hours. After paraffin blocks were made using an embedding machine and sectioned, tissues were H&E staining. Brown fat analysis was graded from 0-3 (none, mild, moderate, extensive) according to the distribution and degree.
- Human mesenchymal stem cells were seeded and cultured for 24-hours (day(-1)). On day 0, media was replaced to differentiated media (0.5 mM IBMX, 1 µM dexamethasone, and 5 µg/ml insulin added to growth media) containing drugs and incubated for 3 days. The medium was changed every 3 days, and the cells were incubated with drug-containing differentiated media for 9 days to fully differentiate into adipocytes. On day 9, cells were fixed 10% formalin and stained with 0.2% Oil Red O, and the lipid droplets were determined under a microscope.

Glycemic Control Effect in HF-FATZO Mice

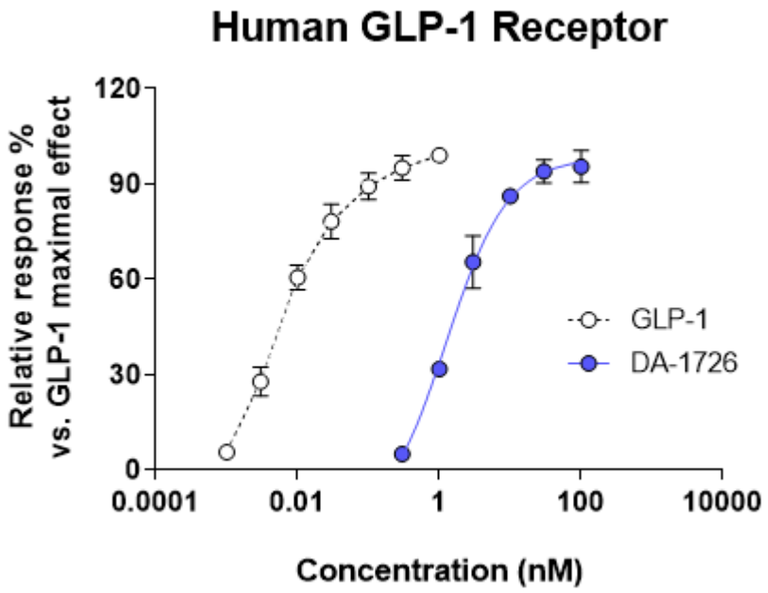
- HF-FATZO mice were injected subcutaneously with a vehicle, DA-1726, or Semaglutide every 3 days for 4 weeks. Food consumption and body weight were recorded daily, blood glucose levels were monitored every 2 weeks, and changes in HbA1c levels were measured at weeks 0 and 4. After sacrifice, the insulin resistance index, HOMA-IR, was calculated from plasma insulin and plasma glucose levels.

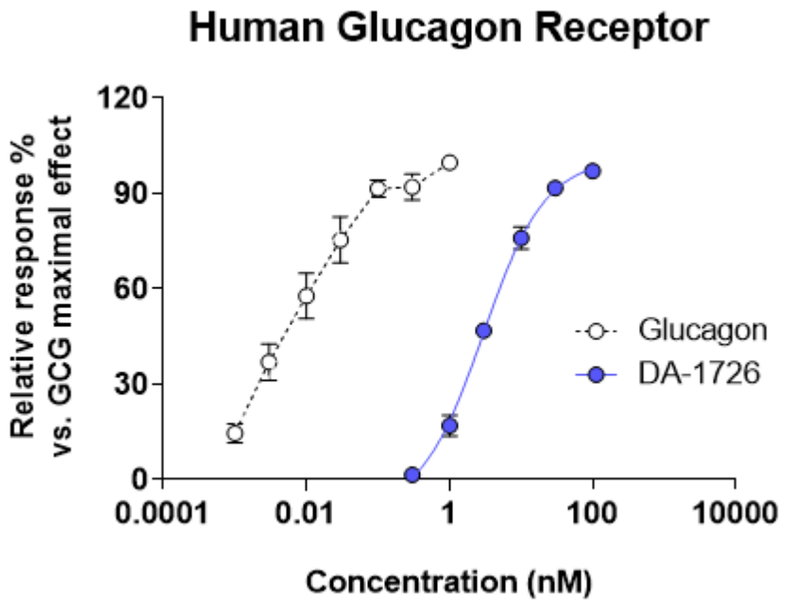
Oral Glucose Tolerance and Hypoglycemia Risk Test in Normal Mice

- Oral glucose tolerance: DA-1726 was subcutaneously administered at 6-hour prior to an oral glucose challenge. Then glucose was loaded by oral gavage and blood glucose level was measured from tail vein blood taken at designated time points.
- Hypoglycemia risk test: Overnight fasted mice were injected subcutaneously with vehicle or test articles after measurement of baseline blood glucose level. Then blood glucose level was measured from tail vein blood taken at designated time points.

