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Effects of biotin supplementation in the diet on insulin secretion, islet gene expression, glucose homeostasis and beta-cell proportion☆

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Abstract

Besides its role as a carboxylase cofactor, biotin has a wide repertoire of effects on gene expression, development and metabolism. Pharmacological concentrations of biotin enhance insulin secretion and the expression of genes and signaling pathways that favor islet function *in vitro*. However, the *in vivo* effects of biotin supplementation on pancreatic islet function are largely unknown. In the present study, we investigated whether *in vivo* biotin supplementation in the diet has positive effects in rodent pancreatic islets. Male BALB/cAnN Hsd mice were fed a control or a biotin-supplemented diet over 8 weeks postweaning and tested for glucose homeostasis, insulin secretion, islet gene expression and pancreatic morphometry. Insulin secretion increased from the islets of biotin-supplemented mice, together with the messenger RNA (mRNA) expression of several transcription factors regulating insulin expression and secretion, including forkhead box A2, pancreatic and duodenal homeobox 1 and hepatocyte nuclear factor 4α. The mRNA abundance of glucokinase, Cacna1d, acetyl-CoA carboxylase, and insulin also increased. Consistent with these effects, glucose tolerance improved, and glucose-stimulated serum insulin levels increased in biotin-supplemented mice, without changes in fasting glucose levels or insulin tolerance. Biotin supplementation augmented the proportion of beta cells by enlarging islet size and, unexpectedly, also increased the percentage of islets with alpha cells at the islet core. mRNA expression of neural cell adhesion molecule 1, an adhesion protein participating in the maintenance of islet architecture, decreased in biotin-supplemented islets. These findings provide, for the first time, insight into how biotin supplementation exerts its effects on function and proportion of beta cells, suggesting a role for biotin in the prevention and treatment of diabetes.
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Keywords: Biotin supplementation; Insulin secretion; Beta cell gene expression; Beta-cell proportion; Islet architecture

1. Introduction

Increasingly, vitamins are being recognized as mediators of gene expression [1,2], illuminating the connection between nutritional signals and biological functions. Vitamin research has identified important transcription factors [3] and has led to the development of new therapeutic agents for different diseases [4–6] including diabetes [7,8]. Although less is known about water-soluble vitamins as genetic modulators, evidence of their effects on gene expression is increasing.

Biotin is a water-soluble vitamin that acts as a covalently bound coenzyme of carboxylases. Unrelated to this role, pharmacological concentrations of biotin modify gene expression (reviewed in Ref. [9]) and have a wide repertoire of effects on systemic processes (reviewed in Ref. [10]). DNA microarray studies and high-throughput immunoblotting studies have aided in the identification of thousands of genes whose expression is modified by biotin at both the transcriptional and the posttranscriptional levels [11,12]. Critical genes for glucose homeostasis, such as hepatic glucokinase [13] and insulin receptor [14], increase their expression in response to biotin supplementation, while the expression of several gluconeogenic

Abbreviations: Foxa2, forkhead box A2; Hnf4α, hepatocyte nuclear factor 4α; Ncam1, neural cell adhesion molecule 1; PDX-1, pancreatic and duodenal homeobox 1; PPARα, peroxisome proliferator activated receptor alpha; PPARγ, peroxisome proliferator activated receptor gamma; SREBF1, sterol regulatory element binding transcription factor 1.

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genes in diabetic rats is decreased by pharmacological concentrations of biotin [15,16].

Studies in vitro by others [17,18] and our group [19,20] have consistently found that acute exposure to pharmacological doses of biotin enhances glucose-stimulated insulin secretion. Treatment of cultured islets with 1 to 10 μmol/l biotin for 30 min to 24 h increase insulin secretion both at basal (5.5 mmol/l) and stimulatory (16 mmol/l) glucose concentrations [17,19,20]. The impact of biotin on insulin secretion is dose dependent [18] and unique among the B vitamins [17].

Pharmacological concentrations of biotin *in vitro* increase the expression of genes that are critical for maintaining the differentiated phenotype of the beta cell, preserving beta-cell mass (proportion of beta cells) and glucose-stimulated insulin secretion [19–22]. Culturing isolated rat islets with biotin increases the expression of pancreatic and duodenal homeobox 1 (*Pdx-1)* [22], a critical transcription factor for the expression of insulin and for several genes involved in insulin synthesis and secretion (reviewed in Ref. [23]). Studies by others using the RIN1046-38 insulinoma cell line [21] and by our group using isolated islets from rats [19,20] have found that pharmacological concentrations of biotin augment the expression of beta-cell glucokinase, the rate-limiting enzyme in glucose-stimulated insulin secretion [24] and a determinant factor in beta-cell regeneration [25]. We have also found that the mechanism by which biotin increases the expression of *Glucokinase* involves enhancing insulin secretion through the cyclic guanylate monophosphate (cGMP)/protein kinase G (PKG) signaling pathway, which increases ATP levels and, thus, beta-cell membrane depolarization. Insulin secretion, in turn, increases beta-cell *Glucokinase* messenger RNA (mRNA) expression via autocrine stimulation of Phosphoinositol-3-kinase (PI3K)/Akt signaling [19].

In line with these effects of biotin on glucose metabolism and insulin secretion, pharmacological doses of biotin lowered hyperglycemia and ameliorated diabetes in some [26–28] but not all [29] studies done in humans. In a group of patients with type 1 diabetes, supplementation with 16 mg/day of biotin with removal of insulin treatment for 1 week considerably decreased hyperglycemia [26]. In Japanese patients with type 2 diabetes [27] and in patients undergoing hemodialysis [28], pharmacological doses of biotin improved glucose tolerance.

