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Loss of β-arrestin2 mediates pancreatic-islet dysfunction in mice

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ABSTRACT

Insulin resistance and defective insulin secretion are two major factors contributing to the pathogenesis of type 2 diabetes. β-Arrestin2 is known to interact with numerous signaling molecules. Our previous study demonstrated that β-arrestin2 regulates insulin sensitivity in both skeletal muscle and liver, yet its role in insulin secretion remains elusive. In this study, we found that β-arrestin2 was abundantly expressed in mouse pancreatic beta cells, while its expression was significantly decreased in obese and diabetic mouse models. Hyperglycemic clamp study showed that the acute and late phase of insulin secretion were impaired in β-arrestin2 knockout mice. *Ex vivo* study showed that β-arrestin2 deficient pancreatic islets exhibited blunted glucose-stimulated insulin secretion. Further analysis demonstrated the number of docked insulin granules in β-arrestin2 deficient islets was markedly decreased compared to wild-type islets, while insulin content and beta cell mass remained unchanged.

Our study establishes a new role for β-arrestin2 in beta-cell functions, and suggests that the down regulation of β-arrestin2 may contribute to impaired insulin secretion in type 2 diabetes.

1. Introduction

Type 2 diabetes mellitus is characterized by peripheral insulin resistance and beta cell dysfunction [1]. The beta cell dysfunction, characterized by initial failure of beta cell to respond to glucose stimulus followed by a progressive reduction in beta cell mass, is the major factor contributing to the development of type 2 diabetes. However, the molecular mechanism underlying the pathogenesis of beta cell failure is poorly understood [2].

β-Arrestins were originally identified as negative regulators of seven-transmembrane receptor-stimulated G protein signaling, mediating receptor signaling, trafficking, and degradation [3]. Recent studies found that β-arrestins perform analogous functions of receptors from structurally diverse classes such as receptor tyrosine kinases and cytokine receptors [4,5]. Moreover, β-arrestins are increasingly found to scaffold and recruit a variety of intracellular signaling molecules, thus mediating the strength and duration of a series of cellular signaling [6,7].

Two types of β-arrestins have been identified: β-arrestin1 and β-arrestin2. Depending on the type of stimulus, β-arrestin1 and β-arrestin2 can bind to different sites of signaling molecules, including the mitogen activated protein kinases ERK, JNK, and p38 as well as Akt [8]. Recent studies revealed that β-arrestins are involved in glucose homeostasis. Over-expression of β-arrestin1 attenuated insulin-induced degradation of insulin receptor substrate (IRS-1), leading to increased insulin signaling downstream of IRS-1 in Rat-1 fibroblasts [9]. In addition, β-arrestin1 was also reported to mediate effects of Glucagon-like peptide-1 (GLP-1) to stimulate cAMP production and insulin secretion in beta cells [10]. We previously reported that insulin stimulates the formation of a new β-arrestin2 signal complex, in which β-arrestin2 allows scaffolding Akt and Src to insulin receptor, while loss or dysfunction of β-arrestin2 results in deficiency of this signal complex and disturbance of insulin signaling in the mouse liver, thereby contributing to the development of insulin resistance and progression of type 2 diabetes [11].

Although the role of β-arrestin2 in peripheral insulin actions has been reported, the role of β-arrestin2 in insulin secretion has not been explored. In this study, we utilized β-arrestin2 knockout (KO) mouse models to examine the role of β-arrestin2 in β cell functions, and to elucidate the underlying mechanisms.

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2. Materials and methods

2.1. Animals

Male β-arrestin2 knockout (KO) mice have been described in our previous study [11]. β-Arrestin2 KO and its wild-type (WT) littermates were fed with a standard chow (STC) (Purina) with 20 kcal percentage of protein, 10 kcal percentage of fat, and 70 kcal percentage of combined simple carbohydrates. high-fat diet (HFD) induced obese male mice were fed with the diet composed of 20 kcal percentage of protein, 45 kcal percentage of fat, and 35 kcal percentage of carbohydrates (Research Diets) for 3 months. Male db/db diabetic mice were obtained Jackson Laboratory. All the mice had free access to food and water and were kept in cages in an artificial 12-h light/12-h dark cycle at 23 ± 1 °C. All the procedures involving the care and use of animals were in accordance with the Shanghai Jiao Tong University Guidelines for the care and use of laboratory animals (Permit Number: SYXK 20110128).

