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The molecular evidence-based interactions between betatrophin and diabetes mellitus : A descriptive analytical clinical research.

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Abstract

Betatrophin is a protein of 198 amino acids. In humans, it is encoded by C19orf80 gene. Angiopoietin-like protein (ANGPTL)8 (TD26, RIFL, Lipasin, Betatrophin), located in the corresponding intron of DOCK 6, is a newly recognised ANGPTL family member that is expressed mostly in liver and adipose tissue, and is markedly upregulated by feeding and suppressed by fasting. It has been implicated in both triglyceride and glucose metabolism. Hepatic overexpression of ANGPTL8 promotes proliferation of pancreatic β cells, causes hypertriglyceridemia, increased insulin secretion and contributes to glucose homeostasis. The objective of this descriptive analytical clinical research was to explore the molecular evidence-based interactions between betatrophin and diabetes mellitus. This descriptive analytical clinical research, illuminating on the multi-directional molecular evidence-based interactions between betatrophin and diabetes mellitus, would always remain a significant milestone in the future revelations of yet more efficacious molecular mechanisms of betatrophin, as a beneficial hypoglycaemic pharmacotherapeutics.

Keywords: Betatrophin, Diabetes mellitus, Endocrinology, Molecular Pharmacology, Evidence Based Medicine.

Introduction

Betatrophin is a protein of 198 amino acids. In humans, it is encoded by C19orf80 gene.

Angiopoietin-like protein (ANGPTL)8 (TD26, RIFL, Lipasin, Betatrophin), located in the corresponding intron of DOCK 6, is a newly recognised ANGPTL family member that is expressed mostly in liver and adipose tissue, and is markedly upregulated by feeding and suppressed by fasting. It has been implicated in both triglyceride and glucose metabolism. Hepatic overexpression of ANGPTL8 promotes proliferation of pancreatic β cells, causes hypertriglyceridemia, increased insulin secretion and contributes to glucose homeostasis. Co-expression of ANGPTL8 and ANGPTL3 increased plasma triglyceride level more than 10-fold, suggesting that the two proteins act together, and co-ordinate the transport of triglycerides to tissues in response to food intake. ANGPTL8, a paralog of ANGPTL3 that arose through duplication of ancestral DOCK gene, regulates post-prandial TAG and fatty acid metabolism by

controlling activation of its progenitor, and perhaps other ANGPTLs. Inhibition of ANGPTL8 provides a new therapeutic strategy for reducing plasma lipoprotein levels.[1, 2, 3, 4, 5, 6, 7]

Objective

The objective of this descriptive analytical clinical research was to explore the molecular evidence-based interactions between betatrophin and diabetes mellitus.

Methods and results

This descriptive analytical clinical research was done to analyse the molecular evidence-based interactions between betatrophin and diabetes mellitus.

The betatrophin protein was initially detected in 2004 as a tumor-associated antigen in patient serum. Betatrophin, also known as TD26/RIFL/lipasin/ANGPTL8/C19orf80, is a novel protein predominantly expressed in human liver. Very few subsequent studies focused on further characterization of this novel protein following its identification. In 2012, betatrophin was shown to correlate with the serum triglyceride (TG) level and regulate lipase activity in mouse for the first time. More recently, in a study, it was demonstrated that murine pancreatic cell proliferation is potently activated by β-cell agonists through stimulation of hepatic betatrophin expression. Accumulating data have highlighted the lipid metabolism function of betatrophin. Till the present times, several betatrophin orthologs have been identified in mammals. Increasing evidence has revealed an association between betatrophin expression and serum lipid profiles, particularly in patients with obesity or diabetes. Stimulators of betatrophin, such as insulin, thyroid hormone, irisin and caloric intake, are usually relevant to energy expenditure or thermogenesis. In murine models, serum triglyceride levels as well as pancreatic cell proliferation are potently enhanced by betatrophin. Intriguingly, conflicting phenomena have also been reported that betatrophin suppresses hepatic triglyceride levels, suggesting that betatrophin function is mediated by complex regulatory processes. However, its precise physiological role remains unclear at present. In hepatoma cells, betatrophin is mainly localized in the cytoplasm with vesicle-like distribution. Several patterns of betatrophin vesicles with variable sizes have been detected. The small dot-like betatrophin vesicles (≤1 μm) are usually solid and dispersed in the cytoplasm. The larger betatrophin vesicles (1–2 μm) become empty and are often associated with lysosome-associated membrane protein 2 (LAMP2) and/or lipid droplet protein perilipin2 (PLIN2), suggesting the involvement of betatrophin in hydrolysis degradation or the lipid regulation pathway. Occasionally, betatrophin vesicles are clumped together and adhered to the large LAMP2 vacuoles (2–10 μm), indicating that a proportion of betatrophin is functionally associated with large multivesicular bodies (MVBs). These phenomena were further demonstrated with organelle density fractionation data showing that betatrophin co-fractionates with light PLIN2 and heavy LAMP2, consistent with its cellular localization. Given that several potential N-myristoylation sites are highly conserved within betatrophin, further molecular research is required to address the association between N-myristoylation and cellular localization.

