Original Article
Pericentrin expression in pancreatic β cells is associated impaired glucose tolerance

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Abstract: Objective: To explore the role and mechanism of pericentrin (PCNT) in impaired glucose tolerance. Methods: Mouse model of specific PCNT reduction in β-cells (PCNTβPCNT) was built using a Tet-on induction system; mouse model of impaired glucose tolerance was built by high-fat feeding. MIN6 cells were divided into control and Si-PCNT groups. Results: An obvious decrease in PCNT, F-actin, and insulin expression in Si-PCNT cells (P < 0.01) was observed, and the stimulating effect of GLP-1 on first phase insulin secretion disappeared in Si-PCNT cells. PCNTβ exhibited impaired first phase insulin secretion and abnormal glucose tolerance (P < 0.05 or P < 0.01). Fewer insulin granules smaller than 300 nm were detected in PCNTβ (P < 0.05). PCNT expression decreased progressively with insulin resistance (P < 0.05 and P < 0.01). First phase insulin secretion and glucose tolerance decreased with PCNT levels. The homeostasis model assessment-insulin resistance was negatively correlated with PCNT expression. Conclusions: PCNT plays an important role in modulating first phase insulin release by adjusting distribution of insulin granules and was closely related to development of impaired glucose tolerance induced by the high-fat diet. PCNT might be a therapeutic target for diabetes prevention.

Keywords: Pericentrin, first phase, insulin secretion, impaired glucose tolerance, prevention

Introduction

Diabetes is a metabolic disorder characterized by the inability of β-cells to secrete enough insulin (INS) to maintain glucose homeostasis [1]. Pancreatic β-cells secrete INS in a biphasic manner referred to as first and second phase INS secretion [2]. Loss of first phase INS secretion is an independent predictor of the onset of diabetes [3]. Restoration of first phase INS secretion has been shown to improve blood glucose levels by suppressing hepatic glucose production and priming INS sensitive tissue to take up glucose [2]. Modulation of first phase INS secretion to delay the escalation from insulin resistance to diabetes is a major challenge in diabetes treatment.

Pericentrin (PCNT) is a highly conserved scaffolding protein that plays a key role in cell cycle control and signal transduction, including the regulation of centrosome structure and function, mitotic spindle formation, and microtubule nucleation [4]. Patients with osteodysplastic primordial dwarfism of Majewski type 2 (MOPDII) exhibit severe INS resistance and early onset of type 2 diabetes (T2D); the PCNT mutation is a major cause of MOPDII, suggesting a link between PCNT dysfunction and abnormal glucose metabolism [5]. Inhibition of PCNT expression in pancreatic β-cells could lead to low expression of F-actin and Syn-4, resulting in excessive INS secretion in the fasting phase and impaired INS secretion in the first phase [6]. Our previous studies showed that the cytoplasm of islet β-cells was enriched in PCNT, that a decreased level of PCNT could lead to excessive INS secretion, and F-actin was a potential target of PCNT-regulated INS secretion [7, 8].

It was speculated that abnormal expression of PCNT in islet β-cells was correlated with the
development of impaired glucose tolerance. This possibility was investigated using MIN6 cells and a transgenic mouse expressing low levels of PCNT specifically in pancreatic islet β-cells (PCNTβ) as well as a mouse model of IR induced by a high-fat (HF) diet were investigated. IR mice model was used to simulate the physiological procedure of impaired glucose tolerance, PCNTβ was set as positive control of lower PCNT in islets, and MIN6 cells were used to explore the possible regulation of INS secretion by PCNT.

Materials and methods

Experimental animals

Two F0 animal models (transgenic short hairpin [sh]PCNT+/− or INS II+/− C57BL/6 mice) were established using the Tet-on induction system. F0 animals were mated with wild type mice to generate F1 animals with stable inheritance. Two animals from different F1 models were mated to generate F2 animals (transgenic short hairpin [sh]PCNT+/− and INS II+/− C57BL/6 mice). Male F2 mice were maintained on a diet containing doxycycline (625 mg/kg) for phenotypic induction (PCNTβ mice) starting at the age of 4 weeks [9]. At 8 weeks of age, these mice were used for experiments. Age- and weight-matched male [sh]PCNT−/− mice from the same cage served as the control group. IR mice were fed a HF diet (414.0 kcal/100 g of food; 38.0% of calories from fat, 12.0% from protein, and 50.0% from carbohydrate) for 4 weeks and 12 weeks [8]. The HF diet for PCNTβ + IR mice contained doxycycline (625 mg/kg).