2.2. Immunohistochemistry

Pancreases were isolated from mice, fixed in 4% paraformaldehyde in 0.1 M phosphate buffer, embedded in paraffin, and cut into 5-μm thick sections at 50-μm intervals. To determine the distribution of β-arrestin2 in pancreas, pancreas sections of lean mice, diet-induced obese mice, and db/db diabetic mice were stained with rabbit anti-β-arrestin2 (Cell Signaling Technology) and mouse anti-insulin (HyTest) antibodies, followed by staining with secondary FITC-anti-rabbit IgG- and Cy3-antimouse IgG-conjugated antibodies, respectively.

2.3. Hyperglycemic clamp

Hyperglycemic clamp was conducted according to the standardized procedures [12]. The procedure involves the chronic cannulation of the right jugular vein to establish a chronic catheter approximately 4–5 days before the intravenous infusion of glucose during the clamp. To assess *in vivo* insulin secretion, a 6 h fasted mouse in a restrainer was infused with 20% glucose until plasma glucose concentrations was maintained at approximately 16–18 mmol/L. Blood samples (50–60 μL) were collected from tail vein during the the hyperglycemia clamp experiment. Glucose levels were measured using a glucose meter (ACCU-CHEK, Roche, Switzerland) and insulin levels were measured using the commercially available enzyme-linked immunosorbent assay (ELISA) kit (10-1150-0196, Mercodia, Sweden). The acute phase of insulin secretion was defined from 0 to 20 min, and the late phase of insulin secretion was from 20 to 90 min.

2.4. Histological and electron microscopic analysis

To measure pancreatic insulin content, the weighed pieces of pancreas were homogenized by sonication in acid–ethanol solution and insulin was extracted [13]. For the measurement of beta cell mass, pancreatic sections were stained with anti-insulin antibody, and the areas of beta cells were quantified using the image analysis software (ImageJ 1.43U). The β-cell mass was evaluated by multiplying the pancreas weight by the percentage of beta cells as described [14].

Electron microscopic analysis was performed by the Electron Microscope Unit at Shanghai Jiaotong University. Briefly, isolated islets of β-arrestin2 KO and WT control were fixed in 2.5% glutaraldehyde. Sections of 100-nm thickness were prepared from the embedded samples. The thin sections were mounted on 150 mesh hexagonal copper grids, stained with 2% aqueous uranyl acetate and Reynold's lead citrate, and visualized on a transmission electron microscope. Docked insulin granules were quantified as described previously [15].

2.5. Isolation of pancreatic islets and glucose stimulated Insulin secretion (GSIS) assay

The pancreases of 12-week old male β-arrestin 2 KO and wild-type mice were perfused with collagenase (C9263-1G, Sigma) and then digested at 37 °C for 15 min. The islets were manually picked under a stereomicroscope. The isolated islets were cultured overnight in RPMI1640 medium with 11 mM glucose, and then incubated in Krebs Ringer bicarbonate (KRB) buffer (pH 7.4) containing varying concentrations of glucose (2.8 mM, 20 mM) for 1 h. The secreted insulin in KRB buffer was collected and assayed for insulin using the Mercodia insulin ELISA kit.

