THE EFFECT OF TREATMENT WITH DIPEPTIDYL PEPTIDASE-4 INHIBITOR ON AN ANIMAL MODEL OF TYPE 1 DIABETES

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INTRODUCTION AND OBJETIVE

Type 1 diabetes mellitus (DM1) is an organ-specific autoimmune disease, mediated by T cells and characterized by the selective destruction of insulin producing pancreatic cells.
Glucagon-like peptide-1 (GLP-1) is gastrointestinal hormone that potentiate glucose-stimulated insulin secretion. Additionally, it stimulate insulin biosynthesis and stimulate proliferation of the beta-cell (Fig.1). After being secreted ,GLP-1 have a very short circulating half-life of 3–5 min due to the action of proteases such as dipeptidyl peptidase IV (DPP-4) (Fig. 2).
Recently, a new class of drugs, dipeptidyl peptidase-4 inhibitors (iDPP4) , has demonstrated therapeutic efficiency in patients with type 2 diabetes mellitus. Furthermore, the use of DPP-4 inhibitors in experimental models of DM1 have shown protection of pancreatic β cells against apoptosis, stimulation of neogenesis of pancreatic islets as well as improvement in the homeostatic glucose control. They act by blocking degradation of the incretin hormone glucagon-like peptide-1 (GLP-1).

Aim: To evaluate the possible effect of the administration of DPP-4 inhibitor in the treatment of experimental type 1 diabetes.

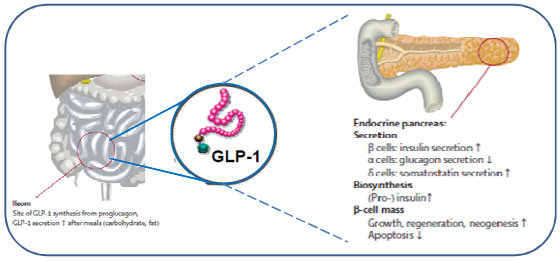

Fig 1. Physiology of GLP-1 secretion and action on pancreas (Adapted from Drucker DJ, Nauck MA, 2006).

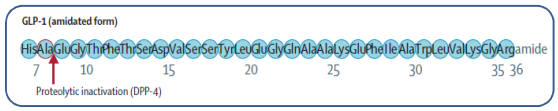

Fig 2. Structure of GLP-1(Drucker DJ, Nauck MA, 2006).

METHODS

•Type 1 Diabetes Induction
Eight-week-old male C57Bl/6 mice will be lightly anesthetized. Streptozotocin (STZ) will be dissolved in 25mM citrate buffer, at pH 4.5, and will be immediately injected intraperitoneally at a dose of 40 mg/kg, for 5 consecutive days.

• Blood Glucose Determination and Diabetes Definition
Blood samples will be taken from the tail vein of nonfasted alert animals, and glucose levels will be determined with the glucometer system *Accu-Chek Active*. Mice will be considered diabetic if glycemia was above 250 mg/dL, on 2 consecutive measurements.

• Dipeptidyl peptidase-4 inhibitor administration
After mice were considered diabetic, they were placed on either normal chow diet (control group) or diet containing iDPP4 (4 g/kg MK0431-Sitagliptin).

• ELISA
Serum active GLP-1 and pancreatic homogenate cytokines (IFN-γ, TNF-α) levels were measured by ELISA 30 days after the iDPP4 administration.

• Flow cytometry analysis
The frequency of $CD4^+CD25^+Foxp3^+$ T cells in spleen was examined by flow cytometry 30 days after the iDPP4 administration.

RESULTS

GLP-1 levels

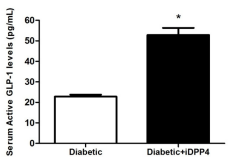

Fig. 3. After 30 days of DPP4i treatment, active GLP-1 was increased (52.83±3.52pg/mL DPP4i group versus 22.83 ± 0.94pg/mL control group)

Th1 cytokines

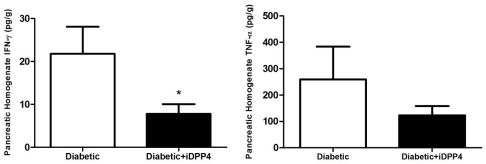

Fig. 4. IFN-γ andTNF-α levels were reduced in pancreatic homogenate (7.81± 2.24; 123.3 ± 34.66 pg/g) when compared to control group (21.78 ± 6.29; 259.5 ± 123.9 pg/g).

Regulatory T cells

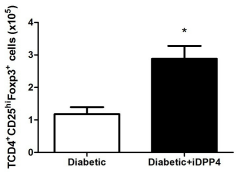

Fig. 5. $CD4^+CD25^{hi}Foxp3^+$ cells were increased in spleen (2.88 ± 3.95 $x10^5$ cells DPP4i group versus $x10^5$ 1.17 ± 2.16 cells control group).

Blood glucose levels

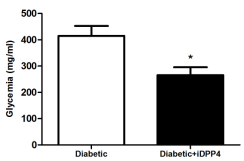

Fig. 6. Fasted blood glucose levels were reduced (265.5 ± 30.17mg/dL) when compared to control group (414.8 ± 38.02mg/dL).

CONCLUSIONS

DPP-4 inhibitor treatment can be associated with immunomodulation, reducing proinflammatory cytokine in the pancreas and increasing regulatory T cells in experimental type 1 diabetes.

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