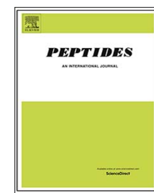
Peptides 94 (2017) 86–90

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides



Circulating levels of cortistatin are correlated with metabolic parameters in patients with newly diagnosed type 2 diabetes mellitus

Wenjia Chen, Yu Fu, Xinhua Yin, Yue Liu*

Department of Cardiology, The First Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China

ARTICLE INFO

Keywords:
Cortistatin
Diabetes mellitus
Insulin resistance
Blood lipids

ABSTRACT

Cortistatin (CST) is a recently discovered cyclic neuropeptide with multiple bioactive effects. The aim of this study was to investigate the relationship between plasma CST and various metabolic markers in patients with newly diagnosed type 2 diabetes mellitus (T2DM). For this study, 60 patients with newly diagnosed T2DM and 38 age- and gender-matched healthy controls were recruited. Fasting plasma glucose (FPG), serum insulin and hemoglobin A_{1c} (HbA_{1c}) levels and a blood lipid profile were obtained with commercially available diagnostic reagents. CST plasma levels were determined using an enzyme immunoassay kit. The results showed that the plasma levels of CST were substantially lower in patients with newly diagnosed T2DM compared with the healthy controls. Plasma CST levels were positively correlated with high-density lipoprotein and negatively related to FPG, serum insulin, the homeostasis model assessment of insulin resistance (HOMA-IR) and HbA_{1c} in all subjects. Further analysis showed that CST levels were positively correlated with systolic blood pressure and negatively correlated with FPG, serum insulin, HOMA-IR and HbA_{1c} in patients with newly diagnosed T2DM. Moreover, logistic regression analyses indicated that plasma CST was correlated with newly diagnosed T2DM. In conclusion, patients with newly diagnosed T2DM had significantly lower plasma levels of CST than healthy controls, and plasma CST was associated with glucose metabolism and insulin resistance, indicating a potential role of CST in the development of T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a group of metabolic diseases characterized by hyperglycemia in the presence of different degrees of impaired insulin secretion and insulin resistance [1]. T2DM is often accompanied by dyslipidemia, obesity and cardiovascular disease. Data from the International Diabetes Federation indicate that DM affected 366 million people worldwide in 2011 and is estimated to affect more than 500 million in 2030 [2]. Moreover, DM increases medical costs and results in lost wages due to morbidity and mortality; thus, it is a global public health problem [3].

Cumulative evidence has shown that endogenous bioactive peptides play an important role in risk stratification, diagnostic assessment, treatment and monitoring of DM. Cortistatin (CST) is a recently discovered cyclic neuropeptide in mammals, including humans [4]. CST has structural homology with somatostatin (SST) and contains an FWKT tetramer that is crucial for somatostatin receptor (SSTR) binding; thus, CST has high affinity for all SSTR subtypes[4]. However, CST, but not SST, can bind to growth hormone secretagogue receptor 1a (GHSR1a) and Mas-related gene 2 receptor [4]. De Lecea L and colleagues demonstrated that the CST gene mapped to 1p36 of human chromosome 1 [5]. Preprocortistatin, the primary expression product of the CST gene, contains a secretory signal sequence at the N-terminus and several predicted dibasic amino acids (KR, RK, KK, RR), which is a putative cleavage site for prohormone convertase [6]. Once the predicted secretory signal sequence is cleaved, procortistatin is further enzymatically cleaved to produce mature CST [6]. CST mRNA has primarily been found in the central nervous system, especially in the cerebral cortex and hippocampus, through in situ hybridization. CST can exert multiple effects via SSTRs, such as inhibiting locomotor activity and convulsions [7]; promoting sleep; and regulating learning, memory and drinking behavior [8]. Using quantitative polymerase chain reaction (qPCR) and reverse transcription PCR (RT-PCR), researchers found CST mRNA in immune tissues, such as monocytes, macrophages and dendritic cells. In experimental animal models of sepsis, rheumatoid arthritis, multiple sclerosis and Crohn's disease, CST has been shown to inhibit inflammation and induce immune tolerance through SSTRs and GHSR1a [9]. CST mRNA is also expressed in

* Corresponding author at: Department of Cardiology, The First Affiliated Hospital of Harbin Medical University, No. 23, Youzheng Street, Nangang District, Harbin, Heilongjiang Province 150001, China.
E-mail addresses: liuyue198002@163.com, yueliu@ems.hrbmu.edu.cn (Y. Liu).

http://dx.doi.org/10.1016/j.peptides.2017.05.008
Received 7 December 2016; Received in revised form 27 April 2017; Accepted 15 May 2017
Available online 17 May 2017
0196-9781/ © 2017 Elsevier Inc. All rights reserved.

endocrine tissues, especially the pancreas. However, several studies have reported that CST had inhibitory effects on insulin secretion but no effect on glucose levels in physiological or pathophysiological processes [10–12]. Using RT-PCR and confocal laser microscopy, Carrasco E et al. found that CST mRNA and protein levels were significantly lower in diabetic postmortem eyes than in nondiabetic donor eyes [13]. However, the relationship between CST and T2DM is unclear.

Therefore, we measured plasma CST in newly diagnosed T2DM patients and healthy subjects and further investigated the correlations between CST and clinical parameters and the metabolic indexes of glucose, lipid metabolism and insulin resistance.