Another study reported the upregulation of betatrophin mRNA in a 3T3-L1 preadipocytes differentiation model. Based on subsequent studies on nutritional regulation, the group proposed that betatrophin is a novel regulator of lipid metabolism. They found that, during insulin-induced fat lipogenesis, betatrophin transcripts were also induced in mouse 3T3 and human adipocyte cells. Interestingly, insulin-induced betatrophin expression was

obligatory in the presence of glucose. Once 3T3-L1 was separately maintained in glucose or insulin, no significant induction of betatrophin was evident. This finding suggests the double-checked and crosstalk between glucose and insulin stimuli are necessary for betatrophin induction. It was also shown that S961, a 43 amino acid peptide that binds the insulin receptor, specifically induces betatrophin expression in liver and white fat. Further investigation led to the conclusion that S961 increases insulin levels through betatrophin and mediates pancreatic cell regeneration. Notably, the S961 concentrations of 5–20 nmol/week used, were sufficient to antagonize the insulin receptor *in vitro* and *in vivo*. However, S961 also showed insulin agonist activity at concentrations of 1–10 nM. Importantly, another study demonstrated that while S961-treated rats exhibit hyperinsulinemia, hyperglycemia and insulin resistance, S961 treatment reduces BAT and WAT adipocyte sizes as well as hepatic glycogen. This finding is inconsistent with other results showing that betatrophin expression is not necessarily positively correlated with lipid content or lipogenesis activity. It was also observed that betatrophin induction during the gestation stage, displays accelerated β-cell replication. Serum levels of TG and non-HDL cholesterol have been shown to be increased in late pregnancy mice whereas the HDL cholesterol level is reduced. In humans, TG, total/HDL/LDL cholesterol contents are further increased at different periods of gestation. Normal gestation shifts the LDL profile towards the smaller, denser lipid species, which are more susceptible to oxidation and lipolysis. The results collectively indicate that betatrophin expression induced by insulin is either directly triggered by elevated mRNA transcription or indirectly coordinated with other insulin-mediated processes.

The thyroid hormone (TH) mediates cell growth, differentiation and homeostasis by binding to the nuclear thyroid hormone receptor. Various regulatory pathways involving TH have been characterized within distinct tissues, stages and species. For maintenance of hepatic lipid homeostasis, the thyroid hormone directs regulation or crosstalk with nutrient-activated nuclear receptors to regulate lipid-associated gene transcription. Intriguingly, on the one hand, thyroid hormone promotes lipid catabolism through decreasing the total amount of cholesterol, low-density lipoproteins, and chylomicron particles. On the other hand, T3 induces upregulation of several lipogenic genes, including acetyl-CoA carboxylase, FAS (fatty acid synthase), and NR1H3 (nuclear receptor subfamily 1, group H, member 3/liver X receptor-α), promoting lipid biosynthesis. Notably, T3 also induces upregulation of several lipid metabolic genes, including low-density lipoprotein receptors, CYP7A1 (cytochrome P450, family 7, subfamily A, polypeptide 1/cholesterol-7α hydroxylase), and LIPC (lipase, hepatic). Although the thyroid hormone stimulates lipogenesis in experimental models, decrease in triglycerides, hepatic triglycerides and VLDL is simultaneously observed. Thus, other thyroid hormone activities, such as increased fatty acid (FA) oxidation, may a additionally contribute to lipid clearance.

In yet another study, it was revealed that betatrophin mRNA is induced by the thyroid hormone in HepG2 cells. Subsequent studies confirmed that transcriptional regulation is dependent on the thyroid hormone receptor that binds to the betatrophin upstream element. Betatrophin is a novel gene dramatically activated by the thyroid hormone.