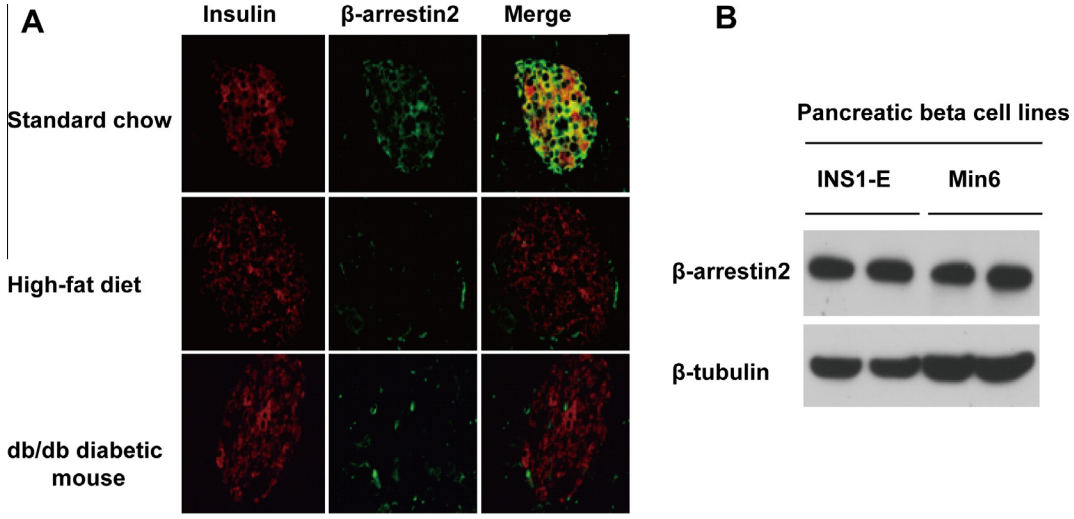

Fig. 1. β-Arrestin2 expressed in mouse islet and pancreatic beta cell lines. (A) Decreased β-arrestin2 expression in pancreatic islets in both dietary and genetic obese mice. Immunofluorescence staining of β-arrestin2 (green) and insulin (red) in pancreatic sections of 12-week-old male C57BL/6J lean mice on standard chow (STC), or high-fat diet (HFD), or db/db obese/diabetic mice. (B) Western blot showed β-arrestin2 expressed in INS1-E and Min6.

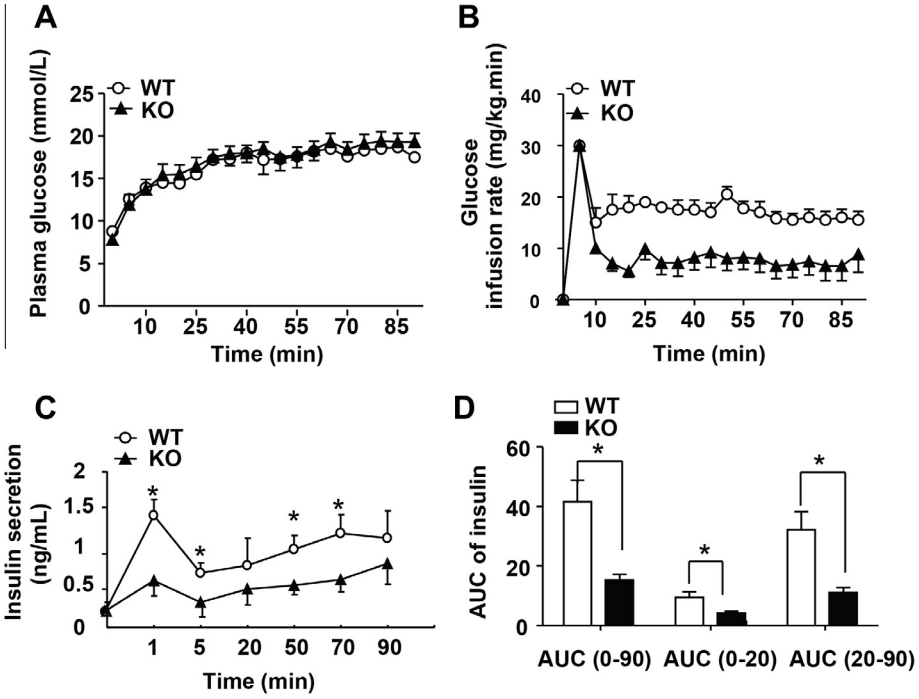

Fig. 2. Impaired insulin secretion in β-arrestin2 KO mice during hyperglycemic clamp. (A) A 90-min clamp was conducted with a primed and variable infusion of glucose to raise and maintain the plasma glucose concentrations at approximately 16–18 mM in the β-arrestin2 KO mice ($n = 8$), and wild-type (WT) littermates ($n = 8$). (B) The glucose infusion rates of the 2 groups were calculated. (C) Plasma insulin was measured at the indicated time points. (D) The values indicate the area under the curve (AUC) for insulin secretion throughout the experiment (0–90 min) or during the acute (0–20 min) or late (20–90 min) phases of secretion. $^*P < 0.05$ ($n = 8$).