RESULTS – 1. Enhanced Activation of GLP-1 or Glucagon Receptor

- **DA-1726 activated human GLP-1 and glucagon receptors and showed full efficacy compared to endogenous ligands**



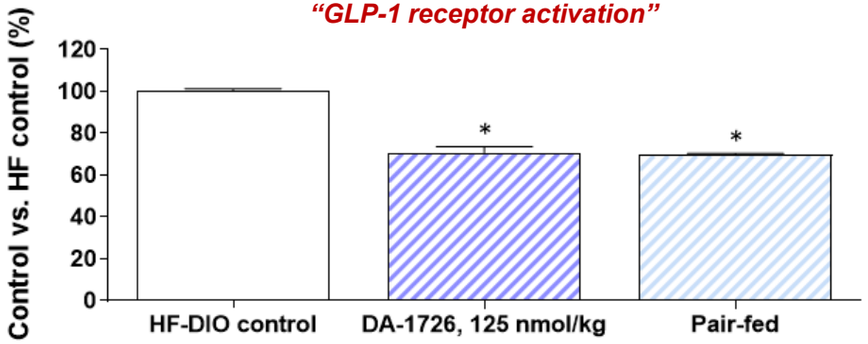


RESULTS – 2. Mode of Action of Body Weight Loss

- **The body weight loss effect of DA-1726 is caused by not only a decrease in food intake but also an increase in energy metabolism**

Cumulative Food Intake

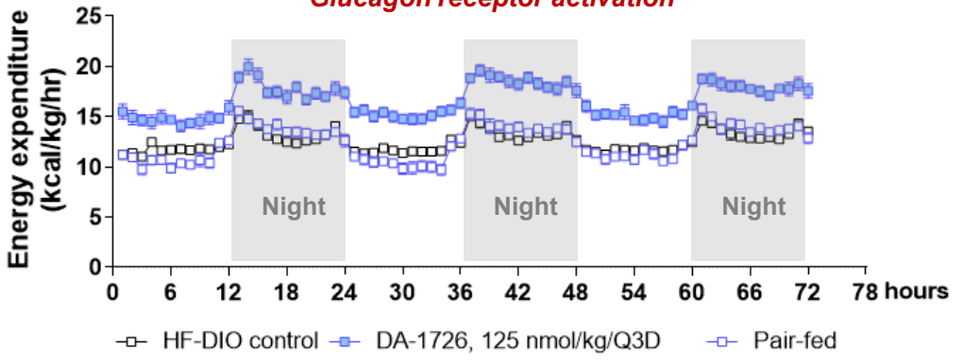
"GLP-1 receptor activation"



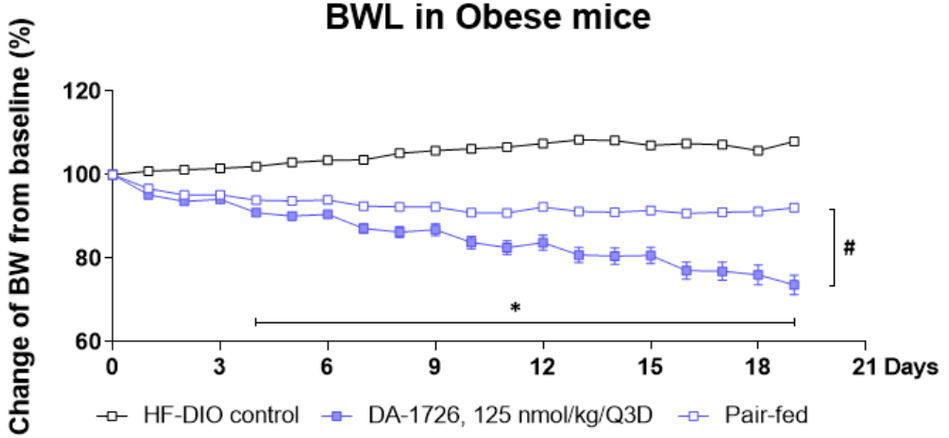
Mean ± SEM, *P<0.05 vs HF-DIO control, One-way ANOVA