Mice were divided into different groups according to random numbers generated by Microsoft Excel. Five mice were kept per cage under conditions of constant temperature (23 ± 1°C) and humidity (50 ± 5%) in a standard 12-h light/12-h dark cycle with free access to food and water at the Academy of Military Medical Sciences. All in vivo experiments were performed at the animal lab of the Academy of Military Medical Sciences [10]. Mice were sacrificed by CO2 after the last intraperitoneal glucose tolerance test (IPGTT). Five mice were sacrificed after each step according to random numbers. Pancreases were harvested quickly after sacrifice, cut into several parts, and maintained under different conditions for further experimentation. The tails of each pancreas were used for transmission electron microscopy (TEM) and western blotting (WB), and the bodies and left tails of each pancreas were used for immunohistochemistry and immunofluorescence experiments.

Animal care and experimentation were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (http://www.lascn.net/Category_1208/Index.aspx) and written approval was obtained from the Ethics Committee of the Chinese People's Liberation Army General Hospital, Beijing, China (Ref. No. 2011-X5-02).

Intraperitoneal glucose tolerance test (IPGTT)

IPGTT was used to evaluate glucose tolerance and islet β cell function in mice. Mice were fasted for 14-16 h, and weighed before the test for calculation of the intraperitoneal glucose dose (2 g/kg body weight). Blood was drawn from the tail vein at -15, 0, 2, 5, 10, 15, 30, 60, 90 and 120 min after injection to measure blood glucose levels. INS concentration was measured at 0, 15, 30 and 120 min after injection using inner canthal vein blood, which was tested 2 days after the glucose tests using the same mice. Prism 7 (GraphPad Software, San DiegoCA, USA) was used to draw graphs and calculations of the area under glucose and INS curves (AUCGlu and AUClns, respectively). IPGTT was performed in 9 mice for each time point (except in the HF mice at 12 weeks).

Blood glucose and insulin measurements

Blood glucose was measured using the GE Reiter GM550 blood glucose meter (Huaguang Biotechnology Co., Nanjing, China). Mouse INS was measured using the enzyme-linked immunosorbent assay kit (Mercodia AB, Uppsala, Sweden) according to the manufacturer’s instructions.

Western blotting

Tissue was harvested from the pancreas of mice and homogenized in lysis buffer at 4°C. The supernatant was mixed with loading buffer and heated at 95°C for 10 min followed by incubation on ice for 10 min. Proteins were separated by 6% and 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis and
transferred to a polyvinylidene difluoride membrane using the semi-dry transfer method. The membrane was blocked with 2% casein for 1 h and incubated overnight at 4°C with primary antibodies against PCNT (1:1000) and F-actin (1:1000) (both obtained from Abcam, MA, USA), cyclin-dependent kinase (CDK) 4 (1:500) and Cyclin D1 (1:1000) (both obtained from Cell Signaling Technology, Danvers, MA, USA); and β-actin (1:2000) (Santa Cruz Biotechnology, CA, USA) which served as the internal control. The membrane was washed 3 times with Tris-buffered saline with 0.1% Tween 20, and incubated with secondary antibodies at room temperature for 1.5 h. The membrane was washed three times with Tween 20, developed, and imaged with an illuminometer. WB was performed for 4 mice per group, according to random number generation and was repeated 3 times.