2.6. Statistical analysis

Data are presented as mean ± SEM. All the experiments were repeated 3 times with representative data shown. Statistical significance was determined by 2-tailed Student *t* tests. A *P* value of less than 0.05 represented a significant difference in all statistical comparisons.

3. Results

3.1. Expression of β-arrestin2 is decreased in pancreatic islets of dietary obese and genetically inherited diabetic mice

To evaluate the physiological relevance of β-arrestin2 in pancreas, the expression level and distribution pattern of β-arrestin2 were detected in beta cell lines and mouse pancreas. Of note, beta cell dysfunction is observed in high-fat diet (HFD)-induced obese mice and genetically inherited db/db obese/diabetic mice [16,17]. Interestingly, the expression level of β-arrestin2 in pancreatic islet was significantly decreased in these obese and diabetic mouse models, suggesting β-arrestin2 might play a pivotal role in the development of beta cell dysfunction (Fig. 1A). Also, β-arrestin2 was highly expressed in cell lines such as Min6 and INS-1E (Fig. 1B).

3.2. β-Arrestin2 KO mice exhibit decreased first and second phase of insulin secretion during hyperglycemic clamp

We previously reported that β-arrestin2 KO mice exhibit glucose intolerance [11]. To further determine whether β-arrestin2 regulated insulin secretion *in vivo*, we assessed glucose-stimulated insulin secretion by hyperglycemic clamp. 12-week old β-arrestin2 KO mice and WT controls were given a primed infusion of glucose to reach and maintain hyperglycemia (16.7 mM) during the 90-min experiment. The infusions successfully increased the plasma glucose levels equally in both groups (Fig. 2A). Notably, β-arrestin2 KO mice required significantly lower glucose infusion rates in order to increase glucose levels by the same magnitude when compared to WT controls (Fig. 2B). Importantly, the acute phase (0–20 min) and late phase (20–90 min) of insulin secretion were substantially lower in β-arrestin2 KO mice, suggesting that β-arrestin2 deficiency impaired glucose-stimulated insulin secretion *in vivo* (Fig. 2C and D). Taken together, glucose intolerance observed in β-arrestin2 KO mice is, at least in part, due to impairment of insulin secretion.

3.3. Glucose-stimulated insulin secretion decreased in β-arrestin2-deficient islets

In order to evaluate the direct effect of β-arrestin2 deficiency on insulin secretion, pancreatic islets were isolated from 12-week old KO mice and WT controls, cultured overnight in RPMI medium with 11 mM glucose, and then incubated with varying concentration of glucose. The basal (2.8 mM glucose) insulin secretion did not differ between the islets obtained from the WT mice and those from the β-arrestin2 KO mice. However, β-arrestin2-deficient islets had decreased glucose-stimulated insulin secretion (20 mM glucose) when compared to WT islets. Collectively, these results indicate that β-arrestin2 deficiency caused specific impairment of glucose-stimulated insulin secretion, thus inducing glucose intolerance (Fig. 3).

3.4. Genetic disruption of β-arrestin2 decreased the number of docked granules, but normal beta cell mass and insulin content in pancreas

Further, electron microscopic analysis of the plasma membrane revealed a dramatically reduced number of docked insulin granules in beta cell from β-arrestin2 KO mice (Fig. 4A). In addition to exocytosis, the impairment of insulin secretion may result from alterations in pancreatic beta cell mass and/or insulin biosynthesis.

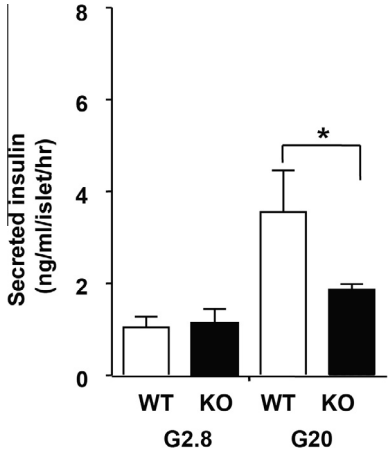

Fig. 3. Glucose-stimulated insulin secretion decreased in β-arrestin2 KO pancreatic islets. $^{*}P < 0.05$ ($n = 6$).

