A Novel GLP1R/GCGR Dual Agonist, DA-1726 Elicits Weight Loss Superior to Semaglutide in Diet-Induced Obese Rats

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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 appetite suppression and energy expenditure through the GLP-1 receptor and glucagon receptor activation, ultimately inducing weight loss.

- DA-1726 is a novel oxyntomodulin analogue currently being prepared for phase I clinical trials for the treatment of obesity. In previous evaluations, it exhibited excellent weight loss and equivalent or superior glycemic control efficacy compared to Semaglutide.

- Herein, we evaluated the weight loss efficacy of DA-1726 in HF-DIO rats, which are known to have good translatability to human studies.

METHODS

Receptor Reporter Assay and Adipogenesis Assay

- The activity of DA-1726 in increasing the transactivation of receptors was confirmed in CHO-K1 cells in which mouse or rat GLP-1 receptor or glucagon receptor were transiently transfected into the cells, respectively.
- Human mesenchymal stem cells were differentiated for 3 days. After 3 days, cells were treated for an additional 10 days using differentiated media containing DA-1726 alone or in combination with glucagon receptor antagonist to fully differentiate into adipocytes, and lipid droplets were analyzed by Oil Red O staining.

Dose-Dependency Study of Body Weight Loss in High-Fat Diet-Induced Obesity Rats

- DIO rats were subcutaneously injected with vehicle or DA-1726 twice a week for 4 weeks. Food consumption and body weight were recorded five times a week.

Comparative Study with Semaglutide of Body Weigh Loss in High-Fat Diet-Induced Obesity Rats

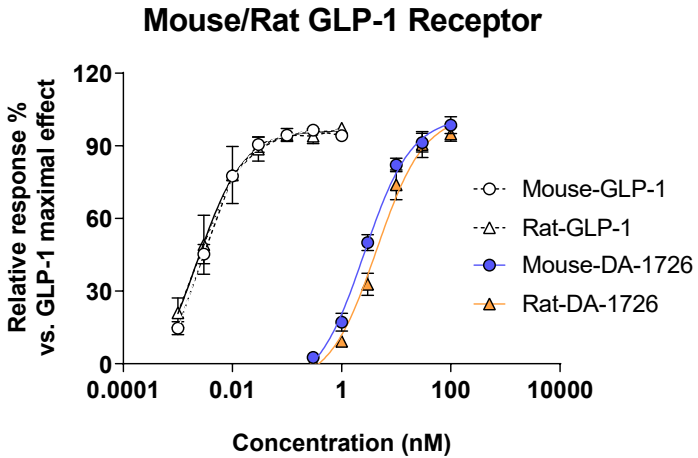
- DIO rats were subcutaneously injected with vehicle, DA-1726, or Semaglutide twice a week for 4 weeks. Food consumption and body weight were recorded five times a week. After treatment, the gene expression of thermogenic-related genes was analyzed in white adipose tissue using quantitative RT-PCR.

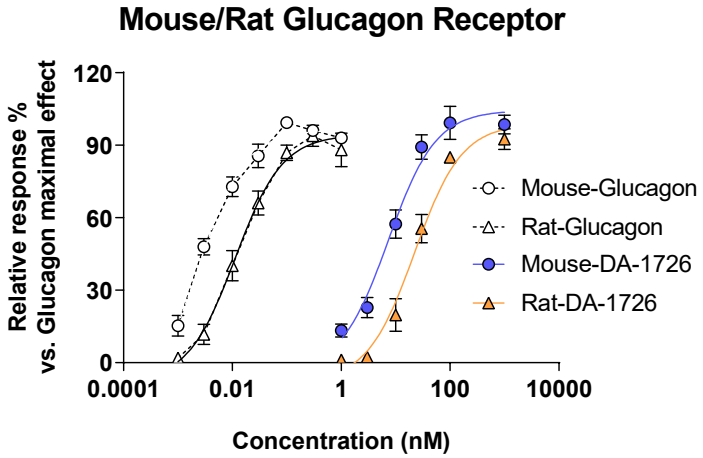
Single-Dosing Study of Changes in Energy Expenditure Markers

- DIO rats were subcutaneously injected once with vehicle, DA-1726, or Semaglutide. Food consumption and body weight were recorded daily for 3 days. After treatment, the gene expression of thermogenic-related genes was analyzed in white adipose tissue using quantitative RT-PCR.