**Immunofluorescence double labeling of pancreatic islet tissue**

Pancreatic tissue was harvested at 4°C and frozen in optimal cutting temperature medium. Frozen slices were cut at a thickness of 4 μm and collected on poly-L-lysine slides, fixed with 4% paraformaldehyde, and washed three times with phosphate-buffered saline (PBS). After blocking with 1% bovine serum albumin (BSA) for 30 min, slices were incubated overnight at 4°C with primary antibodies against PCNT (1:400), INS (1:200), and F-actin (1:100) + INS (1:200). Slices were washed three times with PBS and incubated at room temperature for 1.5 h with fluorophore-conjugated secondary antibodies. Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI) (Abcam, MA, USA). Samples were observed under a fluorescence microscope (Olympus, Tokyo, Japan).

**Immunohistochemical analysis of pancreatic islet tissues**

Mouse tissues were fixed in neutral buffered formalin for at least 3 days, embedded in paraffin, and sliced at a thickness of 7 μm. Slices were deparaffinized and rehydrated using xylene and methanol, microwaved for 15 min in sodium hydrogen phosphate citrate solution for antigen retrieval, then cooled at room temperature in PBS for 10 min. Endogenous peroxidase activity was blocked by incubation in 3% H₂O₂ for 15 min. Tissue samples were blocked with PBS containing 3% BSA for 1 h and then incubated overnight at 4°C with primary antibodies against INS (1:200) and PCNT (1:400) diluted in PBS. Samples were washed three times with PBS and incubated for 1 h at room temperature with biotinylated anti-guinea pig secondary antibodies (Beyotime, Beijing, China; diluted 1:200 in PBS). Immunoreactivity was visualized by incubating slides with streptavidin-conjugated horseradish peroxidase for 40 min followed by diaminobenzidine for 5 min. Slices were analyzed with a U-RFL-T microscope (Olympus).

**Transmission electron microscopy (TEM) analysis of INS secretory granules in pancreatic islet β cells**

Three pieces of tissue (2 × 1 × 1 mm) were obtained from the pancreas of mice and fixed with 3% glutaraldehyde in PBS (0.07 mmol/L; pH 7.4) at 4°C for 2 h, washed with 0.07 mmol/L PBS + 0.19 mmol/L sucrose buffer at 4°C, fixed with 1% osmium acid in PBS (0.24 mmol/L), and then rinsed repeatedly with buffer comprising 0.07 mmol/L PBS and 0.19 mmol/L sucrose. Samples were dehydrated in ethanol, an ethanol/acetone mixture, and acetone before being incubated in a 1:1 mixture of acetone and an embedding agent at room temperature for 30 min, and finally an overnight incubation in 100% embedding agent. Polymerization was carried out at 37°C (12 h), 45°C (12 h) and 60°C (12 h). Tissue blocks were cut into semi-thin slices with an ultrathin microtome and stained with Toluidine Blue. Slices were trimmed according to the location of the islets, yielding 80-nm ultra-thin slices that were stained in the dark with uranyl acetate for 10 min and lead citrate for 10 min. The islets were examined by TEM (Leica, Wetzlar, Germany).

**MIN6 cells culture**

MIN6 cells were obtained from Dr. Xinyu Miao (Department of Geriatric Endocrinology, Chinese People’s Liberation Army General Hospital, Beijing, China) and maintained in 35 mm petri wells (MetTek P35G-0-10-C, MA, USA) in Dulbecco’s modified Eagle medium (DMEM, Gibco, NY, USA) and 15% fetal bovine serum. Cells were incubated at 37°C in a 5% CO₂ humidified incubator. INS concentration in the culture medium was measured at different time points. Intracellular PCNT, INS, and F-actin lev-
els were visualized by trichrome immunofluorescence staining.

**Short interfering (si) RNA-mediated knockdown of PCNT in MIN6 cells**

MIN6 cells were transfected with PCNT or scrambled siRNA (siPCNT and siScr, respectively) using Lipofectamine RNAiMAX Reagent (Invitrogen, CA) according to the manufacturer’s instructions. Briefly, 6 μl of transfection reagent was diluted in 500 μl Opti-MEM and 36 pmol PCNT, and scrambled siRNAs were separately diluted in 500 μl Opti-MEM medium. Diluted siRNA solutions were incubated with different solutions of diluted transfection reagent for 15 min at room temperature. The siRNA-lipid complexes were added to cell suspensions followed by culturing in 6-well plates for 48 h until the cells reached 60-80% confluence. The cells were harvested and used for trichrome staining.

