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Compensatory hyperinsulinemia in high-fat diet-induced obese mice is associated with enhanced insulin translation in islets

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ABSTRACT

A high-fat diet (HF) is associated with obesity, insulin resistance, and hyperglycemia. Animal studies have shown compensatory mechanisms in pancreatic β-cells after high fat load, such as increased pancreatic β-cell mass, enhanced insulin secretion, and exocytosis. However, the effects of high fat intake on insulin synthesis are obscure. Here, we investigated whether insulin synthesis was altered in correlation with an HF diet, for the purpose of obtaining further understanding of the compensatory mechanisms in pancreatic β-cells. Mice fed an HF diet are obese, insulin resistant, hyperinsulinemic, and glucose intolerant. In islets of mice fed an HF diet, more storage of insulin was identified. We analyzed insulin translation in mouse islets, as well as in INS-1 cells, using non-radioisotope chemicals. We found that insulin translational levels were significantly increased in islets of mice fed an HF diet to meet systemic demand, without altering its transcriptional levels. Our data showed that not only increased pancreatic β-cell mass and insulin secretion but also elevated insulin translation is the major compensatory mechanism of pancreatic β-cells.

1. Introduction

Obesity and lifestyle-related diseases are rapidly increasing health threats in both developed and developing countries [1]. In Asian countries, the situation is particularly alarming and appears to be caused by changes in lifestyle, such as inadequate exercise and a westernized diet. For example, there was a marked increase in fat consumption in parallel with the prevalence of type 2 diabetes mellitus (T2DM) in the Japanese population between 1945 and 1980 [2,3].

There is accumulating evidence that high fat intake, especially a high saturated fat component, is associated with obesity, insulin resistance, and hyperglycemia in animal studies [4–6]. In addition, in humans, excess dietary fat consumption promotes insulin resistance [7] and T2DM [8,9]. T2DM is characterized by pancreatic β-cell failure and insulin resistance. The failure of pancreatic β-cells to secrete adequate amounts of insulin to compensate for insulin resistance ultimately leads to T2DM [10]. Some reports have analyzed the effects of a high-fat (HF) diet on pancreatic β-cells. For instance, there are reports that have shown increased β-cell volume [6,11], enhanced glucose induced insulin secretion together with augmented Ca^{2+} signals, and an increased exocytotic response of insulin granules after a high fat load [12]. However, other studies have shown functional deterioration of pancreatic β-cells. A reduction in the transcription of the glucose sensing genes glucose transporter 2 and glucokinase in the pancreas of rats fed an HF diet was also reported [13].

Abbreviations: AHA, L-azidohomoalanine; CHX, cycloheximide; HF, high-fat; ITT, insulin tolerance test; KRB, Krebs–Ringer buffer; MafA, musculoaponeurotic fibrosarcoma oncogene family, protein A; NC, normal chow; OGTT, oral glucose tolerance test; PAL, palmitate; PBS, phosphate-buffered saline; Pdx1, pancreatic and duodenal homeobox 1; RI, radioisotope; T2DM, type 2 diabetes mellitus.

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Pancreatic β-cells are specialized for the synthesis, storage, and secretion of insulin. Each step of this process should be tightly regulated to meet systemic demand. *In vitro*, the biosynthesis of insulin is controlled acutely at the translational level [14], and it can be increased more than 15-fold by glucose stimulation [15,16]. Despite the particular ability of pancreatic β-cells to produce insulin, there are few reports showing the effects of an HF diet on insulin synthesis. In this study, we investigated whether insulin synthesis was altered in correlation with an HF diet for the purpose of obtaining further understanding of the compensatory mechanisms of pancreatic β-cells.

2. Materials and methods

2.1. Animals

Male C57BL/6J mice were purchased from CLEA Japan, Inc. The mice were maintained on a 12-h light and 12-h dark cycle. From the time of weaning (4 weeks of age), the mice were fed either a normal chow (NC) diet (4.8% fat; CLEA Japan, Inc.) or an HF diet (30.3% fat; Oriental Yeast Co.). Blood glucose and plasma insulin were measured as described previously [17,18].

This study was performed according to the guidelines of the Animal Ethics Committee of the Kobe University Graduate School of Medicine.