Interestingly, although the thyroid gland is present in all vertebrates, thyroid hormones affect metabolic rates and

thermogenesis only in homoeothermic species. Such a role appears to be acquired during late evolution, highlighting the phylogenetic character of betatrophin gene evolution in mammals. It was further showed that T3-induced betatrophin is further elevated by ammonium chloride, a weak base lysosomotropic alkalinization agent, implying that a proportion of betatrophin is degraded through the endosomal/lysosomal pathway.[2, 4, 8]

Another study on betatrophin was conducted to figure out the underlying mechanism of betatrophin in insulin resistance (IR) in type 2 diabetes mellitus (T2DM). First, fasting serum betatrophin, fasting blood glucose (FBG), insulin, total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) were detected in T2DM children. The homeostasis model assessment of insulin resistance (HOMA-IR), Gutt insulin sensitivity index (ISIG) and Matsuda insulin sensitivity index (ISIM) were calculated. A T2DM-IR mouse model was induced by high-fat diet, with the expression of GSK-3β and PGC-1α detected. Besides, HepG2 cells were induced by a high concentration of insulin to establish an IR cell model (HepG2-IR). The cell viability, glucose consumption, liver glycogen content, inflammation, and fluorescence level of GSK-3β and PGC-1α were analyzed. The results demonstrated that betatrophin was highly expressed in serum of T2DM children and was positively correlated with FBG, insulin, TC, TG, LDL-C and HOMA-IR, while negatively correlated with ISIG and ISIM. Betatrophin and GSK-3β in the liver tissues of T2DM-IR mice were increased, while the PGC-1α expression was decreased. Betatrophin expression was negatively correlated with PGC-1α and positively correlated with GSK-3β. Silencing of betatrophin enhanced insulin sensitivity through the activation of GSK-3β/PGC-1α signaling pathway. *In* vitro experiments also found that silencing of betatrophin promoted glucose consumption and glycogen synthesis while inhibited inflammation. The findings concluded that silencing of betatrophin could enhance insulin sensitivity and improve histopathological morphology through the activation of GSK-3β/PGC-1α signaling pathway.[9]

In a further study, the effect of betatrophin overexpression by human adipose-derived mesenchymal stem cells (ADMSCs) by in vitro experiments, as well as following their transplantation into a mice with streptozotocin (STZ)-induced diabetes, was evaluated. The overexpression of betatrophin did not affect the ADMSCs in terms of proliferation, differentiation and morphology. However, the co-culture of human islets with ADMSCs overexpressing betatrophin (ADMSCs-BET) induced islet proliferation, β-cell specific transcription factor expression, and the islet production of insulin under the stimulation of glucose or KCl and Arg. In addition, ADMSCs-BET enhanced the anti-inflammatory and anti-apoptotic effects of the co-cultured islets compared with ADMSCs cultured alone. In mice with STZ-induced diabetes, the transplantation of ADMSCs-BET ameliorated the hyperglycemia and weight loss associated with STZ-induced diabetes; ADMSCs-BET also significantly enhanced the ratio of β-cells per islet compared to the transplantation of ADMSCs alone. Thus, this study demonstrated a novel strategy for inducing β-cell regeneration. ADMSCs-BET may replace insulin injections by increasing the number of endogenous insulin-producing cells in patients with diabetes. From this study, it was concluded that the combined strategy of ADMSC transplantation and gene therapy may prove to be a useful therapy for the treatment of diabetes.[10]

Yet another study was conducted to examine circulating betatrophin levels in subjects with different glucose tolerance status and its correlation with insulin resistance. In this study, the serum betatrophin levels were measured using an ELISA in age-, sex-, body mass index-, and blood lipid-matched subjects with normal glucose tolerance (n = 137), isolated impaired fasting glucose (n = 69), isolated impaired glucose tolerance (n = 120), and newly diagnosed T2DM (n = 112) from the Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal Study. The results showed that serum betatrophin levels were elevated in patients with T2DM compared with subjects with normal glucose tolerance, isolated impaired fasting glucose, or isolated impaired glucose tolerance (798.6 ± 42.5 vs 692.7 ± 29.0, $P < 0.05$, vs 682.7 ± 43.0, $P < 0.05$, vs 646.8 ± 34.3 pg/mL, $P < 0.01$). Betatrophin levels positively correlated with the index of homeostasis model assessment of insulin resistance (partial r = 0.11); inversely correlated with quantitative insulin sensitivity check index (partial r = - 0.11), the Gutt insulin sensitivity index (partial r = - 0.12), and the Matsuda insulin sensitivity index (partial r = - 0.11) after controlling for age, sex, body mass index, and blood lipid in all participants (all values of $P < 0.05$). Thus, it was concluded that the circulating betatrophin levels are increased in patients with T2DM and associated with the indexes of insulin resistance.[11]

