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Incretin secretion is not restored by short-term strict glycaemic control in Korean hyperglycaemic patients with type 2 diabetes

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ABSTRACT

Aims: To determine whether short-term strict glycaemic control could restore incretin secretion in type 2 diabetic patients. The factors associated with incretin levels were also investigated.

Methods: A meal tolerance test (MTT) was performed in eighteen poorly controlled (pDM) and fifteen well controlled (wDM) diabetic patients. Fourteen patients in the pDM group underwent follow-up MTT after strict glycaemic control. The secretions of intact glucagon-like peptide-1 (iGLP-1) and total glucose-dependent insulinotropic polypeptide (tGIP) during MTT were calculated by total and incremental area under the curve (TAUC and IAUC) values.

Results: Posttreatment HbA1c level was significantly improved in the pDM group (11.2 ± 0.9 to $7.9 \pm 0.9\%$). However, the secretion of incretin hormones was not increased in the posttreatment pDM group (TAUCiGLP-1, 3612 ± 587 to 2916 ± 405 pmol/L min; TAUCtGIP, 9417 ± 1099 to 8338 ± 903 pmol/L min). IAUCiGLP-1 was negatively correlated ($r = -0.446$, $P = 0.011$) and independently associated ($\beta = -137.2$, $P = 0.027$) with insulin resistance assessed by homeostasis model assessment.

Conclusions: Incretin secretion is not restored by short-term strict glycaemic control. Decreased incretin secretion seems to develop early in the course of type 2 diabetes with increasing insulin resistance, but not to be influenced by glycaemic status.

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1. Introduction

The incretin effect is defined as the amplification of insulin secretion in response to oral glucose ingestion compared with that obtained with intravenous infusion of glucose that results in an identical plasma glucose concentration [1]. While the incretin effect contributes to approximately 70% of the overall postprandial insulin secretion in healthy subjects, it is markedly reduced in type 2 diabetic patients [2,3]. It has been suggested that impairment in secretion or action of the two main incretin hormones, glucagon-like peptide-1 (GLP-1) and

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glucose-dependent insulinotropic polypeptide (GIP), may play an important role in this phenomenon. Recent data showed that the insulinotropic effect of GIP is greatly reduced in diabetic patients, whereas pancreatic beta-cell sensitivity to GLP-1 is relatively preserved [4,5]. In contrast, many studies have demonstrated hyposecretion of GLP-1 in type 2 diabetic patients while GIP secretion was slightly decreased, normal or even increased [5,6].

Exposure of pancreatic beta-cells to chronic hyperglycaemia causes oxidative stress and leads to deterioration of beta-cell function: this is the concept of glucotoxicity [7]. However, the influence of glucotoxicity on the enteroinsular axis is largely unknown. In terms of the action of incretin hormones, several observations have verified the notion that beta-cell responsiveness to GLP-1 or GIP is reversible after improvement of glucose control. Four weeks of strict glycaemic control in type 2 diabetic patients potentiated the effect of GLP-1 on glucose-stimulated insulin secretion by about 30% [8], and in rodent models the downregulation of GLP-1 receptor (GLP-1R) and GIP receptor (GIPR) induced by chronic hyperglycaemia was recovered after normalization of hyperglycaemia that restored incretin sensitivity [9,10]. In terms of the secretion of incretin hormones, only one trial has been reported to date that showed no effect of near normalization of blood glucose level on postprandial GLP-1 and GIP secretion [11]. However, because hyperglycaemia and the degree of insulin resistance are associated with incretin secretion [12,13], it could still be presumed that lowering glucose might have a positive effect.

In this study, we aimed to determine whether reversal of hyperglycaemia through intensive insulin treatment could restore incretin secretion in Asian subjects with type 2 diabetes. We also investigated which endogenous factors are associated with incretin levels.