2.2. Oral glucose tolerance test and insulin tolerance test

An oral glucose tolerance test (OGTT) was conducted as described previously [19]. Briefly, the mice were fasted for 16 h and blood samples were collected before and after the oral administration of glucose (1.5 mg/g body weight). For the insulin tolerance test (ITT), the mice were administered 0.75 U/kg body weight of human regular insulin (Eli Lilly) intraperitoneally after a 4 h fast.

2.3. Islet isolation

Mouse pancreatic islets were isolated by collagenase digestion and Histopaque density-gradient centrifugation as described previously [20–22].

2.4. Histology and electron microscopy

For immunofluorescence, the tissues were cut after they were embedded in paraffin and stained with primary antibodies specific for insulin (Dako) and glucagon (Dako), and secondary antibodies conjugated to Cy3 and FITC (Jackson ImmunoResearch Laboratories). Pancreatic β-cell mass was quantified as described previously [18,20,23]. For electron microscopy, mouse pancreas was fixed in 0.1 M phosphate-buffered saline (PBS), 2% glutaraldehyde, and subsequently post-fixed in 2% osmium tetroxide for 2 h at 4 °C. Then, the specimens were dehydrated in a graded ethanol series and embedded in an epoxy resin. Ultrathin sections were obtained using an ultramicrotomy technique. Ultrathin sections stained with uranyl acetate for 15 min and a lead solution for 5 min were submitted to transmission electron microscope observation (JEM-1200EX; JEOL).

2.5. Measurement of islet insulin content

Islet insulin content was measured by placing 10 size-matched islets into a 1.5-mL tube containing a high-salt buffer, and insulin content was measured with a Mouse Insulin ELISA Kit T (Shibayagi Co.) as described previously [21]. Insulin levels were corrected to total DNA levels.

2.6. Cell culture

INS-1 cells were maintained in RPMI 1640 medium (Sigma–Aldrich), containing 10% fetal bovine serum. For the glucose stimulation study, INS-1 cells were preincubated with Krebs–Ringer buffer (KRB) containing 0.1% bovine serum albumin and 2.8 mM glucose for 2 h, followed by stimulation with the same solution containing either 2.8 or 16.8 mM glucose for 1 h. This incubation was performed with or without 5.0 ng/mL cycloheximide (CHX) (Sigma–Aldrich). For treatment with palmitate (PAL) (Sigma–Aldrich), 0.5 mM PAL was added to RPMI-1640 medium and the cells were incubated for 24 h.

2.7. Real-time RT-PCR

Total RNA was isolated from mouse islets or from INS-1 cells using an RNeasy kit (QIAGEN). Quantitative real-time RT-PCR was performed with the SYBR Green reagent (Promega) and evaluated using an ABI 7900 sequencer (Life Technologies). The relative abundance of mRNAs was calculated with cyclophilin mRNA as the invariant control. Details of the primers used for RT-PCR are provided in Supplementary Table 1.

2.8. Immunoblot analysis

Islets or INS-1 cells were lysed using sonication as described previously [22,24]. The lysates were probed with antibodies to insulin (Cell Signaling Technology) and β-actin (Sigma–Aldrich).

2.9. Insulin synthesis study

For INS-1 cells, they were treated with KRB containing either 2.8 or 16.8 mM glucose and treated with or without CHX as described in Cell culture. For the last 30 min, Click-iT® AHA (L-azidohomoalanine) (Life Technologies) was added and mixed gently. For islets, isolated mouse islets were transferred and incubated in a methionine-free medium (Sigma–Aldrich) for 30 min, following the addition of AHA for another 30 min. The incubations were terminated by washing the cells or islets with ice-cold PBS for 3 times. After the cells or islets were lysed, immunoprecipitation was performed with an anti-insulin antibody (Cell Signaling Technology #L6B10; Abcam #Ab7842). Eluted proteins from the precipitated samples were reacted with biotin-alkyne (Life Technologies) using a Click-iT Protein Reaction Buffer Kit (Life Technologies). After the reaction, acrylamide gel electrophoresis was performed and then probed with streptavidin-HRP (Cell Signaling Technology).