Biotin supplementation also ameliorated hyperglycemia in animal models of diabetes. In KK mice, a genetically diabetic model of moderate hyperglycemia and insulin resistance, biotin administration for 10 weeks lowered postprandial glucose levels and improved both glucose tolerance and insulin sensitivity [30]. In spontaneously type-2 diabetic Otsuka Long-Evams Fatty (OLETF) rats, dietary biotin supplementation also improved glucose tolerance [31].

The evidence that biotin has favorable effects on glucose metabolism has led to the development of commercially available diabetes medications [8,32], containing pharmacological amounts of biotin 40- to 166-fold increase compared with the reference dietary intake of 30 μg/day [33]. However, in spite of the importance of the pancreatic islet in maintaining normal glucose homeostasis, no studies have addressed the effect of *in vivo* biotin supplementation on the pancreatic beta cell. Since beta-cell compensation is critical to prevent diabetes development [34], in the present study, we investigated the effects of biotin supplementation on beta-cell function, gene expression and beta-cell proportion.

2. Materials and methods

2.1. Animal model and experimental design

Three-week old male BALB/cAnN Hsd mice from the animal facility at the Biomedical Research Institute of the National Autonomous University of Mexico were maintained in barrier conditions under 12-h light/dark cycles, and allowed free access to water and food throughout the experiments, except during fasting. The mice were handled according to the principles of laboratory animal care (National Institutes of Health publication no. 85-23, revised 1985, http://grants1.nih.gov/grants/olaw/references/phspol.htm). All procedures were approved by the Ethical Committee for Experimentation of the Biomedical Research Institute of the National Autonomous University of Mexico. The mice were fed for 8 weeks with one of the following diets: biotin-control (TD-01362) or biotin-supplemented diet (TD-01363), containing 1.76 and 97.70 mg of free biotin/kg diet, respectively (Harlan Teklad, Madison WI, USA). Complete information on diet composition has been published elsewhere [35]. After 8 weeks of feeding, the mice were food deprived for 16 h, anesthetized with Sevorane (Sevofluorane, Abbott Laboratories, Mexico DF, Mexico), and blood and pancreas were extracted. Finally, the mice were killed by cervical dislocation.

2.2. Blood insulin and biotin measurements

Blood samples were collected and centrifuged at 10,000×*g* and 4°C for 10 min. Sera were stored at −20°C until used. Insulin concentrations were determined with Ultrasensitive rat insulin EIA enzyme-linked immunosorbent assay (ELISA) kit (ALPCO Diagnostics, Windham, NH, USA) according to the 25-μl sample protocol provided by the manufacturer. Serum biotin was quantified using Biotin ELISA kit (ALPCO Diagnostics). Absorbance was measured using the Labsystems Multiskan MS plate reader (Labsystems, Helsinki, Finland). All measurements were performed by duplicate.

2.3. Blood glucose measurements

Blood glucose concentrations under fasting or fed conditions were determined from tail vein samples using a portable glucose meter (Precision QID, MediSense, Inc., Abbott Laboratories).

2.4. Glucose-stimulated insulin secretion

Groups of 20–30 pair-sized islets were isolated as previously reported [36] and were cultured in biotin-free Dulbecco's modified Eagle medium (11 mmol/l glucose, 400 U/ml penicillin and 200 mg/l streptomycin and 10% dialyzed fetal bovine serum; Gibco, Grand Island, NY, USA). After overnight incubation at 37°C in a humidified atmosphere of 5% CO_2, islets were preincubated for 30 min in Hanks' balanced salt solution (HBSS) with 0.5% bovine serum albumin (wt/vol) and 3 mmol/l glucose. Islets were then incubated for 1 h in HBSS containing 5.6 or 15.6 mmol/l glucose. Insulin in the media was measured using ultrasensitive rat insulin EIA ELISA kit (ALPCO Diagnostics).

2.5. Quantitative real-time polymerase chain reaction

Total RNA isolation and relative quantifications of mRNA were determined by real-time quantitative polymerase chain reaction using an ABI Prism 7700 Sequence Detector instrument (Applied Biosystems, Foster City, CA, USA) as previously reported [36]. See electronic support material (ESM) Table 1 for complete information on the primers used. Samples were analysed by triplicate and corrected for the 18S ribosomal subunit RNA used as internal standard.

2.6. Glucose and insulin tolerance tests

All glucose and insulin tolerance tests were performed between (10:00–11:00 AM). For glucose tolerance test, the mice were fasted overnight (16 h) before the test. Glucose (2g/kg body weight) was injected intraperitoneally, and blood samples were taken before and at 15, 30, 60, 90 and 120 min after the injection. Blood glucose was measured with a glucometer (Precision QID, MediSense, Inc., Abbott Laboratories Company). In addition, blood was collected from the tail vein during the glucose tolerance test for serum separation and insulin measurement.

For insulin tolerance tests, the mice had free access to food until the test. Insulin [1 IU/kg body weight of soluble human insulin Humulin (Eli Lilly, Mexico DF, Mexico)] was injected intraperitoneally, and blood samples were taken before and at 15, 30, 60 and 90 min after the injection of insulin. Blood glucose concentrations were measured with a glucometer as described above. Areas under the curves (AUCs) were calculated using Microcal Origin 6.0 software (Microcal Software, Inc., Northampton, MA, USA).

Table 1
Effect of 8 weeks of biotin supplementation on blood glucose and insulin concentrations

Measurement	Control	Biotin supplemented
Fasting blood glucose (mmol/l)	4.9±0.1	4.9±0.2
Fed blood glucose (mmol/l)	7.6±0.4	7.8±0.2
Fasting serum insulin (pmol/l)	50.6±7.3	54.5±2.8
Fed serum insulin (pmol/l)	76.6±6.4	85.4±3.5

Values are means±S.E.M. n=4–5 for insulin; n=10 for blood glucose.

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