RESULTS – 1. Differences in Drug Properties Between Mice and Rats

- ☑ **DA-1726 showed full efficacy on rodent GLP-1 and glucagon receptors**
- ☑ **The *in vitro* potency of DA-1726 on glucagon receptors in rats was less potent than in mice, although the half-life was longer in rats compared to mice**



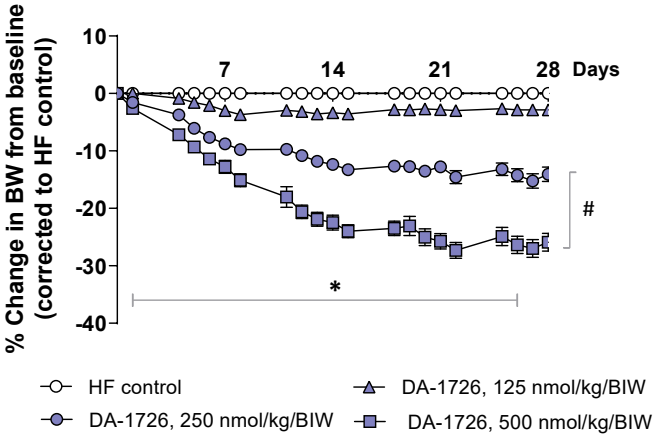


PK parameters	Mouse	Rat
Terminal $t_{1/2}$ (h)	13.8	23.1

RESULTS – 2. Dose-Dependency Study of Body Weight Loss

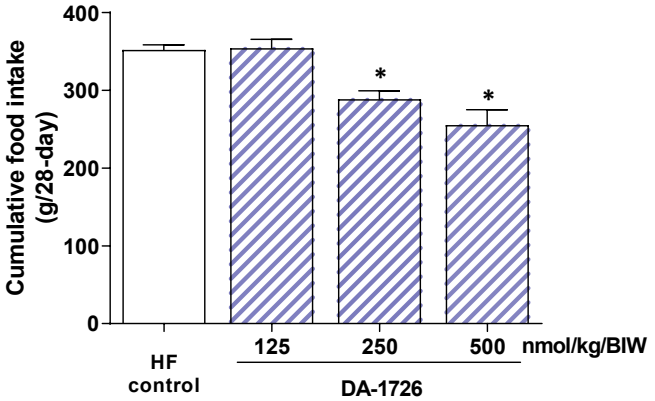
- ☑ **DA-1726 significantly reduced body weight in a dose-dependent manner**
- ☑ **The minimum effective dose of 250 nmol/kg was found in HF-DIO rats**

BWL in Obese Rats



Mean ± SEM, *P<0.05 vs. Day 0 in DA-1726 middle and high groups, #P<0.05 vs. HF control at final time, Two-way RM ANOVA