Immunofluorescence staining analysis with anti-glucagon and anti-insulin antibodies detected a normal distribution of α cells at the periphery and insulin-positive beta cells in the center of islets from β-arrestin2 KO mice (Fig. 4B). Both the pancreatic mass and islet content were similar between KO mice and WT groups (Fig. 4C and D). These results indicating that defective insulin secretion in β-arrestin2 KO mice was mainly due to impaired insulin exocytosis.

4. Discussion

Both insulin resistance and beta cell dysfunction are pivotal in the pathogenesis of type 2 diabetes. Our present study showed that β-arrestin2 deficiency impairs the glucose-stimulated insulin secretion in the pancreatic beta cells. We demonstrated that β-arrestin2 is expressed exclusively in the pancreatic islets, but not in the pancreatic exocrine cells. Deletion of β-arrestin2 significantly impaired glucose-induced insulin secretion in mice, as measured by hyperglycemic clamp. Furthermore, this notion was further supported by our finding that isolated β-arrestin2 deficiency displayed impaired insulin secretion in response to glucose stimulation. In addition, we observed a significant decrease of docked insulin granule in beta cells of β-arrestin2 KO mice. To our knowledge, this is the first study demonstrating that β-arrestin2 deficiency confers deteriorative effects on pancreatic β-cell function.

Electron microscopic analysis of the plasma membrane of beta cells from the β-arrestin2 KO mice localized the site of defect to a significant decrease in the number of docked insulin granules. Our microarray data also showed that exocytosis related proteins, such as syntaxin4, were down regulated in the β-arrestin2 KO mice (data not shown). Therefore, β-arrestin2 regulates glucose stimulated insulin secretion through affecting exocytosis in pancreatic beta cells, but the mechanism need to be further elucidated in future studies.

A growing body of evidence suggests that impaired insulin signaling in pancreatic beta cells leads to impairment of insulin secretion. In human, insulin signaling proteins including insulin receptor (IR), insulin receptor substrate (IRS) and Akt2 are abundantly expressed in pancreatic islets, However, their expression levels are down-regulated in type 2 diabetic patients [18,19]. Genetic mutation in *IRS-1* gene in human associates with decreased insulin secretory granules and impaired insulin secretion in response to glucose [20]. Recent clinical studies demonstrated that insulin potentiates glucose-stimulated insulin secretion in healthy humans [21], while this insulin action is diminished in subjects

