Mini Review

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Patients with Type 2 Diabetes Have Increased Circulating Betatrophin

Abstract

Betatrophin has recently been described as an important hormone to stimulate large expansion of beta cells in response to insulin resistance and obesity in mice. This finding has raised interest in the development of anti-diabetic drugs with betatrophin as the active ingredient. However, circulating levels of betatrophin in patients with type 2 diabetes are not well known. The plasma betatrophin levels of 27 type 2 diabetic patients and 18 controls matched for sex, age and BMI were measured. Study participants were characterized by BMI, waist and hip circumference, fasting blood pressure and plasma lipids, creatinine, glucose, HbA1c, and C-peptide. The HOMA2 indicator has been calculated. Betatrophin was 40% higher in patients with type 2 diabetes. Betatrophin was positively correlated with age in controls and HbA1c in patients with type 2 diabetes. All study participants were insulin resistant with intermediate HOMA2B IR. The average in both groups was greater than 2%. Control individuals had impaired fasting glucose levels. In this report on betatrophin levels in type 2 diabetes and insulin resistance, elevated betatrophin levels were measured in patients with type 2 diabetes. Future studies are clearly needed to characterize precisely the role of betatrophin, if any, in the regulation of human beta cell mass.

Keywords: Betatrophin • Insulin • Diabetic

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Introduction

The hormone betatrophin, mainly produced in the liver, has recently been described as a major promoter of beta cell proliferation in response to obesity and insulin resistance in mice. In fact, a 17-fold increase in beta cell proliferation was observed when this hormone was overexpressed. Secreted proteins have also been found in human blood. Currently, the development of drugs containing betatrophin as an active ingredient is under consideration for the treatment of type 1 and type 2 diabetes. In humans, an increase in beta cell mass of approximately 50% is observed during obesity. Although minimal replication of human beta cells has been observed in such autopsy studies and in a mouse model of insulin resistance induction, human beta cells can proliferate to environmental response to obesity in mice. In contrast, in obese individuals with type 2 diabetes, a deficit of 40-60% of beta cell mass compared with healthy controls of the corresponding BMI has been reported [1-5]. This may simply reflect the loss of beta cells through apoptosis in diabetes and may also reflect an underlying defect in beta cells to adapt and grow, in response to obesity and insulin resistance. The present study aimed to investigate circulating betatrophin levels in type 2 diabetic patients and BMI-matched controls without a diagnosis of diabetes, testing the hypothesis of betatrophin deficiency, in people with diabetes.

Diagnosis criteria

Inclusion criteria were based on WHO diagnostic criteria. Only patients on treatment for hypoglycemia were included. Most patients received metformin as monotherapy or in combination with another oral antidiabetic agent, and one patient was treated with metformin in combination with exogenous insulin. Two patients had ADO in monotherapy and two patients received exogenous insulin. Non-diabetic controls matched for age, sex, and BMI were recruited by advertisement at a local healthcare center. Inclusion criteria for controls that fall outside the parameters described; no history of diabetes and no first-degree relatives with diabetes. All study participants were characterized for weight, height, waist and hip circumference, blood pressure and family history of diabetes, Blood samples taken after a night of fasting. Common laboratory parameters were analyzed at the central laboratory of

Uppsala University Hospital. Separated plasma was obtained in EDTA tubes by centrifugation and then directly frozen. Betatrophin levels were analyzed by Wuhan Eiaab Science ELISA, Wuhan, China; Directory number, E11644h according to the manufacturer's protocol. All samples were analyzed in duplicate and samples with coefficient of variation > 15% were excluded [6-8]. In a previous publication, we confirmed the reliability of ELISA values obtained by western immunostaining with the primary antibody Phoenix Pharmaceuticals, Phoenix, USA; WBK-051-55. Steady-state beta-cell function, insulin sensitivity, and insulin resistance were estimated by an up-to-date homeostasis model assessment and calculated based on fasting blood glucose and plasma C-peptide by computer [9].

The present work shows that plasma betatrophin concentrations in patients with type 2 diabetes mellitus are not lower than normal, but higher concentrations in subjects without diabetes have been noted. Therefore, although resistance to the effects of betatrophin in patients with type 2 diabetes cannot be ruled out, at least there is no obvious betatrophin deficiency to replace it in these individuals [10].

Discussion

Our correlation analysis also determined that plasma betatrophin concentrations in non-diabetic subjects increased with age. In addition, including patients with type 2 diabetes with altered metabolic control, plasma betatrophin concentrations were observed to increase with HbA1c. It should be noted that there is also a positive correlation between plasma betatrophin and plasma creatinine concentrations, which indicates that betatrophin is normally excreted in the urine, although there is no correlation between calculated GFR and betatrophin. Increased circulating betatrophin levels may reflect both increased secretion and decreased clearance of the hormone, but no difference in plasma creatinine or calculated GFR between patients with type 1, type 2 diabetes and their witnesses. Betatrophin belongs to the angiopoietin-like protein family, and in addition to betatrophin, goes by many different names: lipasin, HCC-associated protein TD26, RIFL, and angiopoietin-like protein 8. Overexpression of betatrophin in mice outcomes in increased serum triacylglycerol, and human genome-wide association studies have also shown that variations in genes are associated with lipid levels in the blood. In the present study, there was an inverse correlation between betatrophin levels and total plasma cholesterol. However, it is difficult to explain the relationship between betatrophin values and lipids because some of the patients in the study, especially diabetics, were being treated with lipid-lowering drugs. Indeed, plasma total cholesterol, LDL, and HDL were all reduced in patients with type 2 diabetes compared with controls. As this study included only 45 patients, any sub-analysis of betatrophin levels in patients with or without lipid therapy would be difficult to perform with sufficient statistical power. However, there did not appear to be a clear difference in plasma betatrophin levels between those treated with statins and those who did not.

Conclusion

We conclude that plasma betatrophin levels are increased in patients with type 2 diabetes compared with age, sex and BMI-matched controls with similar levels of insulin resistance. Therefore, there is no obvious betatrophin deficiency to replace in these individuals with diabetes, and as in our previous study in type 1 diabetics, an increase in plasma betatrophin levels appeared to as insufficient to compensate for the development of the disease by triggering large increases in beta cells. Future studies are clearly needed to characterize the exact role, if any, of betatrophin in the regulation of human beta cell mass.

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