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"BETATROPHIN : A NOVEL MEDICAL ADVANCE" : A Medical Book.

A Descriptive Analysis, in Clinical Research.

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INTRODUCTION

Betatrophin

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, 8]

Gene for betatrophin

The gene for betatrophin is located on mouse chromosome 9 (gene symbol: Gm6484), and on human chromosome 19 (gene symbol: C19orf80).[1,2, 3, 4, 5, 6, 7, 8]

Discovery

The link between betatrophin and islet cell proliferation, was discovered by Douglas Melton and Peng Yi from the Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, USA in 2013. The earlier names of betatrophin were TD26, RIFL, Lipasin, and ANGPTL8. Betatrophin is a member of angiopoietin-like gene family and shares extensive homology with ANGPTL4 and ANGPTL3.[1, 2, 3, 4, 5, 6, 7, 8]

METHODS

A Descriptive Analysis, in Clinical Research

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.[3, 5, 9]

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.[10]

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.[11]

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.[12]

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.[13]

DISCUSSION

Functions

Betatrophin acts as a putative peptide hormone found in mice. It causes dramatic pancreatic beta cell proliferation and beta cell mass expansion. On parenteral administration of betatrophin cDNA in mice, it initiates its action at pancreas, for lowering the blood sugar level. The encoded 22kDa protein contains N-terminal secretion signal and two coiled-coil domains, and lacks C-terminal fibrinogen-like domain (unlike other angiopoietin-like proteins), like ANGPTL4 and ANGPTL3. It inhibits lipoprotein lipase and elevates the circulating triglyceride levels in mice. Mice lacking betatrophin/ANGPTL8 exhibits markedly decreased uptake of VLDL-derived fatty acids into adipose tissue and improves glucose tolerance in mice. The antidiabetic drugs or subcutaneous insulin injection (a) do not provide same degree of glycaemic control as functional pancreatic beta cells, and (b) do not prevent debilitating consequences of the disease. Betatrophin causes (a) long-term restoration of normal glycaemic control, and (b) potentially curative therapy.[1, 2, 3, 4, 5, 6, 7, 8]

Mechanism of Action

The liver-specific deletion of insulin receptor, causes a compensatory increase in pancreatic beta cell replication (Michael *et al*, 2000). The overexpression of constitutively active MEK1 (mitogen-activated or extracellular signal–regulated protein kinase) kinase in mouse liver increases replication rate in pancreatic beta cells and improves glucose tolerance through innervation-dependent mechanism (Imai *et al*, 2008). Although, it is unknown how liver signals pancreatic beta cells to proliferate is unknown. The recent work by Kulkarni's group

indicated at the possibility that liver cells secrete a protein that acts directly on the islet cells (El Ouaamari *et al*, 2013; Flier *et al*, 2001).[1, 2, 3, 4, 5, 6, 7, 8]

Molecular Mechanisms

The molecular mechanisms by which ANGPTL8/betatrophin regulates glucose metabolism are poorly understood in human. Two sub-clones of HepG2 cells, ANGPTL8/betatrophin knockouts and ANGPTL8/betatrophin over-expressors, were established using TALENs (transcription activator-like effector nucleases) and through stable transfection, respectively. Over-expression of ANGPTL8/betatrophin enhanced the insulin-stimulated activation of the Akt-GSK3β or Akt-FoxO1 pathway, no matter whether the cells were present with insulin resistance or not. In contrast, knockout of ANGPTL8/betatrophin did not affect the Akt-GSK3β or Akt-FoxO1 pathway unless the HepG2 cells were preset with insulin resistance. ANGPTL8/betatrophin might play an important role in glucose metabolism in the context of insulin resistance.[1, 2, 3, 4, 5, 6, 7, 8]

Secretion

Betatrophin is secreted by liver, in the mice, and by white adipose tissue and brown adipose tissue, in the humans. It is reduced by fasting and elevated upon insulin resistance and during pregnancy.[1, 2, 3, 4, 5, 6, 7, 8]