Energy Expenditure

"Glucagon receptor activation"

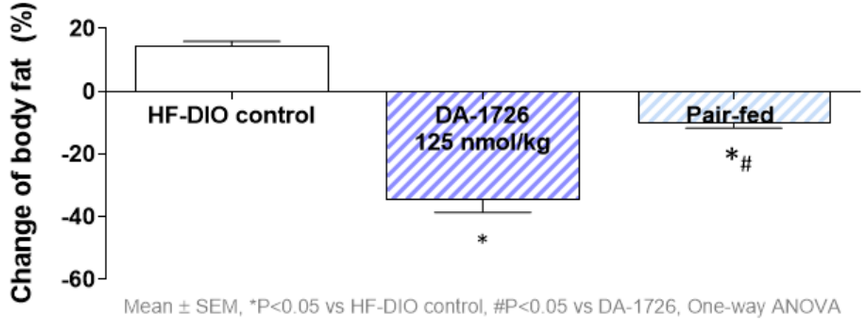


BWL in Obese mice



Mean ± SEM, *P<0.05 vs. Day0 in each group, #P<0.05 vs. HF-DIO control at final time, Two-way RM ANOVA

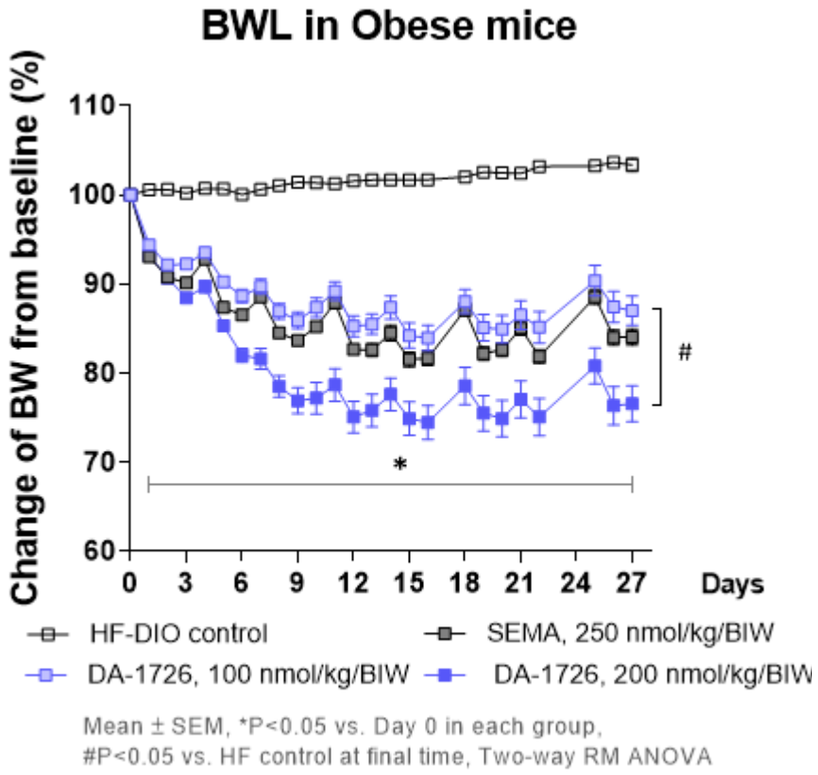
Fat Mass in Obese mice

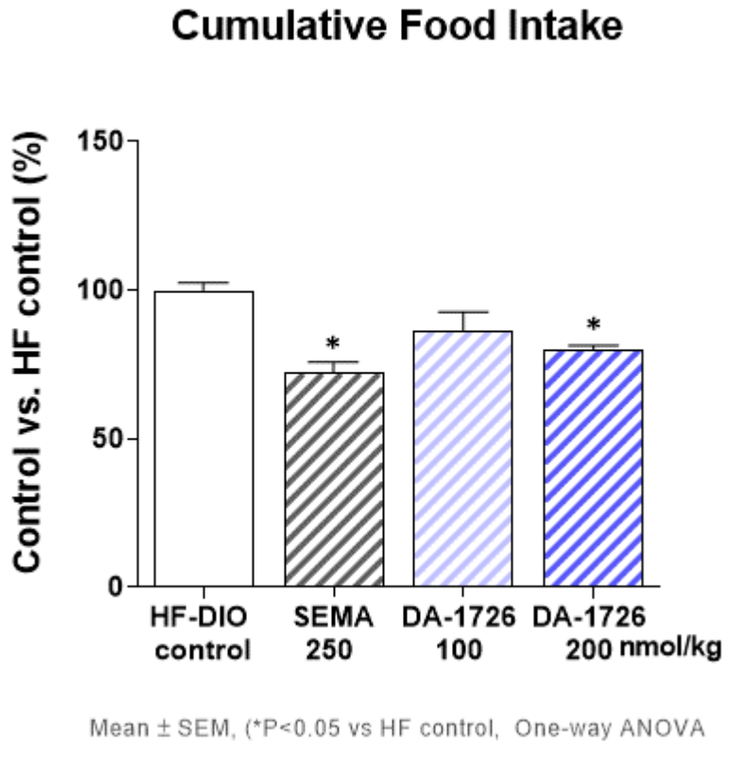


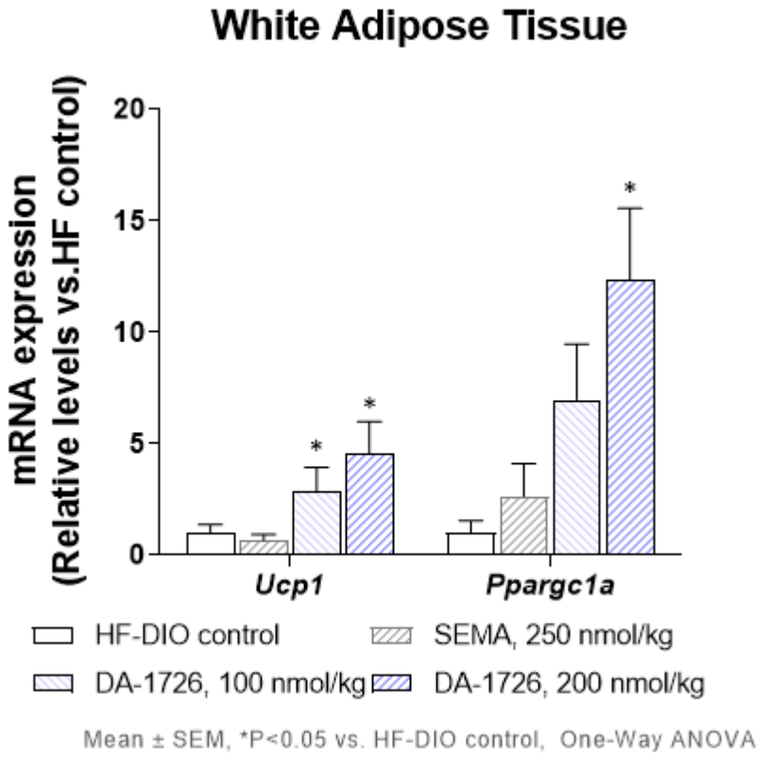
Mean ± SEM, *P<0.05 vs HF-DIO control, #P<0.05 vs DA-1726, One-way ANOVA

RESULTS – 3. Comparison with Semaglutide in Body Weight Loss

- **DA-1726 effectively reduced body weight even though more food intake when compared to the semaglutide-treated group**
- **DA-1726 significantly increased the expression of thermogenic genes (*Ucp-1* and *Ppargc1a*) in white adipose tissue**