**Trichrome immunofluorescence staining**

Cells were grown in glass-bottomed culture dishes at 37°C and 5% CO₂, then washed with PBS, fixed/permeabilized on ice for 30 min in fixation solution (2% paraformaldehyde in PBS), washed four times in PBS, and blocked for 15 min with 1% BSA in PBS. Fixed cells were incubated at 4°C overnight with primary antibodies against PCNT (1:400), INS (1:200), and F-actin (1:100) diluted in PBS with 1% BSA. Cells were then incubated for 1 h in PBS containing 1% BSA and Cy3-conjugated goat anti-rabbit IgG (bs-0295G; 1:100), fluorescein isothiocyanate-conjugated goat anti-guinea pig IgG (bs-0358G; 1:50), and Alexa Fluor 647 goat anti-mouse IgM (bs-0368G; 1:100 dilution), all obtained from Bioss (Beijing, China). Nuclei were counterstained with DAPI. Samples were visualized with a confocal microscope (Radiance 2000; Bio-Rad, Calif Calif) using a 60 x CFI plan Apo objective and a filter optimized for Cherry fluorescence.

**Statistical analysis**

Animal weights are shown as mean ± standard deviation. Prism 7 (GraphPad Software) was used to draw IPGTT and GSIS curves, histograms, and scatter diagrams, and to calculate area under the curve (AUC) for glucose and INS (AUC<sub>Glu</sub> and AUC<sub>INS</sub> respectively). SPSS v.19.0 (IBM SPSS Statistics, NY, USA) was also used to analyze the data as a verification for and supplement to Prism 7. The ANOVA followed by post hoc testing was used to compare multiple groups, with P < 0.05 considered statistically significant.

**Results**

**PCNT regulation of first phase INS secretion in MIN6 cells**

In control cells, the levels of intracellular PCNT, INS, and F-actin were reduced at 15 min after intervention by the secretogogue Exn (Figure 1A, 1B), while INS concentration in the cell culture medium increased (Figure 1C). The intracellular levels of PCNT, INS, and F-actin had exhibited no further decrease 30 min after treatment.

The Si-PCNT MIN6 cells had decreased expression of intracellular PCNT compared to control cells (siScr), and the expression of F-actin and INS decreased with the same tendency as PCNT. There was no obvious alteration in the siPCNT group after treatment with Exn-4 (Figure 2).

**PCNT and F-actin expression in PCNTβ mice**

PCNT expression decreased in the pancreatic islet tissue of PCNTβ mice compared with control mice (Figure 3A-C), indicating successful establishment of the PCNTβ mouse model. No difference in pancreatic tissue cell proliferation, as determined by WB of Cyclin D1 and CDK4 expression, was observed between PCNTβ and control groups, but F-actin expression decreased (Figure 3D). IF analysis showed that F-actin expression was also reduced in PCNTβ mice compared to control mice (Figure 3E).

**Impaired first phase INS secretion, changed INS granule distribution and abnormal glucose tolerance in PCNTβ mice**

Fasting blood glucose was not altered in PCNTβ mice (Figure 4A), but fasting INS level increased (Figure 4B). The area under the INS curve at 0-15 min (AUC<sub>INS0-15</sub>) in the IPGTT test was smaller in PCNTβ mice than in control mice (P < 0.05), whereas the area under the blood glucose curve (AUC<sub>Glu0-15</sub>) was greater in the PCNTβ
mice ($P < 0.05$) (Figure 4A). INS levels in the GSIS test at 30 and 120 min were higher in mutants than in control mice, although the difference was not statistically significant (Figure 4B). Ultrastructural analysis of mouse islet β cells by TEM showed fewer INS granules 0-300 nm below the cell membrane in mutants ($P < 0.01$), although the number of INS granules more than 300 nm below the cell membrane was not different between the two groups (Figure 4C).

