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ORIGINAL ARTICLE

Relationship between serum betatrophin levels and the first-phase of glucose-stimulated insulin secretion

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Betatrophin;
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Summary
Aims: To examine circulating betatrophin concentrations in subjects with different glucose tolerance status and to investigate the relationship between serum betatrophin levels and first-phase of glucose-stimulated insulin secretion.
Methods: Serum betatrophin concentrations were measured in 110 age- and sex-matched subjects: 47 newly diagnosed type 2 diabetes mellitus (T2DM), 29 impaired glucose tolerance (IGT) and 34 normal glucose tolerance (NGT). Oral glucose tolerance test and intravenous glucose tolerance test were performed to assess glucose tolerance and first-phase of glucose-stimulated insulin secretion.
Results: Serum betatrophin levels were significantly higher in the T2DM and IGT group than in the NGT group (2.10 ± 1.16 ng/mL vs 0.77 ± 0.44 ng/mL, 1.73 ± 1.28 ng/mL vs 0.77 ± 0.44 ng/mL; $P < 0.01$). The AIR and AUC among the three groups showed a progressive decrease from the NGT to IGT group with the lowest value in the T2DM group ($P < 0.01$). Betatrophin were found to be positively correlated with BMI, waist circumference (WC), homeostatic model assessment of insulin resistance (HOMA-IR) and triglyceride (TG), and inversely associated with HDL-c (all $P < 0.01$), but not significantly correlated with 0—10 min insulin the area under the curve (AUC) and acute insulin response (AIR) ($P > 0.05$). Stepwise multiple regression analysis showed that HOMA-IR and TG were independently related to betatrophin ($P < 0.05$).

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Conclusion: Serum betatrophin concentrations were higher in T2DM and IGT, and were closely related to glucolipid disorder, insulin resistance, but not related to the first-phase of glucose-stimulated insulin secretion.

Introduction

Pancreatic β cells are perfect sensors of blood glucose levels and secrete just the right amount of insulin into the bloodstream to systemically regulate glucose and energy homeostasis [1]. Unfortunately, increasing evidence indicates that decreased functional beta-cell mass is the hallmark of Type 2 diabetes mellitus (T2DM) [2]. Betatrophin, a new bioactive peptide of 198 amino acids, also known as TD26 [3]/RIFL [4]/Lipasin [5]/ANGPTL8 [6], is encoded by the *Gm6484* gene in mice liver and fat [4—7]. In humans, however, betatrophin is primarily expressed in the liver and encoded by the *C19orf80* gene [3,4].

Recently, expression of betatrophin is found to promote a dramatic proliferation of pancreatic β cells in a S961 induced insulin resistance mouse model [7]. Moreover, transient expression of betatrophin in mouse liver significantly and specifically promotes pancreatic β cell proliferation, expands β cell mass, and improves glucose tolerance [7]. It opens up the possibility of future betatrophin treatment. However, studies on animals found human β cells were completely unresponsive to mouse betatrophin in the transplant setting [8], while mouse β cells responsive to human betatrophin employing ultrasound-targeted microbubble destruction (UTMD) to deliver human ANGPTL8 gene plasmids to normal adult rats [9]. It is not very clear whether human betatrophin is responsive specifically to their own islet β cells.

It is noteworthy that first-phase of insulin secretion to intravenous glucose tolerance test (IVGTT) not only may be a better indicator of early β-cell dysfunction than HOMA-β [10], but gives the best correlation to β cell mass determined histologically [11]. Additionally, previous studies indicated the deficit of first-phase (acute) insulin secretion is a main characteristic in the early stage of T2DM [12,13] and an independent predictor of T2DM [14,15]. The relative importance of first-phase insulin secretion may be greater than the second phase insulin secretion, prompting numerous studies into its regulation. Therefore, we initiated a study to explore the circulating concentrations of betatrophin and the relationship with first-phase of glucose-stimulated insulin secretion and glucose metabolism in subjects with different glucose tolerance status.

Subjects

The trial was conducted from September 2014 to January 2015. A total of 110 individuals (mean age ± SD, 53 ± 13 yr; range, 81—27 yr; 55 males) were recruited and evaluated for glucose tolerance using a 75 g oral glucose tolerance test (OGTT). According to the World Health Organisation diagnostic criteria of diabetes in 1998 [16], the subjects were divided into three groups: 34 with normal glucose tolerance (NGT), 29 with impaired glucose tolerance (IGT) and 47 with type 2 diabetes (T2DM). The type 2 diabetic patients were newly diagnosed without any anti-diabetes treatment, including diet, exercise and medications. All of the subjects were not administrated any medications that are known to affect glucolipid metabolism over the past 3 months. Exclusion criteria included diagnosis of type 1 diabetes, gestational diabetes, lactation diabetes, secondary obesity, acute or chronic diabetes complications, acute inflammation, hepatic and renal disease, or other known major diseases. The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, and all participants provided informed written consent before enrolment in the study.

Materials and methods

Anthropometric measurements

All subjects were asked about the medical history. Height, body weight, waist circumference (WC), hip circumference, blood pressure and other indicators were measured in all subjects with standard protocols. Height, waist, and hip circumferences were measured to a minimum recorded unit of 0.1 cm, and blood pressure was measured twice with a

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