Cumulative Food Intake

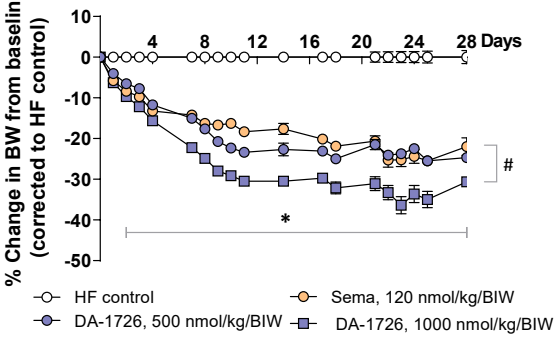


Mean ± SEM, *P<0.05 vs HF control, One-way ANOVA

RESULTS – 3. Efficacy Comparative Study with Semaglutide

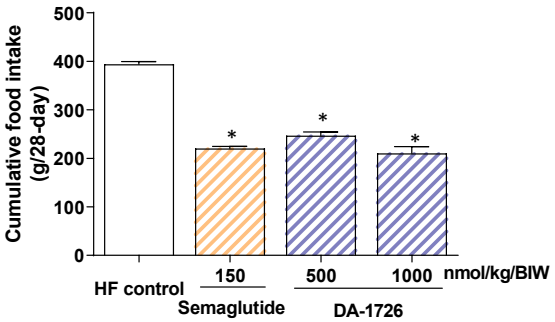
- ☑ **DA-1726 showed an excellent weight loss efficacy than Semaglutide**
- ☑ **DA-1726 exhibited an equal or greater weight loss effect compared to semaglutide, despite having a similar or higher food intake**
- ☑ **The high-dose DA-1726 significantly increased the expression of the thermogenic-related gene (*Ucp1*) in white adipose tissues, supporting increased energy expenditure**

BWL in Obese Rats



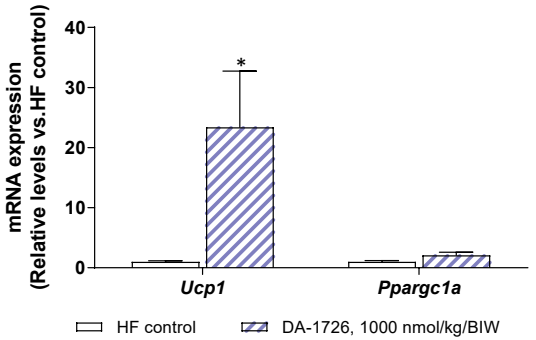
Mean ± SEM, *P<0.05 vs. Day 0 in each group,
#P<0.05 vs. HF control at final time, Two-way RM ANOVA

Cumulative Food Intake



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

White Adipose Tissue

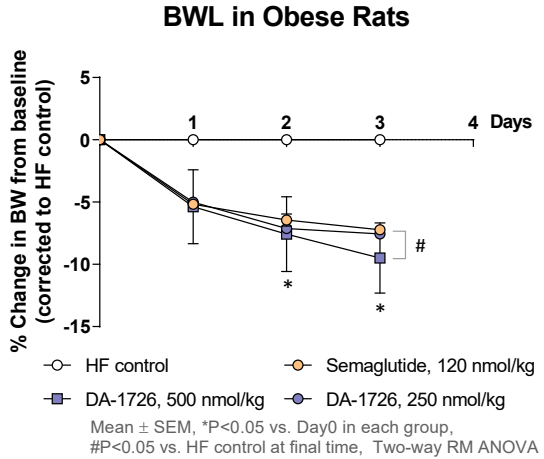


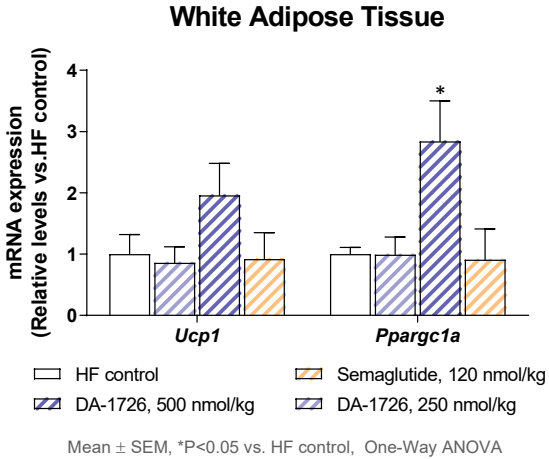
Mean ± SEM, *P<0.05 vs HF control, T-TEST

RESULTS – 4. BWL and Changes in Energy Expenditure Markers

Assessment of gene expression changes after a single dose to investigate direct and indirect effects between increased gene changes and weight loss