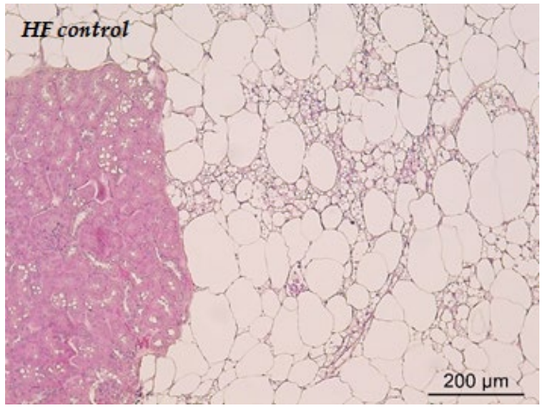


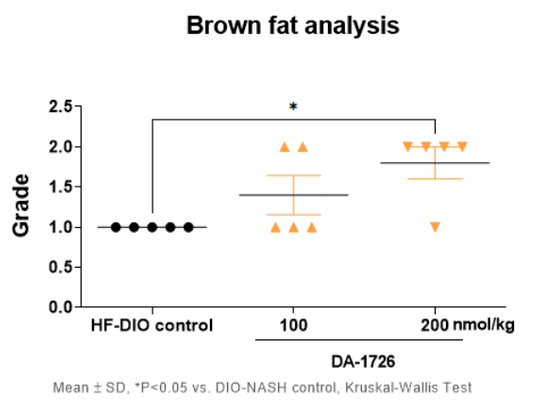


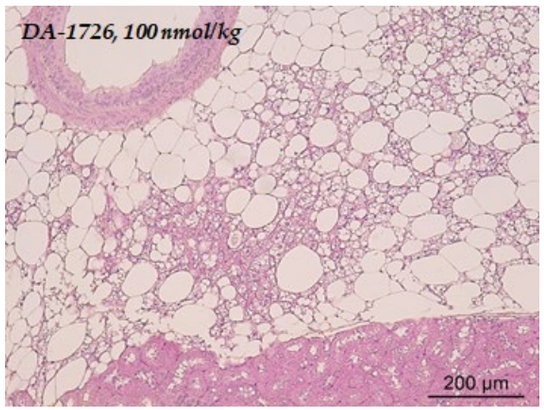
- Abbreviation: SEMA, Semaglutide

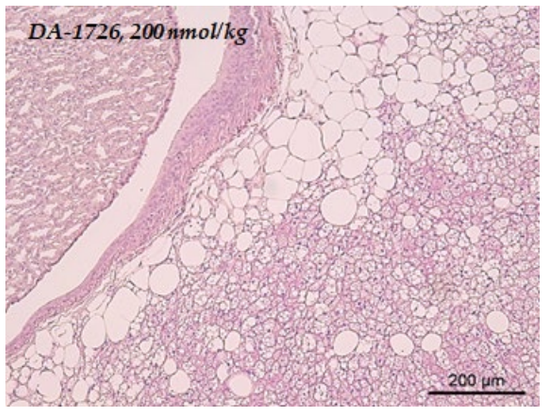
RESULTS – 4. Browning of White Adipose Tissue and Adipogenesis

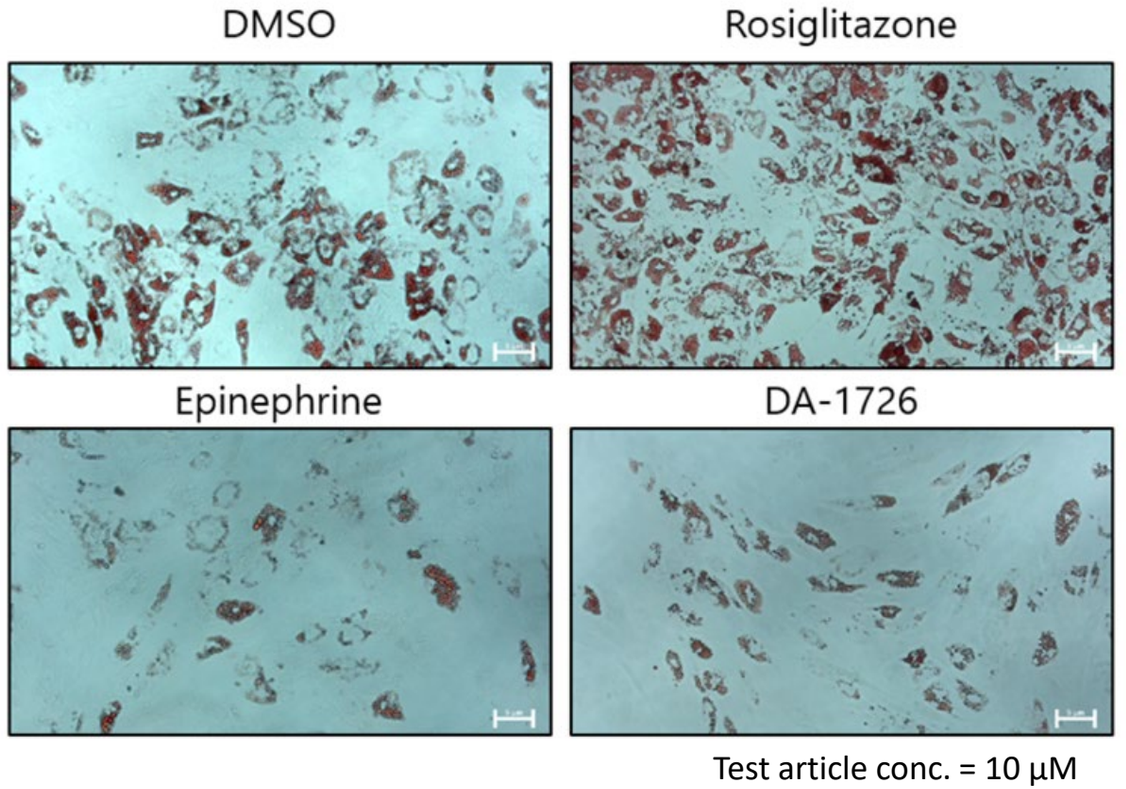
- DA-1726 increased brown adipose-like cells in perirenal white adipose tissue
- DA-1726 reduced lipid droplet formation in human mesenchymal stem cells