2.10. Statistical analysis

Data are presented as the mean ± standard error of the mean. We assessed the significance of differences between independent means by Student's t-test. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Mice fed an HF diet exhibit increased body weight, glucose intolerance, and hyperinsulinemia

Male C57BL/6J mice were fed with either an NC (4.8% fat) or HF diet (30.3% fat) from 4 weeks of age. Mice fed an HF diet displayed increased body weight compared with those fed an NC diet (Fig. 1A). Ad libitum blood glucose levels tended to increase in mice fed an HF diet, but not significantly so (Fig. 1B). Serum insulin levels were significantly increased at 12 weeks of age in mice fed

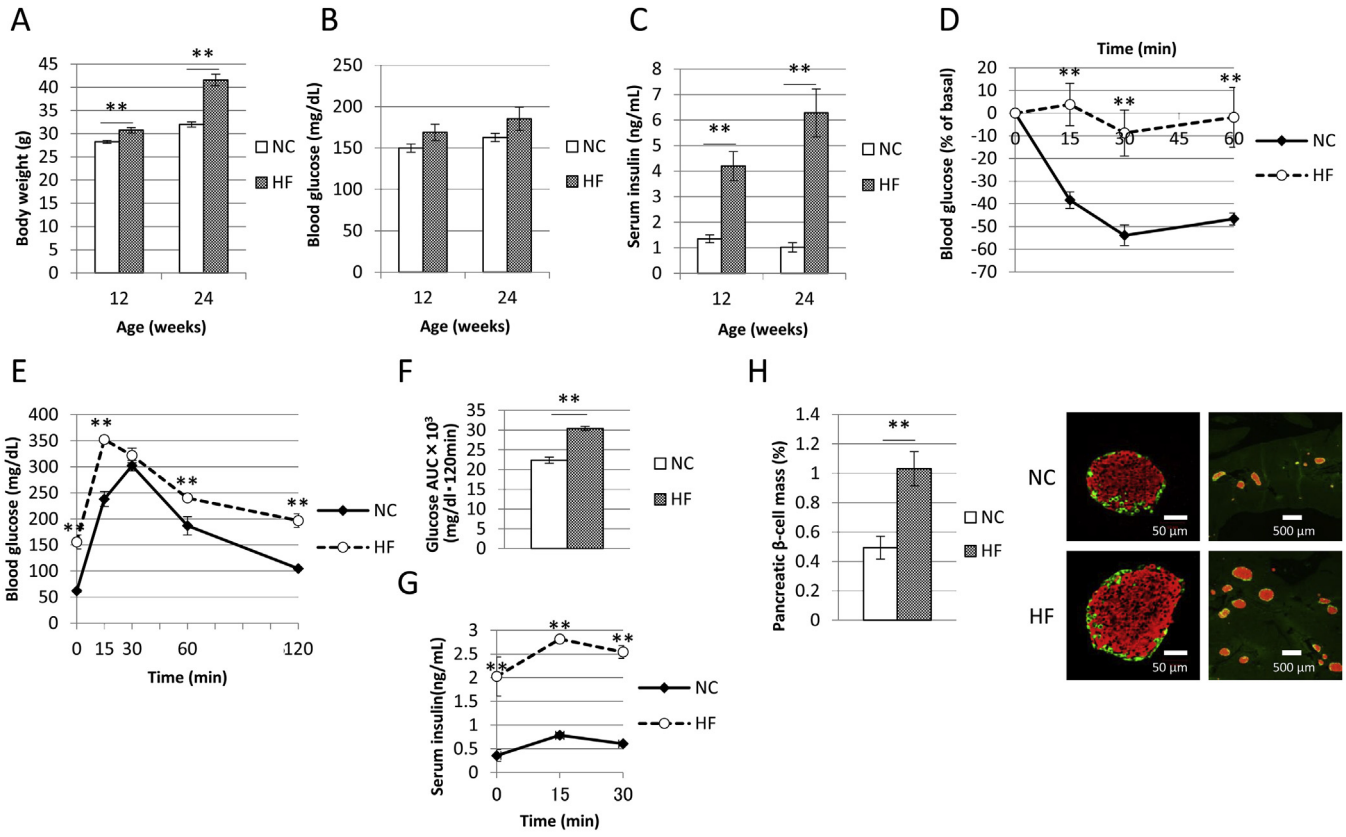

Fig. 1. Effect of a high-fat diet on glucose tolerance and insulin resistance. Body weight (A), ad libitum blood glucose (B), and ad libitum serum insulin levels of mice at 12 and 24 weeks of age (C). The insulin tolerance test was conducted at 24 weeks of age (D). Blood glucose (E), glucose area under the curve (AUC) (F), and serum insulin (G) during the oral glucose tolerance test. Pancreatic β-cell mass (H, left panel) immunostaining of pancreas sections from mice fed a normal chow (NC) and HF diet at 24 weeks of age with antibodies to insulin (red) and glucagon (green). Scale bars: 50 and 500 μm (H, right panel). All data shown are mean ± standard error of 5–10 mice of each group. $^{*}P < 0.05$; $^{**}P < 0.01$.