2. Materials and methods

2.1. Subjects

The protocol used in this study fully complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University, Harbin, China. Written informed consent was obtained from all participants, who exhibited an adequate understanding of the study and its purpose. The inclusion criteria for the T2DM group were as follows: diagnosed with T2DM based on the 2006 World Health Organization criteria of the definition and diagnosis of DM and intermediate hyperglycemia; had no diabetic complications; and received no antidiabetic therapy, including medication or insulin. The exclusion criteria were as follows: acute infection, chronic hepatic and/or renal dysfunction, nutritional disorders, cancer, chronic vascular diseases, such as stroke, coronary artery disease and peripheral arterial diseases, and other severe illnesses. This study consecutively enrolled 60 newly diagnosed T2DM patients and 38 healthy subjects from the outpatient department of the Second Affiliated Hospital of Harbin Medical University.

2.2. Clinical data collection

All subjects completed a self-administered questionnaire for age, smoking history, alcohol consumption, family history of T2DM and medications. Cigarette smoking was defined as having smoked more than 100 cigarettes during one's lifetime. Alcohol drinking referred to the consumption of at least 30 g of alcohol per week for 1 year or more. Standardized protocols were used to determine height, weight and blood pressure. Waist and hip circumferences were measured midway between the iliac crest and the rib cage and were rounded to the nearest 0.1 cm. Body mass index (BMI, kg/m^2) and waist-to-hip ratios (WHRs) were calculated.

2.3. Sample collection and biochemical analyses

Overnight fasting blood samples were drawn from the antecubital vein and placed into tubes containing Na_2-EDTA (1 mg/ml) and 500 kIU/ml aprotinin (Sigma, St. Louis, MO, USA) or heparin. Plasma and serum were obtained immediately by centrifugation at 3000 rpm for 10 min at 4 °C, and these samples were stored at −70 °C until further analyses.

Fasting plasma glucose (FPG), serum insulin, hemoglobin A_{1c} (HbA_{1c}) and a blood lipid profile were obtained using commercially available diagnostic reagents at the clinical biochemical laboratories in the Second Affiliated Hospital of Harbin Medical University. Plasma glucose was quantified using glucose oxidase via an enzymatic colorimetric method. Insulin was determined with a commercially available radioimmunoassay kit (Linco Research, St. Louis, MO, USA). HbA_{1c} (%) was assessed using an automated high-performance liquid chromatography method (Variant II, Bio-Rad, Hercules, CA, USA). Total cholesterol (TC) was determined via an enzymatic colorimetric method using cholesterol esterase and oxidase. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstic acid. Triglycerides were quantified with an enzymatic colorimetric assay using glycerol phosphate oxidase. Low-density lipoprotein cholesterol (LDL-C) was determined by an enzymatic colorimetric method. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (mU/mL) × FPG (mmol/L)/22.5. Plasma CST-17 levels were measured by a commercial enzyme immunoassay kit (Catalog#EK-060-11, Phoenix Pharmaceuticals, Belmont, CA, USA). This kit is specific for human CST-17 and the enzyme immunoassay was performed as previously described with minor modification [14]. Standards and samples are loaded into the wells and any analyte present was bound by immobilized antibodies. After removing any unbound substance, a biotin-conjugated antibody specific to the analyte was added to the wells. After washing, streptavidin-horseradish peroxidase (SA-HRP) is added to the wells. Following a wash, a substrate solution was added and color developed in proportion to the amount of analyte. The color development was stopped and the intensity of the color was measured spectrophotometrically at a wavelength of 450 nm. The minimum detectable concentration of the assay was 0.06 ng/ml. Intra- and inter-assay coefficients of variation were between 10% and between 15%, respectively.

2.4. Statistical analysis

The data were analyzed using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA), and the results are presented as the mean ± SD. For continuous variables, an independent samples *t*-test was employed to compare the differences between two groups. For categorical clinical variables, chi-square tests were used to compare differences between groups. A Mann-Whitney *U* test and Kruskal-Wallis H test were performed for skewed data. Skewed data were logarithmically transformed to approximate a normal distribution. Pearson correlation coefficients were calculated to determine the associations between CST and related variables. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) predicting patients with T2DM based on CST level were calculated using univariate and multivariate logistic regression analyses after controlling for other potential covariates. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical and laboratory characteristics of patients and controls

The clinical and laboratory characteristics of the study subjects are shown in Table 1. There were no significant differences in age, gender, BMI, family history of T2DM, smoking prevalence, alcohol use, WHR, triglycerides, TC, or LDL between patients with newly diagnosed T2DM and the healthy controls. Patients with newly diagnosed T2DM displayed a significantly higher systolic blood pressure (SBP), FPG, fasting serum insulin, HbA_{1c} and HOMA-IR than the healthy controls. However, patients with newly diagnosed T2DM had a substantially lower level of HDL compared with the healthy controls.

3.2. Plasma CST levels of patients and control subjects

The CST values were normally distributed after logarithmic transformation. The newly diagnosed T2DM patients 26.53 ng/ml (range, < 2.5–72.1 ng/ml) had lower CST plasma levels than the healthy controls 34.15 ng/ml (range, < 10.95 to 99.63 ng/ml, P = 0.01) (Fig. 1).

3.3. Relationship between plasma CST levels and metabolic parameters

As shown in Table 2, plasma CST was positively correlated with HDL and negatively related to FPG, serum insulin, HOMA-IR and HbA1c in all subjects. Further analysis showed that CST levels were

Download English Version:

https://daneshyari.com/en/article/5514607

Download Persian Version:

https://daneshyari.com/article/5514607

Daneshyari.com