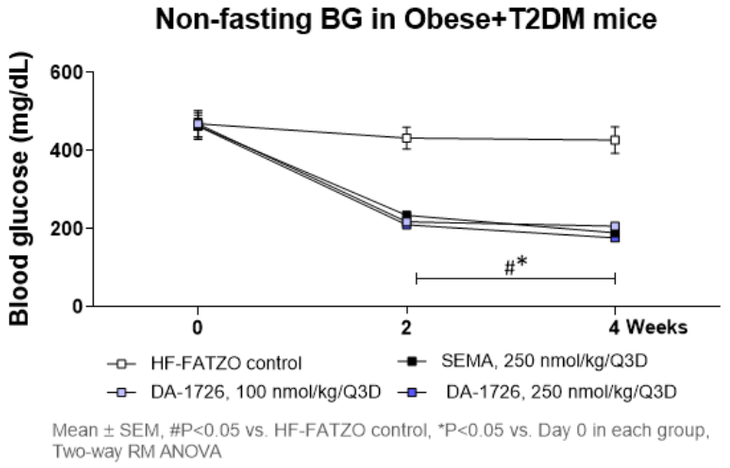




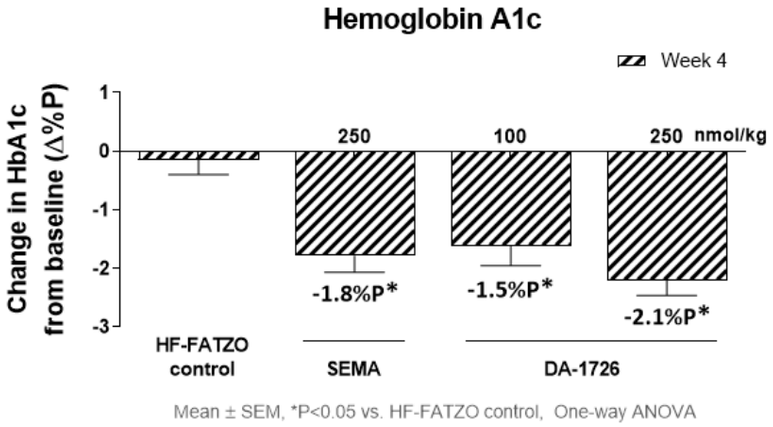
Test article conc. = 10 μM

RESULTS – 5. Comparison with Semaglutide in Glycemic Control Effect

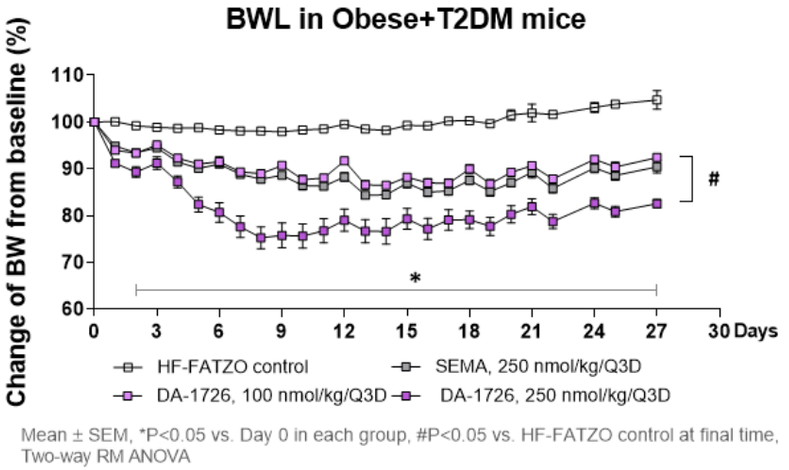
- **DA-1726 represented effective glycemic control similar to the GLP-1 receptor single agonist**
- **DA-1726 significantly reduced fasting insulin and glucose levels, thereby effectively improving insulin resistance (HOMA-IR)**



