1668-P

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

Il-Hun Jung[1], Tae-Hyoung Kim[1], Su Jin Lee[1], Hyung Heon Kim[1,2], Mi-Kyung Kim[1], Yuna Chae[1]*

* e-mail: ynchae@donga.co.kr; Dong-A ST Research Headquarter, Yongin, Republic of Korea; NeuroBo Pharmaceutical, Inc., Boston, MA, USA

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

Methods and Material

Comparative study with Cotadutide

- DIO mice were subcutaneously injected with the vehicle or each compound 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

- DIO mice were subcutaneously injected with the vehicle or each compound 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.

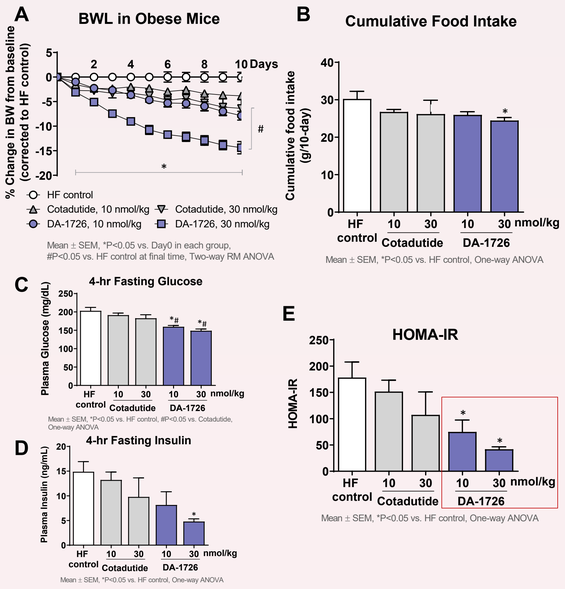
In vivo Hyperglycemia Risk in DIO mice

- DA-1726 was administered twice a week for 3 weeks to evaluate glucose tolerance under low exposure conditions. Then, an intraperitoneal glucose tolerance test was conducted 72 hours after the last administration.

Results

Efficacy Comparative Study with Cotadutide

- DA-1726 showed superior efficacy compared to Cotadutide in reducing body weight in HF-DIO mice (Figure 1A).
- DA-1726 demonstrated greater efficacy than Cotadutide in improving HOMA-IR and significantly reduced plasma triglyceride levels in HF-DIO mice (Figure 1C-G).



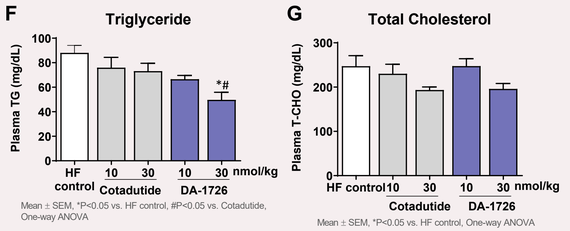


Figure 1. Weight loss and metabolic effect of DA-1726 in diet-induced obesity mice

Efficacy Comparative Study with Tirzepatide

- Despite higher food consumption, DA-1726 demonstrated similar efficacy in weight loss compared to Tirzepatide (Figure 2A-B).
- DA-1726 was more efficacious in improving plasma metabolic parameters compared to Tirzepatide, indicating differential metabolic effects caused by glucagon receptor agonism (Figure 2C).

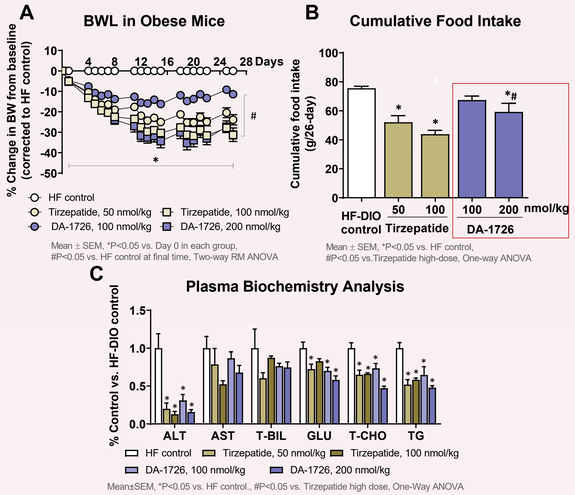


Figure 2. Effects of DA-1726 on weight loss and metabolic parameter changes in diet-induced obesity mice

In vivo Hyperglycemia Risk

- 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 (Figure 3A-B).
- This suggests that DA-1726 shows balanced activity under any conditions.

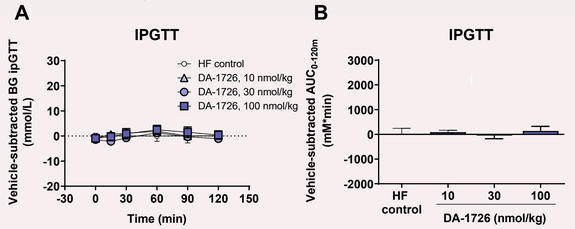


Figure 3. Hyperglycemia Risk of DA-1726 in DIO Mice

Conclusion

- **Compared to GLP-1 receptor-biased dual agonist, DA-1726 showed excellent body weight loss and HOMA-IR improvement in obese mice.**
- **Despite consuming more food, mice on DA-1726 lost just as much weight as those on the GIP receptor and GLP-1 receptor dual agonist.**
- **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.**

Please refer to Poster 1676-P for additional data on DA-1726

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