Long-term Treatment of DA-1241, a Novel GPR119 Agonist, Improved Glucose Control via Preserved Beta Cell Mass in a Progressive Diabetic Mice Model

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ABSTRACT

GPR119 is one of G-protein coupled receptors highly expressed in pancreas and intestine and activation of GPR119 is known to be involved in glucose and lipid metabolism. Although several GPR119 agonists have been under early clinical development, there are few reports on chronic efficacy in animal disease models and some GPR119 agonists suggested an issue on loss of efficacy after repeated administration. To demonstrate the long-term efficacy of our novel GPR119 agonist, DA-1241 was administered for 10 weeks in a progressive diabetic mice model, where single streptozotocin (STZ) injection concomitant with a high-fat diet (HF) feeding, causes dysregulation of glucose and lipid metabolism.

HF/STZ control mice showed overt hyperglycemia, while DA-1241 treatment significantly lowered blood glucose from two weeks after administration and its efficacy persisted during the rest of the treatment period. Hypertriglycemia and fatty liver were attenuated by DA-1241 treatment as well, indicating simultaneous glucose and lipid control at the same dose. Preserved islet structure and higher beta cell mass in DA-1241-treated group support its glucose-lowering effect. However, GSK263A, an another GPR119 agonist, showed no significant effects on glucose control and pancreatic beta-cell mass, with only a trend of a decrease in hepatic triglycerides. In cell-based experiments using hamster insulinoma cells to investigate underlying mechanisms of the effect on beta cells, DA-1241 protected beta cells from death caused by endoplasmic reticulum stress through reducing the expression of stress molecules and stimulated beta cell replication, which may partially account for the higher beta cell mass in DA-1241-treated HF/STZ mice.

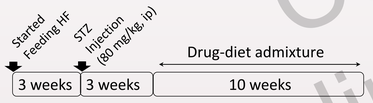
Taken together, this study suggested that **i) DA-1241 has a chronic glucose-lowering effect without tachyphylaxis issue, ii) the metabolic improvement on glucose and lipid by DA-1241 treatment can be observed at a same dose level, and iii) DA-1241 has a direct beneficial effect on pancreatic beta cells**, which may partially contribute to its anti-diabetic effect.

BACKGROUND

- GPR119 is one of Class A GPCR, highly expressed in pancreatic beta cells and intestinal L-cells
- Activation of GPR119 leads to insulin secretion in beta cells and GLP-1 secretion in L-cells.
- Tachyphylaxis issue of some GPR119 agonists
- Limited reports on the protective effects of GPR119 agonist on beta cells
- Herein, this study aimed to evaluate 1) long-term efficacy in glucose control and 2) protective effects on pancreatic beta cells of a novel GPR119 agonist, DA-1241, using progressive type 2 diabetic mice

METHODS

- **High-fat diet (HF)/streptozotocin (STZ)-induced diabetic mice model (n=8/group)**
  - 4-week-old, male ICR mice
  - Dosages: high-fat diet-drug admixtures as 0.03% targeting to 30 mg/kg/day
  - **DA-1241**: a novel GPR119 agonist with a higher intrinsic efficacy under preclinical development
  - **GSK263A**: a previous clinical candidate as a GPR119 agonist