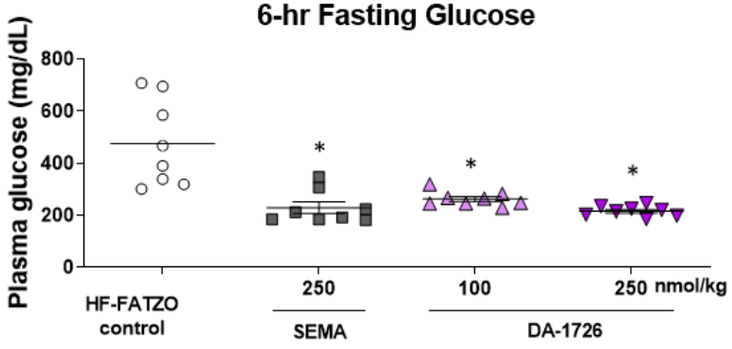
Mean ± SEM, #P<0.05 vs. HF-FATZO control, *P<0.05 vs. Day 0 in each group, Two-way RM ANOVA



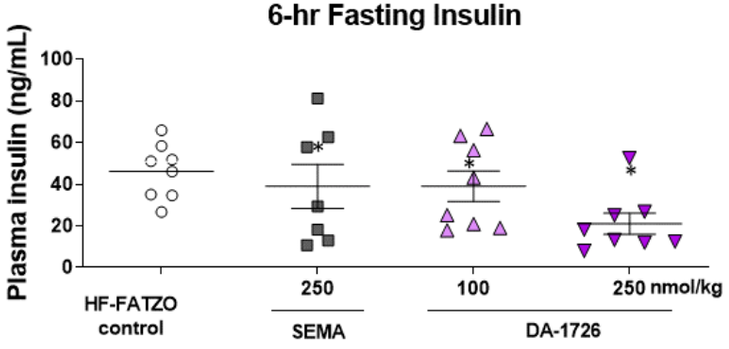
Mean ± SEM, *P<0.05 vs. HF-FATZO control, One-way ANOVA



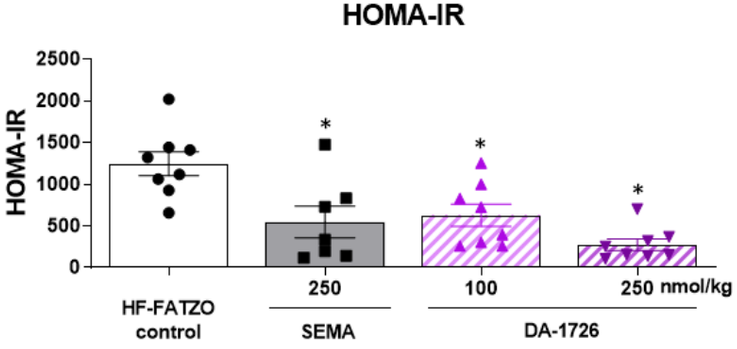
Mean ± SEM, *P<0.05 vs. Day 0 in each group, #P<0.05 vs. HF-FATZO control at final time, Two-way RM ANOVA