an HF diet. At 24 weeks of age, the difference was even greater (Fig. 1C). The ITT demonstrated that 24-week-old mice fed an HF diet exhibited markedly decreased insulin sensitivity (Fig. 1D). The OGTT revealed increased fasting blood glucose and serum insulin levels in mice fed an HF diet (Fig. 1E, G) and also indicated elevated insulin resistance. Glucose levels and serum insulin levels after glucose load were also higher in mice fed an HF diet (Fig. 1E–G). Pancreatic β-cell mass in mice fed an HF diet was increased by approximately 2-fold compared with those fed an NC diet, which was compatible with a previous study [25] (Fig. 1H). These results indicated that significant hyperinsulinemia occurred in obese mice fed an HF diet to compensate for increased insulin resistance.

3.2. Insulin content and insulin secretary granules are increased in islets of mice fed an HF diet

To compare the storage of insulin in pancreatic β-cells of mice fed an NC or HF diet, we next analyzed insulin content in isolated mouse islets. Insulin content in islets of mice fed an HF diet was significantly increased compared with that of mice fed an NC diet (Fig. 2A). Electron microscopy observation of mice pancreatic

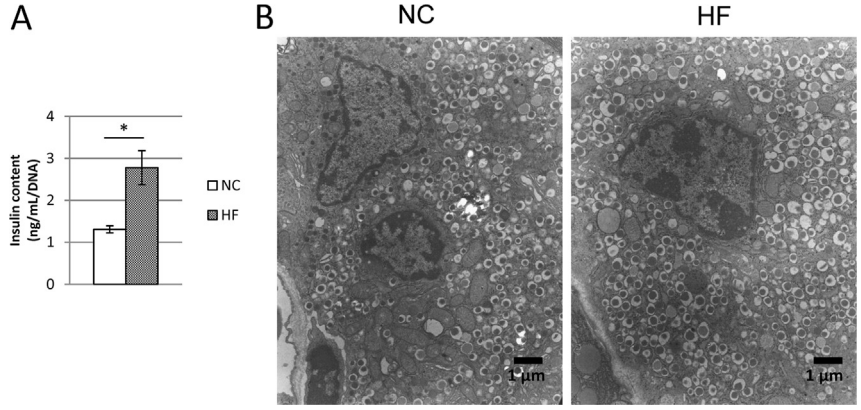

Fig. 2. Insulin storage is increased in pancreatic β-cells of mice fed a high-fat diet. Insulin content was determined and normalized to total islet DNA in 24-week-old mice. Data represents mean ± standard error. $^{*}P < 0.05$ (A). Electron microscopy images of pancreatic β-cells of mice at 24 weeks of age fed a normal chow (NC) or HF diet (B). Scale bars: 1 μm.

β-cells revealed apparently increased numbers and density of insulin granules in HF β-cells (Fig. 2B). These data indicated that insulin storage is increased in pancreatic β-cells of mice fed an HF diet, leading us to hypothesize that increased insulin storage was associated with increased insulin synthesis in β-cells.