Earlier studies demonstrated that mouse body weight and fat mass as well as serum triglycerides and NEFA (non-esterified fatty acid) levels are reduced in betatrophin-null mice whereas serum cholesterol, plasma glucose (fasted and re-fed) and insulin levels are not significantly altered, compared with wild-type littermates. The main decrease in triglyceride species was derived from the VLDL fraction. Serum triglycerides were particularly reduced in betatrophin-null mice after re-feeding. In contrast to serum triglyceride levels, hepatic triglyceride levels were not reduced in betatrophin-null mice. Mice lacking betatrophin expression specifically induce plasma lipase activity whereas they suppress VLDL-TG uptake in WAT after re-feeding. Furthermore, although serum betatrophin levels are associated with atherogenic lipid profiles, betatrophin-null and wild-type mice were similar in terms of VLDL-TG uptake in heart with fasting or re-feeding regimens. Upon knockdown of betatrophin, the intracellular TG content was decreased in 3T3-L1 adipocyte cells, but increased in HepG2 hepatic cells. In another study, it was showed that adenovirus-mediated betatrophin expression in mice liver enhances serum TG levels. Additionally, recombinant betatrophin proteins expressed in *E. coli* lacking eukaryotic modifications were sufficient to

inhibit LPL activity. Quagliarini and co-workers further clarified that the betatrophin-induced serum TG content is ANGPTL3-dependent and co-expression of betatrophin with ANGPTL3 further increases the serum TG level. Interestingly, overexpression of betatrophin in ANGPTL3-deficient mice conversely reduced the serum TG, cholesterol and NEFA levels. These results suggest that ANGPTL3 levels are critical for the switch of betatrophin function. Moreover, thyroid hormone-induced betatrophin-mediated lipolysis, in concert with the thyroid hormone suppresses ANGPTL3 activity. Yet another study focused on the insulin receptor antagonist, S961, which induces hyperglycaemia, hyperinsulinaemia and glucose intolerance in mice. Microarray analysis showed that betatrophin is potently induced by S961 in mouse liver and white adipocytes. The group further detected the secreted form of betatrophin, as observed from ectopic expression, in the culture supernatant and plasma of Hepa 1–6 and liver cells, respectively. More importantly, overexpression of betatrophin in mouse liver significantly induced pancreatic β-cell proliferation, mass expansion and insulin production. The percentages of dividing cells were markedly enhanced by betatrophin in pancreatic cells, whereas no significant alterations were observed in liver, WAT or BAT cells. Betatrophin also promoted increments of the Ki67-positive signal and the proliferation activators cyclin A1, cyclin F and E2F2, while inhibiting the suppressors cdkn1a and cdkn2a in pancreatic islet cells. Betatrophin-overexpressing mice showed lower blood glucose and elevated fasting insulin in plasma. In contrast to S961, insulin resistance was not induced by betatrophin overexpression. Taken together with previous findings, insulin-induced betatrophin might not act through insulin receptor. At the high level of serum glucose, insulin promotes betatrophin expression in the presence of glucose. Elevated betatrophin protein further activates β-cell proliferation and insulin production which promotes glucose uptake in storage cells. Once the glucose levels are decreased and insufficient for insulin-induced betatrophin, positive feedback was blocked. On the other hand, hyperglycaemia was induced by S961-inhibited insulin receptor and glucose uptake. Thus, insulin-induced TD26 and consequent β-cell proliferation and insulin production would not cease under hyperglycemia. These findings may explain why insulin resistence was induced by S961, but not induced by betatrophin. Thus, betatrophin may provide a novel therapeutic approach for the treatment of diabetes through pancreatic cell regeneration.[3, 4, 6, 9]

Clinical Significance

Betatrophin treatment augments or replaces insulin injections by increasing the number of endogenous insulin-producing cells in diabetics. It is also therapeutically used in the treatment for type II diabetes, and perhaps even type I diabetes.[1, 2, 3, 4, 5, 6, 7, 8]

The research studies and clinical trials conducted with betatrophin would certainly remain innumerous wise landmarks in the development of more appropriate, more efficacious, safer, more obtainable and more economic anti-diabetic prophylactic and therapeutic approaches.

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CONFLICTS OF INTEREST

No conflicts of interest.

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