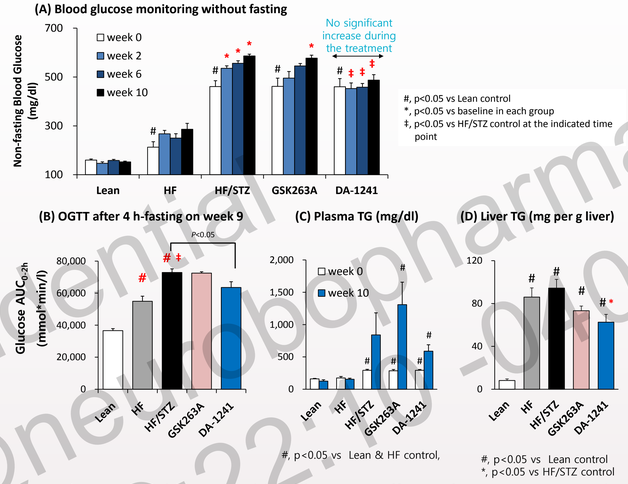


- **HIT-T15, hamster insulinoma cell line**
  - **Thapsigargin (Tg)**, non-competitive inhibitor of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA); deprivation of endoplasmic calcium storage induces endoplasmic reticulum (ER) stress, thereby leading to beta-cell death
  - ***Beta-cell protection assay & FACS analysis***: Cells were deprived of serum for 16 h followed by treatment of test compounds in the presence of 0.3 μM Tg for 8 h. Cellular viability was assessed by CCK-8 reagent (Dojindo)
  - ***qPCR for BiP and CHOP*** using LightCycler480 (Roche)
  - ***[3H] Thymidine incorporation assay*** for the last 6 h during the 72 h-treatment period

RESULTS

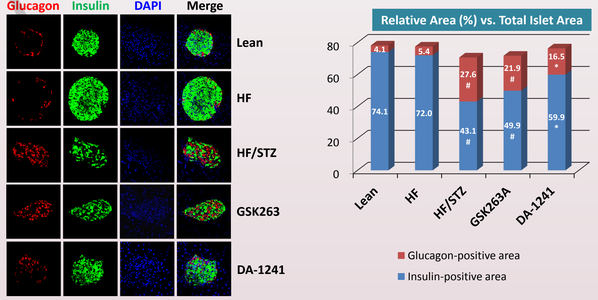
- In HF/STZ diabetic mice, there were no significant changes in body weight and food intake among treatment groups after 10-week treatment.

1) Long-term control of glucose and lipid levels by DA-1241



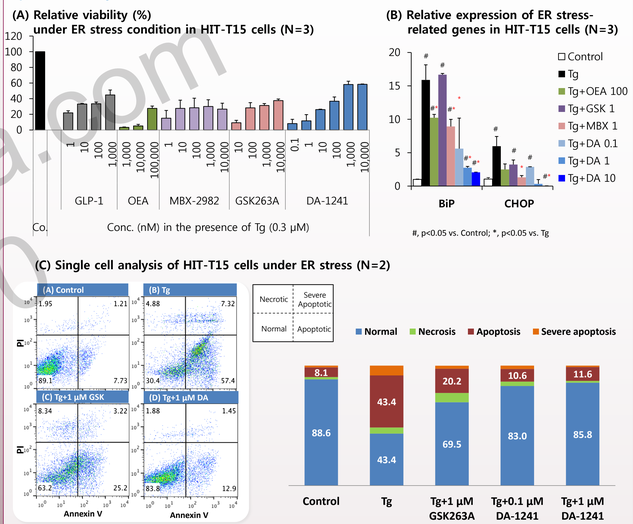
- In HF/STZ mice, glucose- and lipid-lowering effects of DA-1241 persisted during the 10-week treatment period.

2) Preservative effects of DA-1241 on pancreatic islets

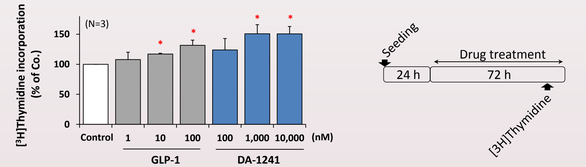


- In HF/STZ mice, long-term treatment of DA-1241 preserved the islet structure with an increased beta-cell area and a decreased alpha-cell area compared to total islet area.

3) Beta-cell protective effect of DA-1241 in hamster beta cells



4) Stimulation of beta-cell replication in hamster beta cells



CONCLUSION

1) **DA-1241 has a chronic glucose-lowering effect without tachyphylaxis issue. The metabolic improvement on glucose and lipid by DA-1241 treatment can be observed at the same dose level.**
2) **Anti-diabetic effect of DA-1241 is partly attributed to the pancreatic protective effect in the pathogenesis of type 2 diabetes.**
3) **DA-1241 has a direct preservative effect on beta cells through protecting beta cells from ER stress-induced death and stimulating beta-cell replication.**

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