3.3. Proinsulin levels, but not insulin mRNA levels, are increased in mice fed an HF diet

In order to investigate the effect of insulin demand on insulin genes in pancreatic β-cells, we first confirmed the expression of insulin mRNA in a rat pancreatic β-cell line, INS-1 cells, after glucose load. Increased glucose concentration did not affect the expression of insulin mRNA (Fig. 3A, B). However, there was a marked increase in insulin protein levels (Fig. 3C), which was suppressed by the translation inhibitor CHX. Next, we treated INS-1 cells with PAL to investigate the direct effect of saturated fatty acids on pancreatic β-cells, as it is the major saturated fatty acid contained in the HF diet. Insulin mRNA levels in INS-1 cells treated with PAL for 24 h were not altered (Fig. 3D, E), nor was there a significant difference in the expression of the insulin precursor proinsulin (Fig. 3F), indicating that PAL treatment for 24 h did not have any influence on insulin production. We also analyzed the expression of insulin mRNA in isolated mouse islets. There was no significant change in *Ins-1* and *Ins-2* mRNA levels between islets from mice fed an NC or HF diet (Fig. 3G, H). Conversely, the expression of proinsulin was markedly increased in islets from mice fed an HF (Fig. 3I). These data suggested that an HF diet was associated with changes in insulin translation, rather than insulin transcription, in pancreatic β-cells. Gene expression of the representative insulin transcription factors pancreatic and duodenal homeobox 1 (*Pdx1*) and musculoaponeurotic fibrosarcoma

