Differentiated Metabolic Effects of DA-1726, a Balanced GLP1R/GCGR Dual Agonist

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Abstract: 1668-P

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SAN DIEGO, CA / HYBRID | JUNE 23–26, 2023

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 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 pharmacological effect of DA-1726 compared to other competitor peptides, as well as the hyperglycemic risk under low-exposure conditions.

METHODS

Comparative Study with Cotadutide of Body Weight Loss in High-Fat Diet-Induced Obesity Mice

- DIO mice were subcutaneously injected with vehicle, DA-1726, or Cotadutide daily for 10 days. Food consumption and body weight were recorded daily. After treatment, mice were fasted for 4 hours before the autopsy, and HOMA-IR values were calculated by measuring plasma insulin and glucose.

Comparative Study with Tirzepatide of Body Weight Loss in High-Fat Diet-Induced Obesity Mice

- DIO mice were subcutaneously injected with vehicle, DA-1726, or Tirzepatide twice a week for 4 weeks. Food consumption and body weight were recorded five times a week. After treatment, major plasma parameters were analyzed through blood chemistry analysis.

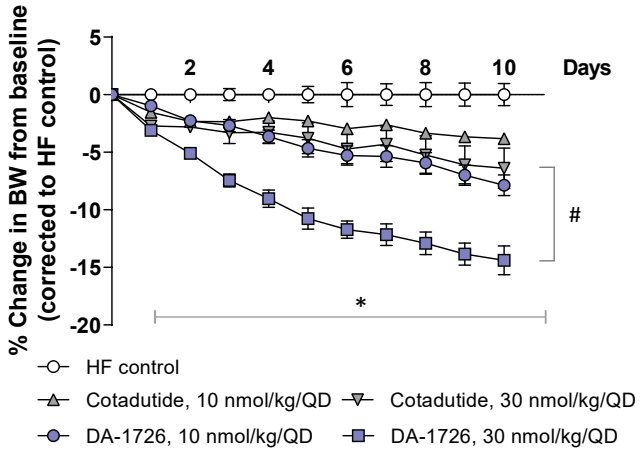
In vivo Hyperglycemia Risk in High-Fat Diet-Induced Obesity Mice

- To evaluate glucose tolerance under low exposure conditions, DA-1726 (at doses of 10, 30, and 100 nmol/kg) was administered twice a week for 3 weeks. After 3 weeks of injections, an intraperitoneal glucose tolerance test (ipGTT) was conducted 72 hours after the last dose, which was considered the time point when the steady state was reached.

RESULTS – 1. Efficacy Comparative Study with Cotadutide

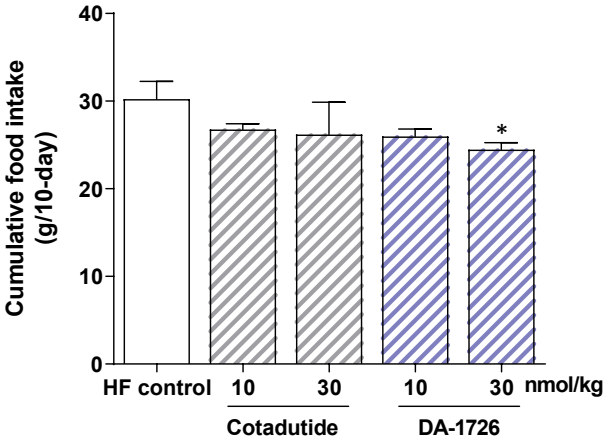
☑ **DA-1726 showed superior efficacy compared to Cotadutide in reducing body weight in HF-DIO mice**