2. Subjects and methods

2.1. Patients

Thirty-three patients with type 2 diabetes participated in the study. Fifteen of these had well controlled diabetes (wDM) with less than 5 years duration of diabetes and a glycated hemoglobin (HbA1c) level that had never exceeded 7.5%. Eighteen had poorly controlled diabetes (pDM) with less than 15 years duration of diabetes and an HbA1c level over 9% on recruitment. Subjects aged between 40 and 70 years with body mass index (BMI) between 22 and 27 kg/m^2 were included. All subjects were without anaemia, had normal renal and hepatic function and did not have severe diabetic complications such as cardiovascular disease, cerebrovascular disease, proliferative diabetic retinopathy or gastroparesis. All were insulin-naïve and patients taking oral hypoglycaemic agents (OHA) other than sulphonylurea or metformin, or taking medications known to affect gastric motility, were excluded. All subjects agreed to participate after providing oral and written consent. The Institutional Review Board of the Clinical Research Coordinating Center at St. Vincent's Hospital approved the study protocol (No. VC08EIMF0093).

2.2. Study protocol

A meal tolerance test (MTT) was performed once for the wDM group and twice (before and after intensive glycaemic control with insulin treatment) for the pDM group. Patients in the pDM group were initially admitted for insulin dose titration and education. The target blood glucose level was <120 mg/dL for fasting and <180 mg/dL for the postprandial period. A follow-up MTT was performed for 14 patients in the pDM group because four patients refused or were lost to follow-up. The MTT was performed after 2 months of treatment, but if the HbA1c level had not decreased by 2%, the MTT was delayed for another month (mean follow-up period: 2.4 months). Eleven of the 14 patients were treated by injecting biphasic insulin aspart (NovoMix® 30, Novo Nordisk, Bagsvaerd, Denmark) twice a day while the other three patients used only basal insulin glargine (Lantus®, Sanofi-aventis, Paris, France). All antidiabetic treatment was withdrawn at least two days before MTT. After an overnight fast, the subjects were tested in a seated position with restriction of major movements. A cannula was inserted into a vein on the dorsum of one hand, and a heating pad was applied to obtain arterialized blood. The mixed meal consisted of a calorie bar and a drink containing 470 kcal (49% carbohydrate, 37% fat and 14% protein; fiber content 7.2 g) and this was consumed within 10 min. Blood was drawn 15 and 0 min before and 15, 30, 45, 60, 90, 120, 180 min after ingestion of the meal to chilled EDTA tubes pretreated with 10 μL of dipeptidyl peptidase (DPP)-IV inhibitor (Millipore, Billerica, MA) and 10 μL of protease inhibitor containing aprotinin (Sigma–Aldrich, St. Louis, MO) per mL blood. Blood samples were also added to a NaF tube for plasma glucose measurement. All samples were centrifuged at 4 °C within an hour and stored at −70 °C until analysis.

2.3. Analytical methods and calculations

The plasma concentrations of insulin, C-peptide, glucagon, intact GLP-1 (iGLP-1) and total GIP (tGIP) were measured by multiplexed biomarker immunoassays using Luminex® xMAP® technology. The human endocrine panel (Cat. No. HENDO-65K, Millipore) was used for insulin, C-peptide, glucagon and iGLP-1 assays and the human gut hormone panel (Cat. No. HGT-68K, Millipore) was used for tGIP assay. Because the insulinotropic effect of GIP is greatly reduced in diabetic patients, we measured total form without discriminating between the active and inactive forms. However, we measured the active form of GLP-1, which can reflect the true extent of incretin action. The intra-assay and inter-assay coefficients of variation were, respectively, 2.6 and 7.2% for insulin, 7.3 and 4.2% for C-peptide, 4.9 and 7.1% for glucagon, 5.1 and 7.4% for iGLP-1 and 7.0 and 12.0% for tGIP. Plasma glucose levels were determined by the hexokinase method.

The degrees of insulin resistance and beta-cell function were assessed by homeostasis model assessment (HOMA-IR and HOMA-B, respectively). The insulinogenic index (Δinsulin 0–30 min/Δglucose 0–30 min) was calculated as a marker of early-phase insulin secretion.

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