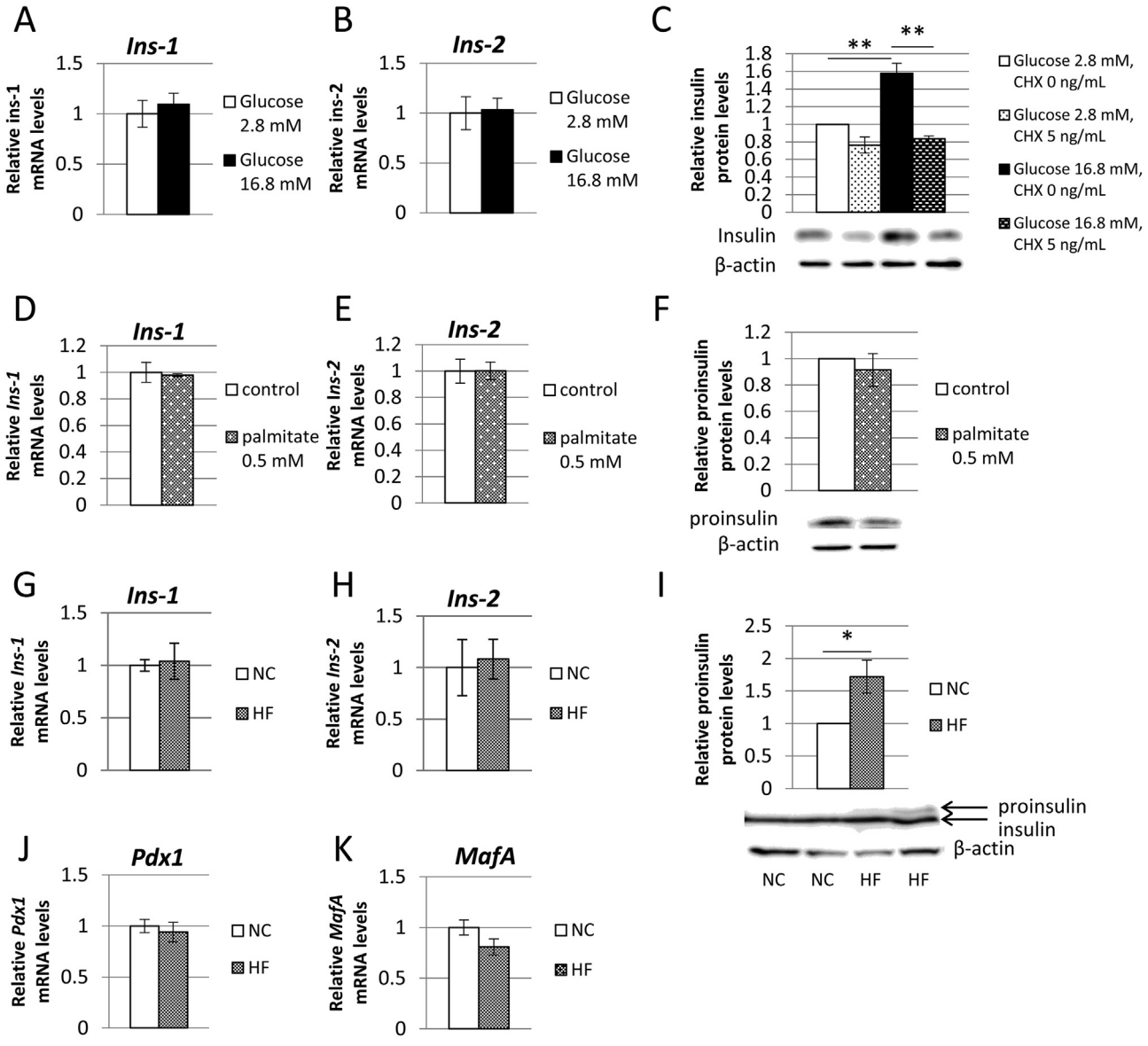

Fig. 3. Proinsulin levels, but not insulin mRNA levels, are increased in mice fed a high-fat diet. INS-1 cells were preincubated with Krebs–Ringer buffer containing 2.8 mM glucose for 2 h, and then further incubated with either 2.8 or 16.8 mM glucose for 1 h. The cells were lysed and subjected to real-time RT-PCR analysis (A, B) or immunoblot analysis with an antibody against insulin (C). INS-1 cells were treated with 0.5 mM palmitate for 24 h. The results of real-time RT-PCR analysis (D, E) and immunoblot analysis (F) are shown. Mouse islets were isolated and subjected to real-time RT-PCR analysis (G, H, J, K) and immunoblot analysis with anti-insulin antibody (I). Results are shown as mean ± standard error. $^{*}P < 0.05$, $^{**}P < 0.01$. CHX, cycloheximide; NC, normal chow.

oncogene family, protein A (*MafA*) was not altered between islets of mice fed an NC or HF diet (Fig. 3J, K), which was also supportive of our hypothesis that insulin transcription was not altered in pancreatic β-cells of mice fed an HF diet.

3.4. Insulin translation is enhanced in pancreatic islets of mice fed an HF diet

To perform a more direct assessment of insulin translational levels, we used the non-radioisotope (RI) chemical, AHA. Incorporation of AHA into newly synthesized insulin during a brief time period, followed by immunoprecipitation using an anti-insulin antibody, was measured. We first measured insulin translation in INS-1 cells treated with glucose and CHX. Insulin translation was significantly elevated in INS-1 cells treated with high glucose (16.8 mM), which was identical to previous reports using an RI [15,26]. Enhanced translation was suppressed by the addition of the translation inhibitor CHX (Fig. 4A, B). We also compared the AHA-proinsulin levels in islets from mice fed an NC or HF diet, and found that AHA incorporation was prominently enhanced in proinsulin of mice fed an HF diet compared with those fed an NC diet (Fig. 4C, D), indicating that insulin translation is enhanced in pancreatic β-cells of mice fed an HF diet.

4. Discussion

With the use of a mouse model with an HF diet, we have demonstrated that mice fed an HF diet are obese, insulin resistant, hyperinsulinemic, and glucose intolerant. Pancreatic β-cell mass was increased, and there was more storage of insulin in islets of mice fed an HF diet. In addition, we revealed significantly enhanced insulin translation in islets of mice fed an HF diet. Increased insulin translation, as well as increased pancreatic β-cell mass, seems to be one of the reasons why islet of mice fed an HF diet are capable of storing and secreting more insulin to compensate for systemic demand. To our knowledge, this is the first report to apply non-RI chemicals to analyze insulin translation in pancreatic β-cells. Some reports have applied [^{35}S]methionine to evaluate nascent insulin synthesis [15,27]. Our data showed that AHA labeling and subsequent biotin-alkyne reaction can be a safer and more convenient substitution for the use of RIs. There are reports indicating that elevated endoplasmic reticulum stress plays a role in the impairment of insulin biosynthesis [28,29]. Our method could be applied as an early marker of the onset of endoplasmic reticulum stress, which consequently leads to pancreatic β-cell failure.

Under an insulin resistant state, it was reported that pancreatic β-cell mass was increased by neuronal relay, mediated by inter-organ communication originating in the liver [30]. However, by which mechanism insulin translation is enhanced in our HF mouse model is unclear. Our data have shown that PAL, the major component of HF, does not trigger HF-induced insulin translation. However, insulin translation in islets of mice fed an HF diet is enhanced in association with increased insulin demand.