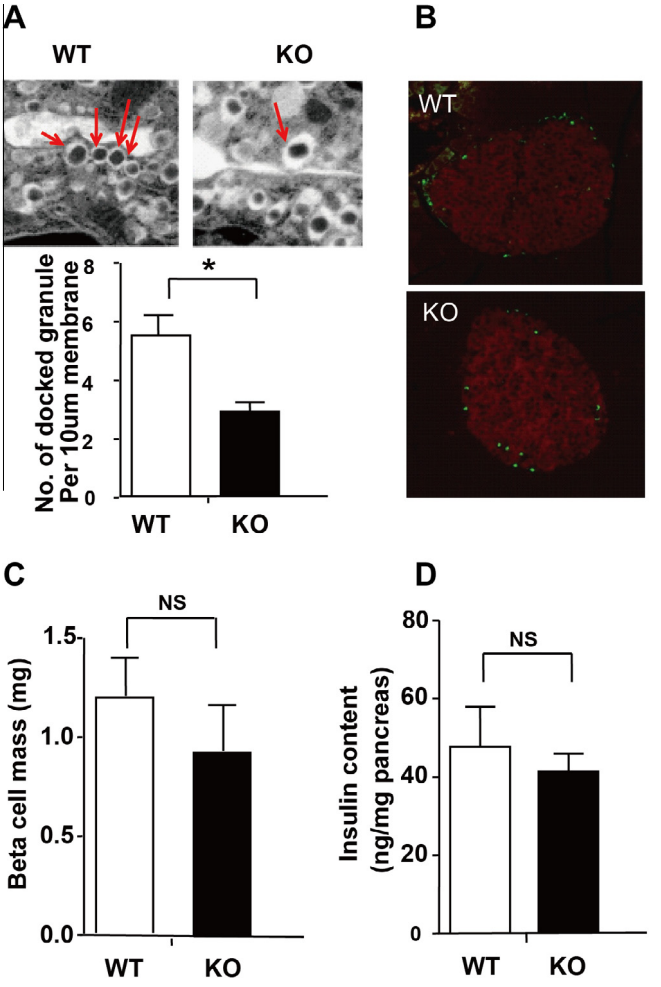

Fig. 4. Genetic disruption of β-arrestin2 decreased the number of docked granules in the 12-week-old β-arrestin2 KO and wild-type mice. (A) Electron microscopic images of docked insulin granules (denoted with arrows), and quantification of the number of docked granules in the isolated islets (islet number: 9–10). (B) Immunofluorescence of alpha cell (green) and beta cell (red) in pancreas of β-arrestin2 KO and wild-type mice. (C) Pancreatic β-cell mass was calculated in the β-arrestin2 KO and wild-type mice. (D) Insulin content was measured in the β-arrestin2 KO and wild-type mice. $^{*}P < 0.05$ ($n = 4$), NS, not significant.

with insulin resistance and type 2 diabetes [22]. In animal studies, the expression levels of insulin signaling proteins in islets are also decreased in mouse models with type 2 diabetes [23]. Our previous study demonstrated that β-arrestin2, as a scaffold protein, recruits Akt and Src kinase to insulin receptor in response to insulin stimulation in hepatocytes and muscle cells, we found that loss of function of β-arrestin2 results in a deficiency of this signal complex and disturbance of insulin signaling, contributing to the development of insulin resistance in the liver and muscle. Indeed, we found that the expression of β-arrestin2, as an insulin signaling molecule, is also dramatically decreased in pancreatic islets of db/db diabetic mice. Genetic inactivation of insulin-signaling molecules in beta cells, including IR, PI3K, Akt, and APPL1 significantly induces defective insulin secretion, leading to diabetes in mice [14,24–26]. Moreover, previous studies have suggested that abbreviated insulin signaling leads to decreased number of docked insulin granules in beta cells [26,27]. In current study, we also found that number of docked insulin granules is markedly reduced in islets of β-arrestin2 KO mice. Therefore, it is highly possible that β-arrestin2 may regulate insulin secretion in beta cells via the insulin signaling pathway.

Heterotrimeric G protein (Gαβγ)-coupled receptors constitute the largest family of cell-surface receptors and are the major mediators of hormonal and neuronal signals in the modulation of insulin secretion [28]. Several GPCRs, such as GPR40, GPR119, and GPR120, have been reported in the regulation of beta cell function [29,30]. These GPCRs can activate Gαs to stimulate cAMP production, thereby potentiating glucose-stimulated insulin secretion via a protein kinase A-dependent and protein kinase A-independent pathways. It is well-established that β-arrestins act as adaptor proteins in mediating the association between GPCRs and their downstream signaling molecules. β-Arrestin1, shares more than 70% amino acid sequence identity with β-arrestin2, has been shown in regulating beta cell functions. β-Arrestin1 interacts with GLP-1 receptor, potentiating glucose-stimulated insulin secretion [10]. Indeed, we found that the potentiating effect of GLP-1 on glucose-stimulated insulin secretion is blunted in β-arrestin2 deficient islets (unpublished observation). Furthermore, β-arrestin1 is indispensible for the potentiating action of pituitary adenylate cyclase-activating polypeptide on glucose-induced insulin secretion and ERK1/2 activation in pancreatic islets and rat β cells [31]. Therefore, β-arrestin2 might also play important roles via these GPCR signaling pathways in pancreatic beta cells.

In conclusion, we provide direct genetic evidence for a role of β-arrestin2 in regulation of insulin secretion *in vivo* and *ex vivo*. In type 2 diabetes, expression levels of β-arrestin2 are not only decreased in peripheral insulin responsive tissues but also decreased in pancreatic beta cell. We proposed that reduction of β-arrestin2 contributes to the development of insulin resistance in peripheral tissues and impaired insulin secretion in pancreatic islets, thereby leading to development of type 2 diabetes. These findings provide novel insights into the basic cellular/molecular mechanisms that regulate insulin secretion in pancreatic β-cells and could have important implications for understanding the pathogenesis of type 2 diabetes.

Acknowledgments

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