Glucagon-like peptide-1 promotes α to β cell transdifferentiation in the absence of MafA

*Yuting Li[1], Hisashi Oishi[2], Satoru Takahash[3], Chuan Zhang[1]**

[1]The second Hospital of Jilin University, China.

[2]Nagoya City University Graduate School of Medical Sciences, Japan

[3]University of Tsukuba, Japan

**Correspondence: Chuan Zhang Email : wangs93@sina.com*

Introduction

Diabetes is a chronic disease caused by the relative or absolute lack of functional pancreatic β cells and is characterized by chronic hyperglycemia. Type 1 diabetes causes absolute insulin deficiency due to the autoimmune-mediated destruction of pancreatic β cells. Type 2 diabetes is characterized by insufficient insulin secretion and insulin resistance. Therefore, research to treat diabetes by restoring β cell functions has become particularly important. Glucagon-like peptide-1 (GLP-1) which is the most potent known incretin and enhances glucose-dependent insulin release, is a short peptide hormone secreted by intestinal epithelial L cells. GLP-1 is secreted and induces insulin gene transcription and insulin biosynthesis. GLP-1 can also enhance β cell functions, inhibit β cell apoptosis, regulate appetite, increase satiety, inhibit energy absorption and increase the sensitivity of muscle and liver cells to insulin to regulate glucose metabolism. In addition, GLP-1 plays important roles in the differentiation and regeneration of pancreatic β cells. Among mice with 70% of the pancreas excised, GLP-1 receptor MafA-deficient mice show worse glucose tolerance and significantly lower islet β cell counts than wild-type mice, indicating that GLP-1 plays a potential regulatory role in β cell regeneration.

Purpose

- To investigate glucagon-like peptide-1 promotes α to β transdiffetiation in the absence of MafA.

Patients & Methods

- ***Animals and Treatment with GLP-1 and saline.*** Male MafA-deficient mice were injected GLP-1 or Saline (50 μg/kg body weigh) daily for 4 weeks.
- ***Blood glucose level and body weight measurements.*** Blood glucose measurements were taken using a blood glucose meter and tested every 3 days.
- ***Immunohistochemical analysis.*** The numbers of immunofluorescent islet α cells and β cells were analyzed using Image-Pro Plus 6.0 (Media Cybernetics, Inc., Rockville, MD, USA).
- ***cDNA synthesis and real-time quantitative PCR.*** Islets were isolated as described above, total RNA was isolated from the islets, and real-time quantitative PCR was performed using specific PCR primers (Table 1). PCR was performed with a CFX96TM real-time PCR detection system (Bio-Rad, USA). The specific PCR primers are listed in Supplementary. Using β-actin as an internal reference, the relative expression of each gene was calculated by the 2-ΔΔCt method.

Results

- ***GLP-1-treated mice exhibit improved blood glucose levels without hypoglycemia.*** Compared to those in the saline-treated MafA-deficient mice, the blood glucose levels in the GLP-1-treated MafA-deficient mice gradually decreased, and normal blood glucose levels were reached within 5 days of treatment. When the experiment was terminated, the blood glucose level was maintained for 2 weeks. Compared with the saline-treated MafA-deficient mice, the GLP-1-treated MafA-deficient mice exhibited significantly reduced blood glucose levels at all time points after glucose injection.
- ***In GLP-1-treated mice, the food intake and body weight Changed.*** Compared to the saline-treated MafA-deficient mice, the GLP-1-treated MafA-deficient mice had significantly reduced food intake in the first 4 days, and their food intake continued to decrease on days 6-8 before gradually increasing. The food intake of the GLP-1 treatment group was similar to that of the saline treatment group after 16 days. During the 4 weeks of the experiment, the weight gain of the mice in the GLP-1 treatment group was significantly lower than that of the mice in the saline treatment group.

Figure1.
Blood glucose concentrations were measured after 12 h without food (n=5 per group). The saline-treated MafA-deficient mice (n=5) served as controls.

