1676-P

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

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None

Background

- Oxyntomodulin (OXM) increases appetite suppression and energy expenditure through the GLP-1 receptor and glucagon receptor activation, ultimately inducing weight loss.
- DA-1726 is a novel OXM analogue currently being prepared for phase I clinical trials for treatment of obesity. In previous evaluations, it exhibited excellent weight loss and equivalent or superior glycemic control efficacy compared to Semaglutide.

Objective

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

Methods and Material

Receptor reporter assay

- Increased transcriptional activation was measured in CHO-K1 cells transiently transfected with each receptor.

Animal study

- DIO rats were subcutaneously injected with the vehicle or each compound twice a week for 4 weeks, or as a single dose. The food intake and body weight were recorded either 5 times per week or daily for 3 days. The expression of thermogenic-related genes was analyzed in white adipose tissue.

Adipogenesis assay

- After differentiation of hMSC was induced and treated with DA-1726 alone or in combination with glucagon receptor antagonist for 13 days, lipid droplets were analyzed by Oil Red O staining.

Results

Drug Properties

- The in vitro potency of DA-1726 on glucagon receptors in rats was less potent than in mice (Figure 1A-B). The half-life was longer in rats compared to mice (Table 1).

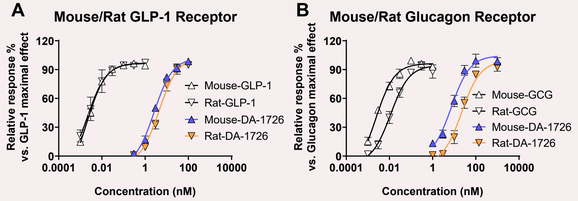


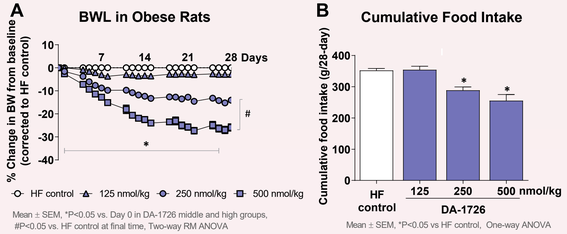
Figure 1. Activation of GLP-1 or glucagon receptors by DA-1726 in CHO-K1 Cells

Table 1. Half-life of DA-1726 in rodent model

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

Dose-Dependency of Body Weight Loss

- DA-1726 significantly reduced body weight in a dose-dependent manner (Figure 2A-B).



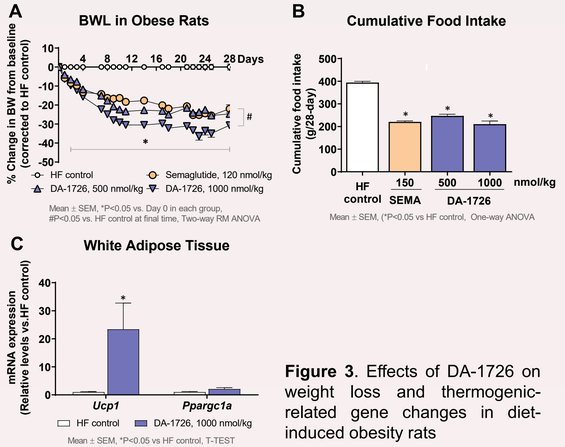
Mean ± SEM, *P<0.05 vs. Day 0 in DA-1726 middle and high groups, #P<0.05 vs. HF control at final time, Two-way RM ANOVA

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

Figure 2. Weight loss effect of DA-1726 in diet-induced obesity rats

Efficacy Comparative Study with Semaglutide

- DA-1726 exhibited an equal or greater weight loss effect compared to semaglutide, despite having a similar or higher food intake (Figure 3A-B).
- The high-dose DA-1726 significantly increased the *Ucp1* expression in white adipose tissues (Figure 3C).



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

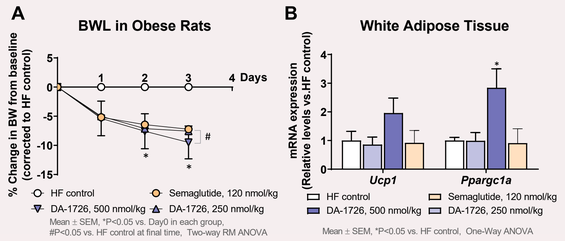
Mean ± SEM, (*P<0.05 vs HF control, One-way ANOVA

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

Figure 3. Effects of DA-1726 on weight loss and thermogenic-related gene changes in diet-induced obesity rats

Weight Loss and Changes in Energy Expenditure Markers

- DA-1726 significantly increased *Ucp1* and *Ppargc1a* expression in white adipose tissue despite single administration (Figure 4B).
- This suggests that major genetic changes associated with energy expenditure directly influence the induction of weight loss.



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

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

Figure 4. Body weight loss and changes in energy expenditure markers

Adipogenesis in Human Mesenchymal Stem Cells

- The adipogenesis inhibitory effect of DA-1726 was attenuated when co-administered with a glucagon receptor antagonist (Figure 5).
- This means that the glucagon receptor actions contribute to reduced adiposity by inhibiting adipogenesis.

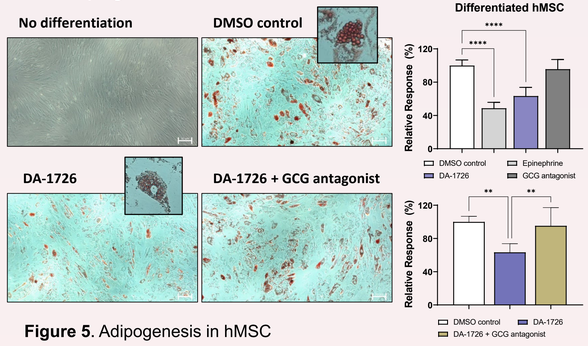


Figure 5. Adipogenesis in hMSC

Please refer to Poster 1668-P for additional data on DA-1726

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Conclusion

- DA-1726 is believed to exhibit effective weight loss effects through appetite suppression, promotion of fat burning, and inhibition of fat production.
- Therefore, DA-1726 is expected to elicit significant weight loss effects in humans, with a novel mechanism.