A study measured for the first time the betatrophin concentrations in humans, which tested the hypothesis that there would be no difference in circulating betatrophin concentrations between patients with type 1 diabetes and healthy individuals. In this study, betatrophin concentrations in plasma of 33 patients with type 1 diabetes and 24 age-matched healthy controls were measured by ELISA. The study participants were characterised for blood lipids, BMI, plasma glucose and HbA1c, and, for the diabetic patients, their insulin requirements and any residual C-peptide concentrations. The study findings presented that plasma betatrophin concentrations were normally ~300 pg/ml, but were approximately doubled in patients with type 1 diabetes. In the patients, there were no correlations between betatrophin and age, blood lipids, BMI, glucose control or insulin requirement, whereas in controls betatrophin levels increased with age. BMI, blood pressure and triacylglycerol, LDL-cholesterol and HDL-cholesterol levels were similar in patients and healthy controls. Therefore, it was concluded that the circulating concentrations of betatrophin are increased in type 1 diabetes in contrast with what was recently described in an insulin-deficient mouse model. However, increased betatrophin concentrations do not protect against loss of C-peptide. Betatrophin treatment in type 1 diabetes would therefore probably not be successful without the use of supraphysiological doses or a combination with immune regulatory treatment.[12]

Discussion

In a study, it was observed that the new hormone, betatrophin, derived from liver and white adipose tissue, which was found to promote beta cell proliferation in a mouse model of insulin resistance induced by S961, an antagonist of the insulin receptor. Therefore, this possessed a significantly increased possibility and proximity for the development of anti-diabetic therapeutics.

Several studies had shown that a significantly higher serum betatrophin levels among type 2 diabetics. But, many studies had also demonstrated the decline of the expression of betatrophin index. Yet in other studies, no statistically significant relationship between betatrophin

levels and type 2 diabetes mellitus was observed. Thus, these studies provided a three-directional plausible hypothetical evidence-based medical interaction between betatrophin activity and diabetes mellitus.

In a study, circulating levels of betatrophin were found to be approximately 40% higher in the type 2 diabetes patients in relation to their controls. There was a lower HOMA2%B among the type 2 diabetic patients, which reflected beta-cell function at steady state in relation to controls. There was no difference in HOMA2%S, or insulin sensitivity, and HOMA2 IR, or insulin resistance. The plasma levels of cholesterol, HDL cholesterol, and LDL cholesterol were comparatively higher among the controls. A positive correlation existed between betatrophin concentrations and age, which was not found among the type 2 diabetic patients. While a positive correlation between plasma betatrophin levels and HbA1c was found among the type 2 diabetic patients. There was a tendency towards the occurrence of a positive correlation between plasma betatrophin and plasma creatinine. Also, a tendency towards a negative correlation between plasma betatrophin and plasma cholesterol was observed.

Another study, contradicting the above-mentioned study results, demonstrated no difference in plasma betatrophin levels between type 2 diabetes patients and nondiabetic controls in a retrospective study of stored plasma samples.

Yet another study was conducted to examine circulating betatrophin levels in subjects with different glucose tolerance status and its correlation with insulin resistance. In this study, the serum betatrophin levels were measured using an ELISA in age-, sex-, body mass index-, and blood lipid-matched subjects with normal glucose tolerance, isolated impaired fasting glucose, isolated impaired glucose tolerance, and newly diagnosed T2DM from the Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal Study. The results showed that serum betatrophin levels were elevated in patients with T2DM compared with subjects with normal glucose tolerance, isolated impaired fasting glucose, or isolated impaired glucose tolerance. Betatrophin levels positively correlated with the index of homeostasis model assessment of insulin resistance; inversely correlated with quantitative insulin sensitivity check index, the Gutt insulin sensitivity index, and the Matsuda insulin sensitivity index after controlling for age, sex, body mass index, and blood lipid in all participants. Thus, it was concluded that the circulating betatrophin levels are increased in patients with T2DM and associated with the indexes of insulin resistance.

A study measured for the first time the betatrophin concentrations in humans, which tested the hypothesis that there would be no difference in circulating betatrophin concentrations between patients with type 1 diabetes and healthy individuals. In this study, betatrophin concentrations in plasma of patients with type 1 diabetes and 24 age-matched healthy controls were measured by ELISA. The study participants were characterised for blood lipids, BMI, plasma glucose and HbA1c, and, for the diabetic patients, their insulin requirements and any residual C-peptide concentrations. The study findings presented that plasma betatrophin concentrations were normally ~300 pg/ml, but were approximately doubled in patients with type 1 diabetes. In the patients, there were no correlations between betatrophin and age, blood lipids, BMI, glucose control or insulin requirement, whereas in controls betatrophin levels increased with age. BMI, blood pressure and triacylglycerol, LDL-cholesterol and HDL-cholesterol

levels were similar in patients and healthy controls. Therefore, it was concluded that the circulating concentrations of betatrophin are increased in type 1 diabetes in contrast with what was recently described in an insulin-deficient mouse model. However, increased betatrophin concentrations do not protect against loss of C-peptide. Betatrophin treatment in type 1 diabetes would therefore probably not be successful without the use of supraphysiological doses or a combination with immune regulatory treatment.