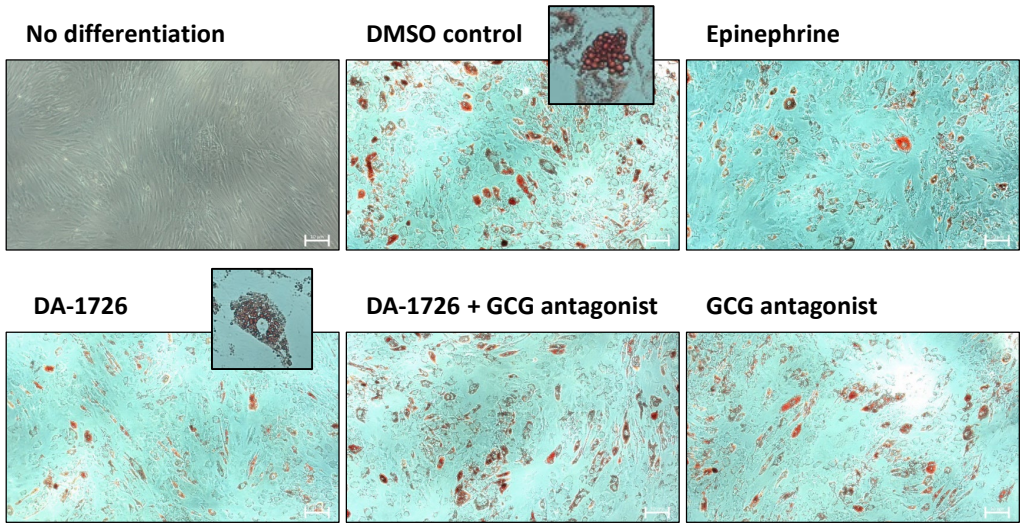
- ☑ **DA-1726 induced a small but significant weight loss 3 days, and the gene expression in white adipose tissue was significantly increased in the high-dose group**
- ☑ **This suggests that major genetic changes related to energy expenditure have a direct impact on inducing weight loss**

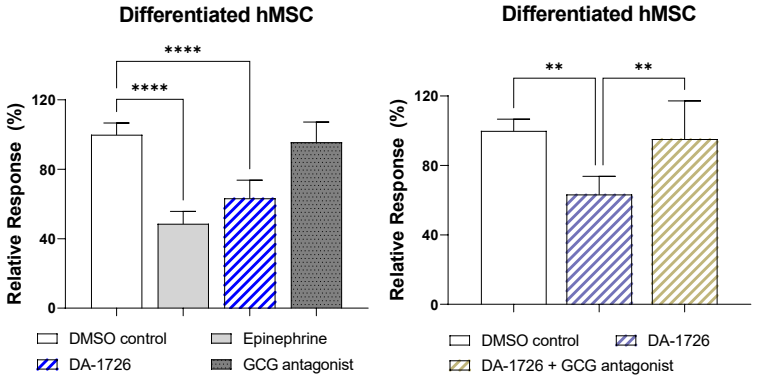




RESULTS – 5. Adipogenesis in Human Mesenchymal Stem Cells

- ☑ **The DA-1726-treated group showed a lower level of adipogenesis compared to the control group. However, this effect of DA-1726 was attenuated when co-administered with glucagon receptor antagonist**
- ☑ **These data suggest that the glucagon receptor actions of DA-1726 contribute to reduced adiposity by inhibiting adipogenesis**





Conclusion and Summary

- DA-1726 significantly reduced body weight in a dose-dependent manner in obese mice, showed effective weight loss compared to Semaglutide, and significantly increased Ucp-1 expression in white adipose tissue.
- Even a single administration of DA-1726 increased the expression of *Ucp-1* and *Ppargc1a* in white adipose tissue, indicating a direct effect that contributes to weight loss.
- DA-1726 also reduced lipid droplet formation in human MSC via glucagon receptor activation.
- Taken together, it suggests that the glucagon receptor action of DA-1726 contributes to reduced adiposity by enhancing fat burning and inhibiting adipogenesis.
- Therefore, DA-1726 is expected to elicit significant weight loss effects in humans, with a novel mechanism.