It has been reported that insulin itself does not have a role in insulin biosynthesis [26]. Increased circulating insulin in mice fed an HF diet does not seem to be the mediator of increased insulin translation. Elevated blood glucose can be a candidate, as glucose induces insulin translation through the cooperative action of a stem-loop in the 5′-untranslated region and a conserved sequence in the 3′-untranslated region [31]. To investigate the possibility that glucose is also a mediator of the enhancement of insulin translation *in vivo*, insulin translation analysis in mice fed an HF diet without hyperglycemia is needed. It is possible that other unknown neuronal or hormonal factors mediate enhanced insulin translation.

Previously, we reported that in islets isolated from obese, insulin resistant *db*/*db* mice, there was a significant increase in the expression of ribosome-related molecules [32]. There is a possibility that ribosome-related genes are also increased in our mice fed an HF diet, which leads to increased biosynthesis of ribosomes and increased translation of insulin.

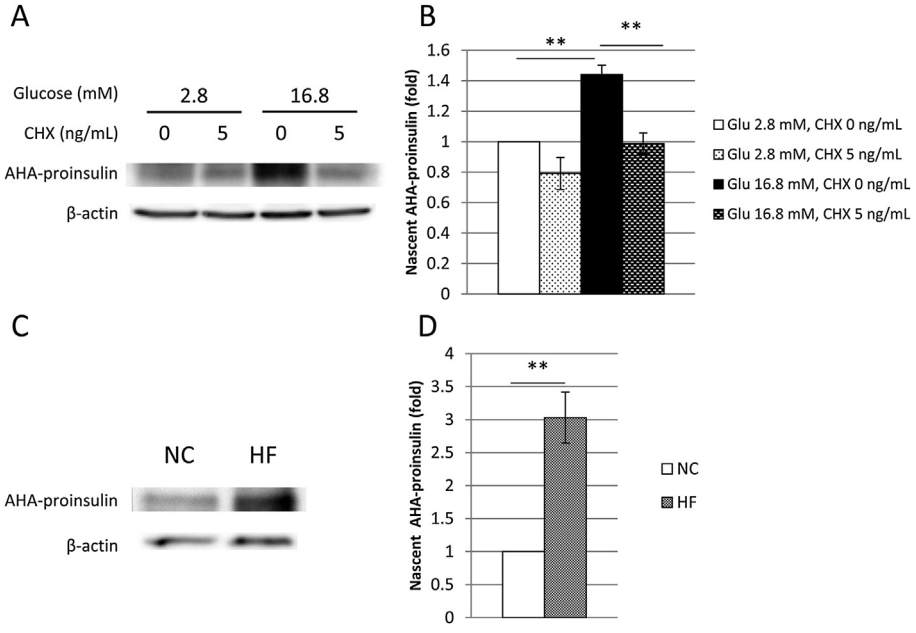

Fig. 4. Insulin translation is enhanced in pancreatic islets of mice fed a high-fat (HF) diet. Nascent translation of proinsulin was assessed after L-azidohomoalanine (AHA) labeling and immunoprecipitation using an anti-insulin antibody, followed by labeling with biotin-alkyne. Newly translated proteins are visualized by SDS-PAGE. INS-1 cells were pre-incubated in 2.8 mM Krebs–Ringer buffer containing 2.8 mM glucose (Glu) for 2 h, and then further incubated with either 2.8 or 16.8 mM glucose for 1 h with or without cycloheximide (CHX). AHA was added for the last 30 min (A), and its quantification (B). Islets were isolated from 24-week-old mice either fed a normal chow (NC) or HF diet, followed by incubation with methionine-free medium for 1 h. AHA was added for the last 30 min (C), and its quantification (D). All data represent mean ± standard error of at least three individual experiments. $^{**}P < 0.01$.

In conclusion, we revealed that enhanced insulin translation is one of the major compensatory mechanisms of pancreatic β-cells during HF diet feeding as well as increased pancreatic β-cell mass and insulin secretion.

Conflict of interest

None.

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.02.024.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.02.024.

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