In a similar study, is was found that Log transformed circulating betatrophin was significantly increased in diabetic patients compared to healthy subjects. In a correlation analysis, age, HbA1c, fasting plasma glucose and Log triglyceride were strongly associated with Log betatrophin in all subjects. In type 1 diabetes, a correlation existed between Log betatrophin and Log CPR. Thus, evidence of significantly elevated circulating betatrophin is found in Japanese diabetic patients, which also suggests a possibility of association between the level of betatrophin and the levels of glucose and triglycerides.

Several reports have shown that serum betatrophin is increased in patients with diabetes, but this was not positively correlated with BMI. There was also no correlation of circulating betatrophin with BMI. Another study found that serum levels of lipasin/betatrophin were increased in overweight and obese subjects, which suggested that contradictory results. In a study, it was found that circulating betatrophin was decreased in patients with obesity and T2DM. In a measurement of a human recombinant betatrophin, two different kits showed linear regression, but arrived at a different result in serum samples measurement. While showing different results, serum betatrophin and BMI were negatively correlated in a former kit and positively correlated in a latter kit, thus pointing out the possibility that proteolytic cleavage of betatrophin might affect the difference determined by the kits, which was also influenced by the particular antibodies used against the N- or the C-terminus. Some studies support an elevation of serum betatrophin in diabetic patients, although the exact changes in serum betatrophin are yet to be determined. The role of betatrophin introduced (under the kidney capsule) into C57BL6/J mice islets and human beta cells in immunodeficient NOD-Scid mice was studied, and a marked increase in DNA replication in murine beta cells was found, whereas the human beta cells did not show any response. This suggested that the present form of betatrophin from mice might not induce proliferation of human beta cells, while human response to an altered or modified form of betatrophin, is yet to be studied. Another recent study showed that betatrophin did not affect mouse beta cell proliferation in betatrophin knockout mice, in mice with overexpression of betatrophin in the liver, and in mice administered S961, an insulin receptor antagonist. These controversial results might manifest due to the induced alterations or modifications brought about in the physiological mechanisms of mice, which instead might show altered or modified physiological responses to betatrophin. In one retrospective study, the correlation between circulating betatrophin with log CPR in linear regression, was analysed in three groups. In this study, only T1DM showed positive correlation. Another study revealed that circulating betatrophin was elevated in T1DM, and that it had no correlation C-peptide concentration. A prospective study with a large number of patients is needed to examine the potential protective effects of betatrophin on pancreatic beta cells in humans. Age,

glucose markers (HbA1c, FPG), and TG had strong association with betatrophin in correlation analysis. In yet another study, a positive correlation was found between betatrophin and age in non-diabetic controls, and a positive correlation was also found between betatrophin and HbA1c in patients with T2DM. Betatrophin is a novel lipid metabolism regulator that inhibits lipoprotein lipase (LPL) activity and increases the TG level. One study showed that betatrophin was associated with plasma atherogenic lipids in obesity and type 2 diabetes, and not associated with beta cell function and glucose homeostasis. In Angptl8 (betatrophin) knockout mice, serum TG was reduced after refeeding and low TG was associated with reduced very low-density lipoprotein secretion and increased LPL activity, but not with glucose impairment in glucose tolerance tests. Betatrophin (ANGPTL8) inhibits LPL activity directly or indirectly by promoting ANGPTL3 cleavage, since cleavage of ANGPTL3 inhibits LPL activity directly. In a study, it was demonstrated that Angptl8 (betatrophin) knockout mice have a low plasma TG level and that mice overexpressing betatrophin have an increased plasma TG level, which suggested that betatrophin might be an essential hormone for the maintenance of the TG level. A low-frequency and rare coding-sequence variant of ANGPTL8 (betatrophin) in humans results in low levels of TG. Thus, betatrophin might be an important hormone that explains high TG level in the pathophysiological mechanisms of diabetes.[5, 6, 7, 8, 9, 10, 11, 12]

Conclusion

This descriptive analytical clinical research, illuminating on the multi-directional molecular evidence-based interactions between betatrophin and diabetes mellitus, would always remain a significant milestone in the future revelations of yet more efficacious molecular mechanisms of betatrophin, as beneficial hypoglycaemic pharmacotherapeutics.

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