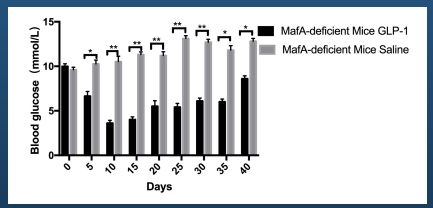
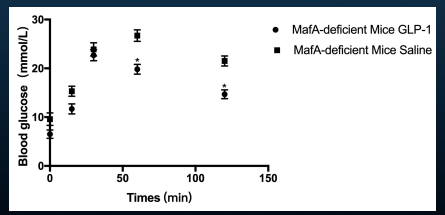


Figure 2.
Glucose tolerance tests were performed with the GLP-1-treated MafA-deficient mice. The MafA-deficient mice were treated with GLP-1 or saline. Two weeks later, the mice were fasted for 12 h and injected with glucose, and blood glucose levels were measured (n=5). The saline-treated MafA-deficient mice (n=5) served as controls.



Results (continued)

Fi.gure 3
Food intake (n=5 per group) was measured. Saline-treated MafA-deficient mice (n=5) served as a control.

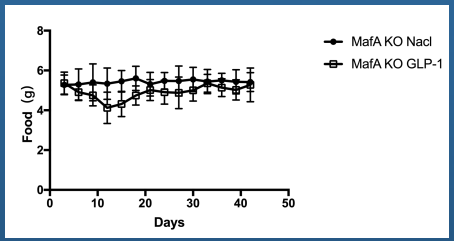
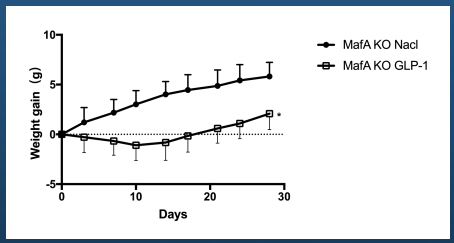


Figure 4.
Body weights were measured weekly in male mice (n=5).



- ***Mice injected with GLP-1 increase β cell regeneration by promoting α-β cell transdifferentiation.*** Compared with saline treatment, GLP-1 treatment increased the β cell/α cell ratio in MafA-deficient mice and the nascent β cells may be derived from α cells. These results indicate that GLP-1 can increase nascent β cell production by promoting the transdifferentiation of α cells into β cells under the condition of MafA deletion.
- ***GLP-1-treated mice may induce the conversion of α cells into β cells by inducing PDX-1 production.*** We detected the changes in related transcription factors by real-time quantitative PCR and found that compared with the MafA-deficient mice in the saline treatment group, the MafA-deficient mice in the GLP-1 treatment group exhibited significantly increased insulin and PDX-1 mRNA levels.

Figure 5.
Glucagon- or insulin-positive cells were counted and expressed as the ratio of β/α cells in the saline-treated MafA-deficient mice or GLP-1-treated MafA-deficient mice.

Results (continued)

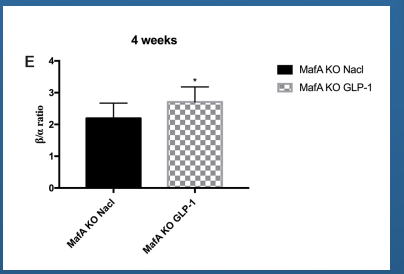
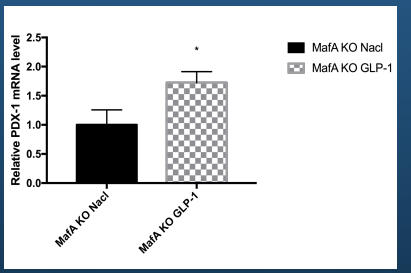


Figure 6.
The expression of PDX-1 mRNA was analyzed by RT-qPCR and normalized to the β-actin expression.



Conclusion

- In conclusion, we found that GLP-1 reduced fasting blood glucose levels in MafA-deficient mice and improved glucose tolerance. GLP-1 contributes to the proliferation of new islet β cells, which may be a source of new islet cells, in the absence of MafA. GLP-1 can induce an increase in PDX-1 expression, thereby inducing the conversion of α cells into nascent β cells.

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