BWL in Obese Mice



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

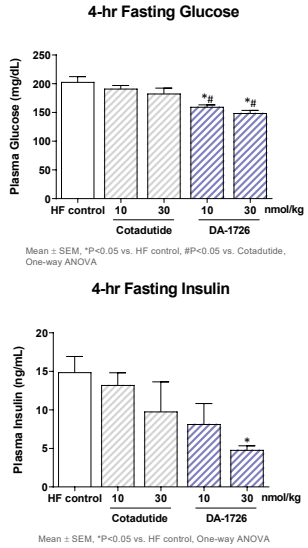
Cumulative Food Intake

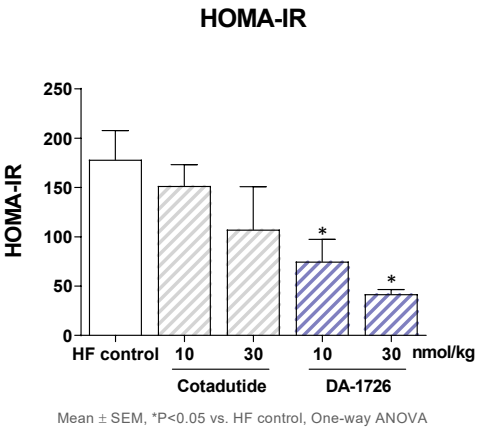


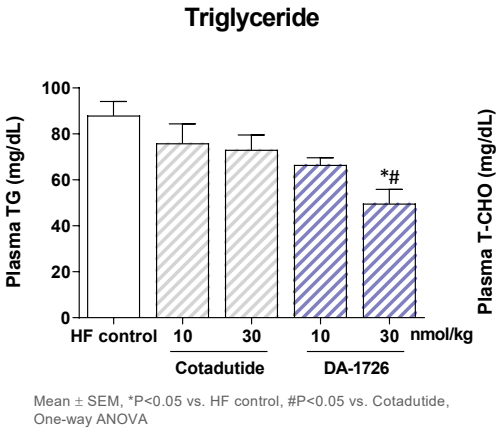
Mean ± SEM, *P<0.05 vs. HF control, One-way ANOVA

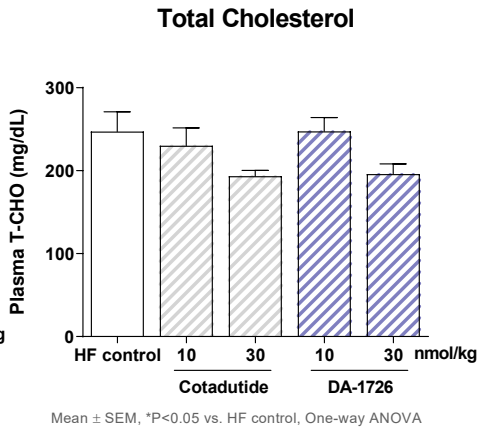
RESULTS – 1. Efficacy Comparative Study with Cotadutide cont.

☑ **DA-1726 demonstrated greater efficacy than Cotadutide in improving HOMA-IR and significantly reduced plasma triglyceride levels in HF-DIO mice**