**Correlation of PCNT expression with the degree of abnormal glucose tolerance in mice on high-fat diets**

The time schedule of animal models is shown in Figure 5A. After 4 weeks on a HF diet, expres-
sion of PCNT and F-actin in islets were lower in IR mice than control mice ($P < 0.05$). After 12 weeks on a HF diet, PCNT expression in IR mice was further decreased to a level which comparable to that in PCNT$^\beta +$ IR mice ($P > 0.05$; Figure 5B).

AUC$_{INS0-15}$ in the IPGTT was reduced in IR mice on HF diets ($P < 0.01$), whereas AUC$_{Glu0-15}$ increased, although the former was not significantly changed. Compared with the IR group, PCNT expression and AUC$_{INS0-15}$ in PCNT$^\beta +$ IR mice was lower ($P < 0.01$), but AUC$_{Glu0-15}$ was higher ($P < 0.05$). Fasting INS and AUC$_{INS0-15}$ increased whereas AUC$_{INS0-15}$ decreased in IR mice relative to values observed at 4 weeks, matching the fasting INS, AUC$_{Glu0-15}$ and AUC$_{INS0-15}$ respectively, values of PCNT$^\beta +$ IR mice at 12 weeks ($P > 0.05$) (Figure 6A-D). AUC$_{INS0-15}$ was positively correlated with PCNT expression (Figure 6E), and AUC$_{Glu0-15}$ was negatively correlated with PCNT expression (Figure 6F) from the baseline, and from 4 weeks to 12 weeks. Glucose levels at 30-120 min were not different between IR and PCNT$^\beta +$ IR mice after 4 and 12 weeks on HF diet ($P > 0.05$).

The homeostasis model assessment (HOMA) had a negative relationship with PCNT, especially when the PCNT level was moderate (Figure 6G). Results showed that the lower PCNT groups (IR and PCNT$^\beta$) had a sharper tendency to change than the higher PCNT group (control) (Figure 6H).

**Discussion**

In this study MIN6 cells were found to have lower INS and F-actin at 15 min after intervention with the secretogogue Exn (glucagon-like peptides 1 (GLP-1) agonists), and exhibited no further decrease after 30 min, whereas PCNT knockdown in MIN6 cells abolished the effects of Exn regulation on first phase INS secretion.
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A

Control
PCNTβ

22 kDa
PCNT B
PCNT A/S
42kDa
β-actin

Control
PCNTβ

B

PCNT
Insulin
PCNT
Insulin

DAPI
Merge
DAPI
Merge

Control
PCNTβ

C

Control
PCNTβ

D

Control
PCNTβ

30 kDa
CDK4
42kDa

36 kDa
CyclinD1
42kDa

42kDa
β-actin

Control
PCNTβ

E

F-actin
Insulin
F-actin
Insulin

DAPI
Merge
DAPI
Merge

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Figure 3. PCNT and F-actin expression in PCNTβ mice. (A) PCNT expression detected by western blotting. (B) Immunofluorescence and (C) immunohistochemical analyses of PCNT expression in islets of PCNTβ and control mice. PCNT levels were lower in the islets of PCNTβ compared to control mice. (D) Cyclin D1, CDK4, and F-actin expression in PCNTβ and control groups detected by western blotting. (E) Immunofluorescence analysis of F-actin expression. Red, F-actin; insulin is indicated in green and DAPI is indicated in blue. Scale bar = 50 μm. Data shown are mean ± SEM. **P < 0.01, n.s indicates no significance.
Exn regulates INS secretion based on blood glucose levels and is considered to be an on-demand hypoglycemic agent. Knockdown of PCNT in adipocytes had no effect on proximal INS signaling but produced a twofold impairment in INS-stimulated glucose uptake, approximately commensurate with an associated defect in cell proliferation and adipogenesis [11]. In contrast to traditional sulfonylureas, GLP-1 increases intracellular Ca²⁺ concentration and stimulates INS release by activating protein kinase (PK) A-dependent and -independent and phosphoinositide 3-kinase (PI3K) pathways via cyclic (c)AMP signaling [12-15]. Thus, it is predicted that PCNT is important in first phase INS secretion.