Mean ± SEM, *P<0.05 vs. HF-FATZO control, One-way ANOVA



Mean ± SEM, *P<0.05 vs. HF-FATZO control, One-way ANOVA

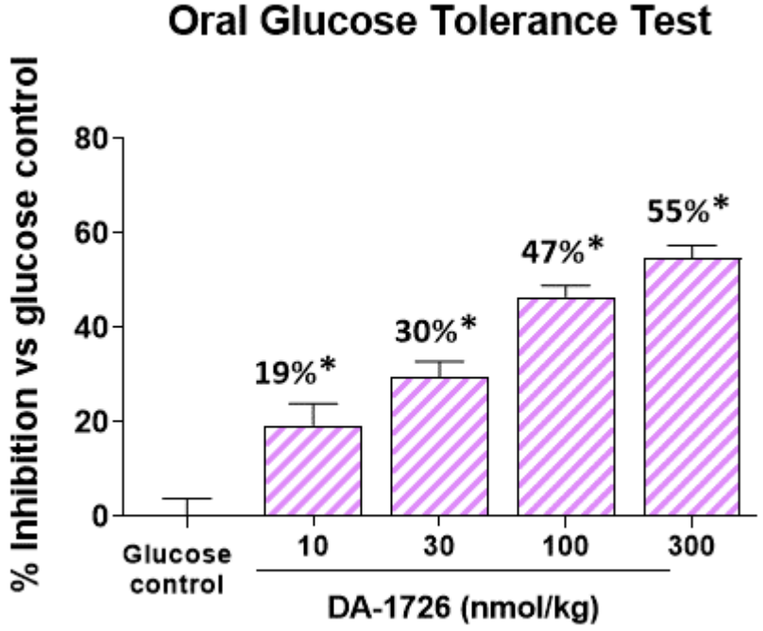


Mean ± SEM, *P<0.05 vs. HF-FATZO control, One-way ANOVA

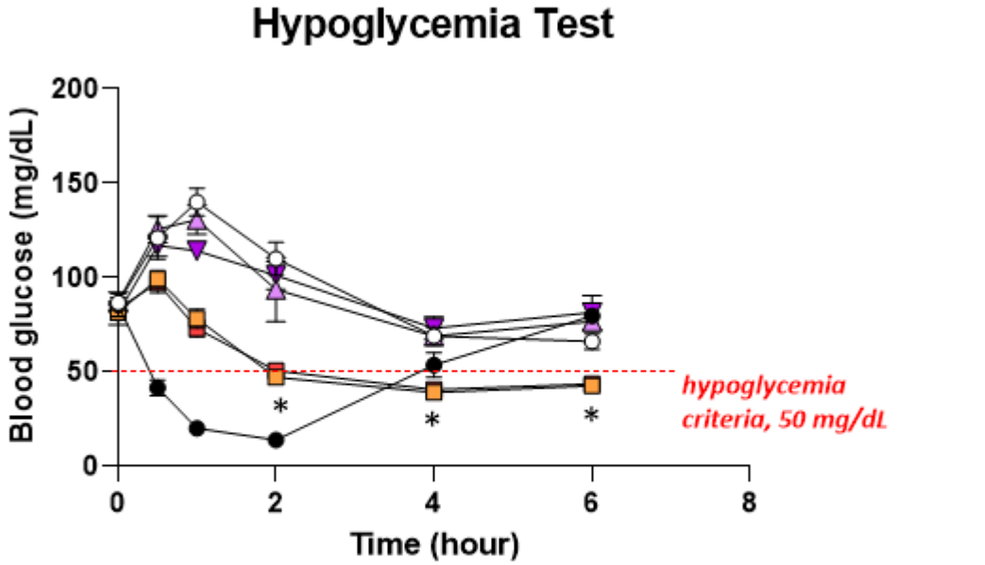
- Abbreviation: SEMA, Semaglutide

RESULTS – 6. Postprandial Glucose Control and Hypoglycemic Risk

- **DA-1726 significantly reduced postprandial glucose excursion in a dose-dependent manner**
- **There is no issue of hypoglycemia or hyperglycemia caused by DA-1726 at the same condition compared with semaglutide**



Mean ± SEM, *P<0.05 vs. Glucose contol, One-Way ANOVA



Mean ± SEM, *P<0.05 vs. 0-h SEMA group, One-Way RM ANOVA

- Abbreviation: SEMA, Semaglutide

SUMMARY

- **DA-1726 is a dual agonist with balanced activity against GLP-1 and glucagon receptors.**
- **In obese mice, body weight loss effect of DA-1726 is caused by not only a decrease in food intake but also an increase in energy metabolism.**
- **Compared to semaglutide, DA-1726 showed effective body weight loss in obese mice. And DA-1726 significantly increased the expression of thermogenic genes (*Ucp-1* and *Ppargc1a*) in white adipose tissue.**
- **DA-1726 increased brown adipose-like cells in perirenal white adipose tissue and reduced lipid droplet formation in human mesenchymal stem cells.**
- **DA-1726 has a superior body weight loss and similar glycemic control compared to semaglutide in obese and hyperglycemia mice.**
- **DA-1726 has no issue with hypoglycemia or hyperglycemia during the fasting state.**