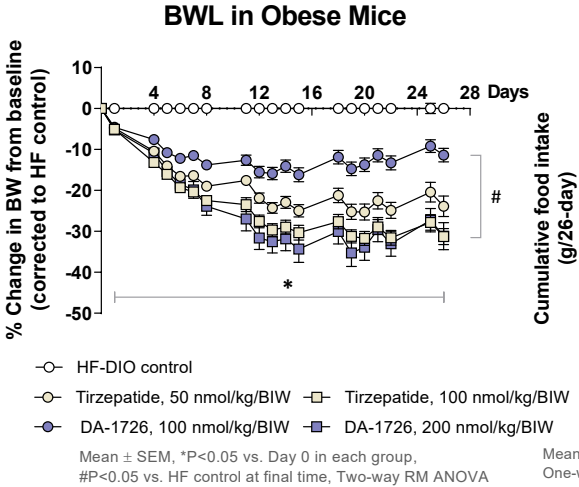




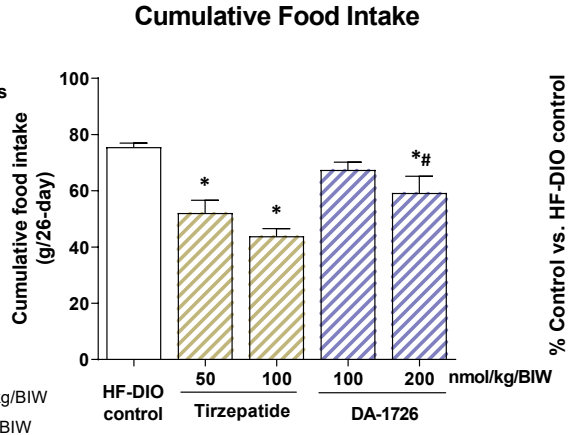


RESULTS – 2. Efficacy Comparative Study with Tirzepatide

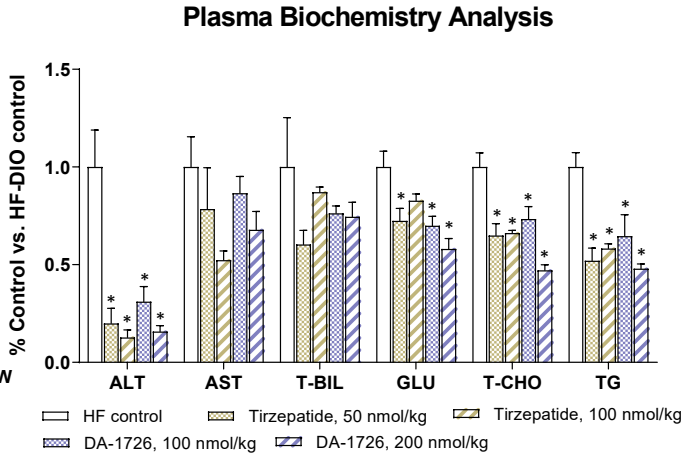
- ☑ **Despite higher food consumption, DA-1726 demonstrated similar efficacy in weight loss and was more effective in improving plasma metabolic parameters compared to the dual agonist of GLP-1 receptor and GIP receptor**



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, #P<0.05 vs.Tirzepatide high-dose, One-way ANOVA

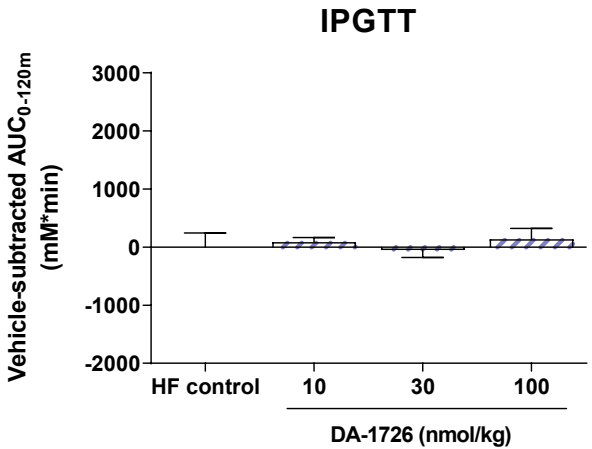


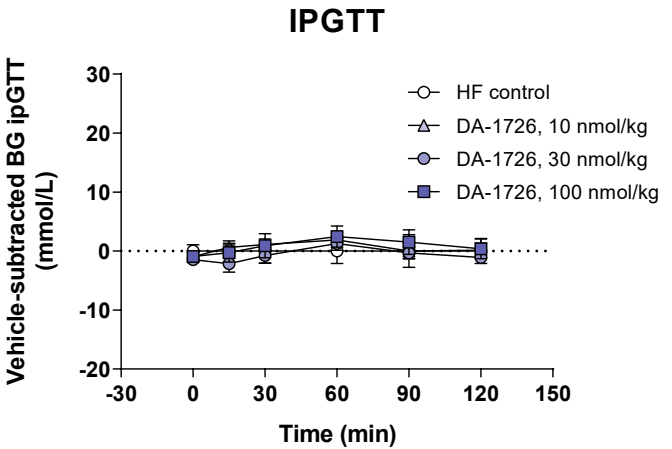
Mean±SEM, *P<0.05 vs. HF control., #P<0.05 vs. Tirzepatide high dose, One-Way ANOVA

RESULTS – 3. *In vivo* Hyperglycemia Risk in DIO Mice

Concerns remain with oxyntomodulin analogues that they may elevate blood glucose when glucagon action is enhanced and GLP-1 action is reduced

☑ **DA-1726 showed no issues with glucose tolerance in the intraperitoneal glucose tolerance test performed under conditions of minimal exposure after repeated administration for 3 weeks**





Reference) PLoS One. 2022;17(3):e0264974.

Conclusion and Summary

- Compared to Cotadutide, DA-1726 showed excellent body weight loss and HOMA-IR improvement in obese mice, these data suggested that DA-1726 was superior to a GLP1R-biased dual agonist in metabolic effects.

- Additionally, DA-1726 demonstrated the differential metabolic effect attributed to glucagon receptor agonism, as it exhibited similar efficacy in weight loss and a superior effect in improving metabolic parameters compared to Tirzepatide, despite consuming more food.

- DA-1726 did not show an issue of aggravating glucose tolerance under low drug exposure conditions, suggesting that DA-1726 is an effective peptide in controlling glycemic control as well as body weight.

- Taken together, these data suggest that DA-1726 is a well-balanced GLP-1 receptor and glucagon receptor dual agonist and is expected to have effective weight loss and glycemic control in humans.