INS secretory granule turnover consisted of several highly regulated processes allowing for proper β-cell function and INS secretion. While quantitative measurements performed decades ago demonstrated the preferential secretion of young INS, new experimental approaches aim to investigate INS ageing at the granular level [16]. One previous study showed that human INS secretion and exocytosis are critically dependent on the availability of membrane-docked granules and that T2D is associated with reduced granule docking. Glucose was found to accelerate granule docking, an effect that was absent in T2D [17]. PCNTβ mice and found impaired IPGTT 0-15 min INS secretion and glucose tolerance were

Figure 4. Impaired first phase insulin secretion, changed insulin granule distribution and abnormal glucose tolerance in PCNTβ mice. A. IPGTT 0-15min, AUC<sub>Glu0-15</sub> and AUC<sub>INS0-15</sub> in PCNTβ and control groups. B. IGPTT and GISIS 0-120 min. C. TEM analysis of the distribution of insulin granules in mouse islet β cells. Scale bars, 5 μm (upper panels) and 0.3 μm (lower panels). (Bottom right) Mean density of insulin granules in islet β cells (number/μm²). Three mice per group were tested and nine islet β cells per mouse were analyzed. Data shown are mean ± SEM. *P < 0.05, **P < 0.01, n.s indicates no significance.

Figure 5. PCNT expression in islets decreases with time on high-fat diet. A. The time schedule of animal models. B. Immunofluorescence analyses of PCNT expression in control, IR and PCNTβ + IR groups after 4 and 12 weeks on the high-fat diet. Red, PCNT is indicated in red, PCNT, insulin is indicated in green, and DAPI is indicated in blue. Scale bar, 50 μm. *P < 0.05, **P < 0.01, n.s indicates no significance.
further observed, however, there were no differences in INS levels and glucose tolerance at 30 min. TEM showed a significant reduction in the number of INS granules in the ready-release pool (RRP), although there was no obvious abnormality in the number of INS granules in the RGP region.

INS secretion after glucose stimulation can be divided into two phases: the first phase occurs at about 10 min after stimulation, and the second phase can last several hours [2]. There are two classes of granules in β cells that are involved in the first and second phases. Granules < 100 nm from the cell membrane are anchored to the membrane and responsible for rapid INS secretion after hyperglycemia (first phase), and are referred to as the RRP [18, 19]. However, these granules account for only about 1% of the total granules in islet β cells [20, 21]. Granules in the second phase are not attached to the cell membrane, these
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are known as the RGP, and constitute the second phase of INS secretion [22, 23]. To the best of our knowledge, the current study represents the first successful construction of β cell PCNT knockdown mice. Using this PCNTβ mouse line, we were able to verify that a decrease of intracellular PCNT and F-actin in murine islet cells was closely related to an abnormal distribution of INS granules and was consequently related to abnormal first phase INS secretion and impaired glucose tolerance.

Inhibition of PCNT expression in pancreatic β cells could lead to low expression of F-actin and Syn-4, resulting in excessive INS secretion in the fasting phase and impaired INS secretion in the first phase [6]. In HF diet induced IR mouse models, which simulate the physiological progress of early diabetes, PCNT expression in pancreatic islets decreased gradually with HF diet duration. First phase INS secretion and glucose tolerance decreased progressively in accordance with PCNT levels, and PCNT and HOMA-INS insulin had a linear relationship.

A HF diet is a common cause of abnormal glucose level in T2D patient. During the early stage of impaired glucose tolerance, pancreatic β cells increase INS secretion to compensate for the decrease in INS sensitivity [24]. As damage to pancreatic islets becomes more severe, the early phase of impaired INS secretion begins [25]. Abnormal or impaired first phase INS secretion is a characteristic of early diabetes and plays an important role in the occurrence and development of abnormal glucose tolerance. Therefore, it was confirmed that decreased PCNT expression in islet β cells was linked to impaired first phase INS secretion and the development of high fat induced abnormal glucose tolerance.

In summary, this study found that PCNT was regulated with the distribution of INS granules and first phase INS secretion in pancreatic islet cells, playing an important role in the development of impaired glucose tolerance. These results may provide a new avenue for the pursuit of effective diabetes prevention.

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Disclosure of conflict of interest

None.

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